

ARTICLES

TIME FOR A FRESH LOOK AT STRICT LIABILITY FOR PHARMACEUTICALS

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INTRODUCTION

Strict tort liability has a bad reputation. Too often, the pejorative term “absolute” liability is used to describe strict liability’s non-fault character, though strict liability has never been absolute. There has always been something unique about an activity or event that gave rise to theories of strict liability—blasting with dynamite, harboring wild animals, or selling products with inevitable manufacturing flaws. These and other examples support liability for harm done regardless of fault for various reasons: the high potential of harm; exclusive control by the actor of the risk and lack of choice by the injured; a violation of community norms from uncommon conduct, or; some combination of these or other notions of fairness. The most modern example is, of course, strict products liability, best illustrated by the Restatement (Second) of Torts § 402A.¹ Section 402A was adopted by the American Law Institute in 1965 to support liability for the defeat of consumer expectations from inevitable product failure that only the manufacturer could anticipate and, therefore, control.² But limitations were waiting to be discovered to narrow § 402A’s reach—to prevent “absolute” liability—the most significant of which was comment *k*, the unavoidably dangerous exception, which withheld from the reach of § 402A products whose danger was unavoidable, a significant exception.

The comment *k* exception was primarily applied to exempt pharmaceuticals from strict products liability.³ Scholars have criticized comment *k* from a variety of perspectives, but one thing is certain: it opened a wide window to protect pharmaceutical manufacturers from strict liability, even though pharmaceuticals produce inevitable known harms that cannot be reduced.⁴ One would think that the reasons behind strict products liability—risk distribution and allocation of inevitable loss to a party better able to bear it, deterrence of the production of dangerous products, upholding expectations of quality, and safety—would support

¹ RESTATEMENT (SECOND) OF TORTS: SUPPLIERS OF CHATTELS § 402A (AM. LAW INST. 1965).

² See *id.* at cmt. c.

³ See *id.* at cmt. k.

⁴ See, e.g., Joseph A. Page, *Generic Product Risks: The Case Against Comment k and for Strict Tort Liability*, 58 N.Y.U. L. REV. 853, 862–63 (1983) (discussing ALI deliberations regarding comment *k*, which exempts inherently dangerous products from the ambit of strict liability).

such liability. But in fact, in the clear majority of jurisdictions, it does not.⁵ Comment *k* has had a powerful liability-limiting effect.

Over the ensuing 50 years from the promulgation of § 402A, products liability in general has seen a retrenchment from strict liability. The Restatement (Third) of Torts: Products Liability⁶ openly adopted negligence principles for design and warning claims, and created an entirely new provision to protect pharmaceutical manufacturers even more robust than comment *k*.⁷ Regarding pharmaceutical liability, the trend away from any liability at all has been remarkable.

Why, then, does this Article propose taking a fresh look at strict liability for pharmaceutical injuries? What has changed since the adoption of the Products Liability Restatement, which endorsed a virtual immunity from liability for pharmaceuticals? Such a suggestion is likely to be met with cries of “absolute liability” and concern for a chilling effect on innovation for much needed therapeutic treatments. There are three primary reasons this Article proposes a reassessment for strict tort liability in this context. First, the expansive federal preemption doctrine that the United States Supreme Court has fashioned in the last decade defeats almost all state tort liability for pharmaceuticals, particularly for generic pharmaceuticals which comprise over 85 percent of the prescriptions in this country.⁸ Second, both the pre-marketing approval process and the post-marketing risk assessment regulatory structures fundamentally cannot adequately identify, communicate, and reduce adverse drug events and, consequently, those events are increasing and likely to continue to do so.⁹ Third, the structure of pharmaceutical marketing, increasingly unregulated, has influenced prescribing practices in ways that compound the likelihood and severity of adverse drug events.¹⁰

These trends in pharmaceutical marketing practices, coupled with the systemic limitations on information-gathering and response in the regulatory system, has created a demand for pharmaceuticals that increases the likelihood of adverse drug events with no meaningful mechanism to identify and reduce the risks presented. While the legal landscape has become barren to the use of tort liability to compensate for the inevitable risk of adverse drug effects, the medical care landscape has become more fertile for those side effects to occur. The convergence of these trends supports a reevaluation of the use of strict, non-fault liability on producers of pharmaceuticals for the harms their products cause.

⁵ See *id.*

⁶ RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY (AM. LAW INST. 1998).

⁷ *Id.* § 6 cmt. d. For a discussion of § 6, see *infra* notes 59–64 and accompanying text.

⁸ See *infra* note 156 and accompanying text (Part III).

⁹ See *infra* notes 174, 176.

¹⁰ See *infra* note 222.

Part I provides a brief and basic explanation of pharmaceutical liability treatment. Part II explains the impact of federal preemption doctrine, which has dramatically limited the operation of tort law in pharmaceutical liability cases. Part III explains the parallel trends in the marketing and use of pharmaceuticals that increase the incidence of adverse drug events, affect prescribing practices, and fail to enhance informed practitioner and consumer choice in use of pharmaceuticals. Part IV provides support for the application of strict liability given the convergence of these trends. This Part also provides a theoretical justification for strict liability in tort for pharmaceuticals based in both traditional strict liability for ultra-hazardousness and modern norms of community expectations of responsibility and care particularly salient for pharmaceutical injuries.

I. LEGAL LANDSCAPE OF LIABILITY FOR PHARMACEUTICAL INJURIES

The intersection between the regulation of pharmaceuticals and liability for injuries from those pharmaceuticals has a long history of complement and coordination. The Federal Food, Drug, and Cosmetic Act (FDCA)¹¹ was enacted in 1938 to respond to the deaths of over 100 people from the use of an untested elixir for children.¹² Thus, at that time, the premarket approval process was created. Since then, the FDCA has been amended to expand its power, typically stemming from a public health emergency. Examples include the use of thalidomide in the 1950s and 1960s that caused severe birth defects, or the use of Dalkon Shield intrauterine device that caused serious illnesses and deaths in thousands of women, illustrating the concern over medical devices.¹³ The Food and

¹¹ Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301–39 (2018).

¹² See Ebnunole Anlyikalye et. al., *Cheers to 80 Years of the Food, Drug, and Cosmetic Act*, LAW360 (June 22, 2018, 1:35 PM), <https://www.law360.com/articles/1056172/cheers-to-80-years-of-the-food-drug-and-cosmetic-act>. See generally Cara Brumfield, *A Generic a Day Keeps the Lawyer Away*, 17 NEV. L.J. 429, 432–33 (2017); Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1761–62 (1996); see generally JAMES T. O'REILLY & KATHARINE A. VAN TASSEL, *FOOD AND DRUG ADMINISTRATION* (4th ed. 2018) (providing a comprehensive general treatise on the operation of the FDCA).

¹³ See Merrill, *supra* note 12, at 1764, 1804–05; DANIEL CARPENTER, *REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA* 119 (2010) (recalling a disastrous era of self-regulation in the 1940s and 1950s that led to increased FDA power). See also Jeremy A. Greene, *Reform, Regulation, and Pharmaceuticals—The Kefauver-Harris Amendments* at 50, 367 NEW ENGLAND J. OF MED. 1481, 1482 (2012) (describing context of 1962 FDCA amendments which introduced efficacy requirements; retrospective review of all drugs approved between 1938 and 1962 identified at least 600 which were “ineffective” and withdrawn from the market).

Drug Administration now has wide-ranging authority over new drugs, biologics, and medical devices.¹⁴

The regulatory structure for pharmaceuticals is complex.¹⁵ The approval process for pharmaceuticals in the United States is considered the most demanding and rigorous in the world.¹⁶ However, the process is an *approval* mechanism: the FDA does not tell manufacturers what to research and develop. It does set policy, however, based on congressional directives and its own assessments of public health needs.¹⁷

The FDA's approval mechanism is driven by the statutory obligation to approve drugs that are "safe and effective."¹⁸ The FDA relies on the information provided to it by manufacturers in the pre-market New Drug Application process.¹⁹ In order for the FDA to consider a drug safe, the drug's "probable therapeutic benefits must outweigh its risk of harm."²⁰ Four phases of studies are required for a new drug to be approved, the final phase requiring clinical trials involving human pa-

¹⁴ The available sources on the regulatory scope of the FDA include Brumfield, *supra* note 12, at 433–39; O'Reilly, *supra* note 12; DAVID G. OWEN & MARY J. DAVIS, ON PRODUCTS LIABILITY § 19.1 (4th ed. 2018); U.S. FOOD AND DRUG ADMIN., <https://www.fda.gov/> (last visited April. 30, 2019).

¹⁵ Explanations of the regulatory structure for pharmaceuticals abound. *See, e.g.*, Merrill, *supra* note 12, at 1753; O'Reilly, *supra* note 12; U.S. FOOD AND DRUG ADMIN., *supra* note 14. The FDA website has explanations and overviews.

¹⁶ *See* BLANCHARD RANDALL IV, CONG. RESEARCH SERV., RL30989, *The U.S. Drug Approval Process: A Primer* 1 (2001). Whether the rigor of the approval process produces drugs whose efficacy is meaningful therapeutically is another question. Indeed, many have questioned whether the efficacy standard is anything more than illusory. *See, e.g.*, Jonathan J. Darrow, *Pharmaceutical Efficacy: The Illusory Legal Standard*, 70 WASH. & LEE L. REV. 2073, 2075, 2134 (2013).

¹⁷ *See* 21st Century Cures Act, PUB. L. NO. 114–255, § 3022, 130 STAT. 1033 (2016) (arguing that the FDA should lower its regulatory standards to speed drugs to market, urging the Agency to approve drugs with less evidence); *see also* Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345 (2007). Debates in the 1990s about the "drug lag" between European approval times and U.S. approval times led to accelerated review times. *See* K. Viscusi and R. Zeckhauser, *Regulating Ambiguous Risks: The Less than Rational Regulation of Pharmaceuticals*, 44 J. LEGAL. STUD. 387, 391 (2015) (median time to approval cut in half between 1993 and 2003).

¹⁸ 21 U.S.C. § 321(p)(1)–(2) (2018). *See also* Wyeth v. Levine, 555 U.S. 555, 567 (2009) (evaluating implied preemption of product liability claims under the FDCA's drug labeling provisions) ("Before 1962, the agency had to prove harm to keep a drug out of the market, but the amendments required the manufacturer to demonstrate that its drug was 'safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling' before it could distribute the drug. In addition, the amendments required the manufacturer to prove the drug's effectiveness by introducing 'substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.'").

¹⁹ *See* Margaret Gilhooley, *Vioxx's History and the Need for Better Procedures and Better Testing*, 37 SETON HALL L. REV. 941, 942–43 (2007) (analyzing the weaknesses in the FDA regulatory model).

²⁰ *Mutual Pharm. Co., Inc. v. Bartlett*, 570 U.S. 472, 477 (2013) (quoting *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 138–40).

tients.²¹ Upon establishing safety and effectiveness requirements, the FDA mandates particular warning and informational literature to be made available to prescribing physicians, typically based on that suggested by the manufacturer. Once the FDA approves a drug, the manufacturer is prohibited from making any major changes to the “qualitative or quantitative formulation of the drug product, including inactive ingredients, or in the specifications provided in the approved NDA.”²²

The pre-market approval process can take years. Thus, responding to criticism of lengthy approval times, Congress adopted the Prescription Drug User Fee Act of 1992, which assesses a fee to a pharmaceutical company who has filed a New Drug Application to expedite approval.²³ FDA approval-phase times have generally declined substantially for all types of applications since the mid-1990s following this legislation.²⁴

Generic pharmaceuticals are approved through an Abbreviated New Drug Application (ANDA) process, the result of the Hatch-Waxman Amendments to the FDCA in 1984, which were intended to make it easier to bring generic equivalents to the market with a view to reducing the price of pharmaceuticals.²⁵ Generic pharmaceuticals are required to have identical labeling to the brand-name product and the chemically equivalent formulation.²⁶ They are less expensive and are intended to reduce health care costs and increase competition. Generics represent 84 percent of total prescriptions dispensed in 2012 and 28 percent of total

²¹ See generally 21 U.S.C.A. § 355 (West 2017); U.S. FOOD AND DRUG ADMIN., *supra* note 14.

²² 21 C.F.R. § 314.70(b)(2)(i) (2018); see 21 U.S.C. § 355 (2012).

²³ Prescription Drug User Fee Act, Pub. L. No. 102–571, 106 Stat. 4491 (1992) (current version at 21 U.S.C. 379(h) (2012)).

²⁴ Joseph A. DiMasi, *Innovating by Developing New Uses of Already-Approved Drugs: Trends in the Marketing Approval of Supplemental Indications*, J. CLINICAL PHARMACY & THERAPEUTICS (2013); Viscusi & Zeckhauser, *supra* note 17, at 390 (citing Mary Olson, *Eliminating the U.S. Drug Lag: Implications for Drug Safety*, Journal of Risk and Uncertainty 47: 1–30 (2013)). Daniel Carpenter et al., *Approval Times for New Drugs: Does the Source of Funding for FDA Staff Matter?*, HEALTH AFFAIRS: WEB EXCLUSIVE (Dec. 17, 2003), available at https://www.pharmamedtechbi.com/~media/Images/Publications/Archive/The%20Pink%20Sheet/65/051/00650510017/031222_fda_funding_study.pdf; see also Mary K. Olson, Response, *Explaining Reductions in FDA Drug Review Times: PDUFA Matters*, HEALTH AFFAIRS: WEB EXCLUSIVE, at W4-S1–W4-S2 (2003 Jul.–Dec.) (PDUFA of 1992, which introduced user fees for new-drug review, had a greater impact on reducing drug approval times than the analysis of Carpenter and colleagues found; analysts examined review times aggregated by year of approval, instead of the year that the drug application was submitted, finding that even after increased agency resources over time were controlled for, the user fee reform led to a substantial reduction in drug review times).

²⁵ Drug Price Competition and Patent Term Restoration Act of 1984, 98 Stat. 1585 (1984) (current version at 21 U.S.C.A. § 355(j)); see generally, OWEN & DAVIS, *supra* note 14, § 14.4.

²⁶ 21 U.S.C.A. § 355(j)(2) (West 2017).

pharmaceutical spending.²⁷ In the retail setting, when a generic option is available, it is dispensed in place of brand name products 95 percent of the time.²⁸

Once a drug is approved for marketing—including the approval of the labeling and instructional materials that accompany the product—the manufacturer maintains responsibility for updating the labels and for providing the FDA with risk information acquired after approval. The FDA uses that information to monitor the reported side effects of drugs after they are in use.²⁹ This post-approval risk information may lead to labeling changes. For example, brand name manufacturers may acquire new information that then suggests the need to “add or strengthen a contraindication, warning, precaution, or adverse reaction,” or to “add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product.”³⁰ As of 2007,³¹ the FDA has the authority to require labeling changes and prevent the sale of adulterated and misbranded drugs.³² It rarely forces an approved drug from the market.³³

As of 2007, manufacturers are required to gather information on post-marketing adverse events and report those events to the FDA.³⁴ This

²⁷ Michael Bartholomew, *Top 200 Drugs of 2012*, PHARMACY TIMES, (Sept. 24, 2014) <https://www.pharmacytimes.com/publications/issue/2013/july2013/top-200-drugs-of-2012>; see also Brumfield, *supra* note 12, at 439 (“By 2010, brand-name drugs accounted for only 28.8 percent of all drugs dispensed, with generics leading the way with 71.2 percent of all sales.”).

²⁸ Bartholomew, *supra* note 27.

²⁹ See 21 U.S.C. § 355(e), (k)(1) (2012).

³⁰ 21 C.F.R. § 314.70 (c)(6)(iii)(A), (C) (2018) (“changes being effected” regulation).

³¹ 21 U.S.C. § 355-1 (2012) (Risk Evaluation and Mitigation Strategies). The FDA has released a guidance document for the pharmaceutical industry on required safety-related drug label changes. See U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: SAFETY LABELING CHANGES—IMPLEMENTATION OF SECTION 505(o)(4) OF THE FD&C ACT (2013), available at <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm250783.pdf>.

³² See 21 U.S.C. §§ 351, 352 (2012).

³³ FDA website discussing the post-marketing monitoring function of the Center for Drug Evaluation and Research: “A vital part of CDER’s mission is to monitor the safety and effectiveness of drugs that are currently available to the American people. To meet this goal, FDA has in place post-marketing programs that monitor marketed human medical products for unexpected adverse events. These programs alert the Agency to potential threats to the public health. Agency experts then identify the need for preventive actions, such as changes in product labeling information and, rarely, re-evaluation of an approval decision.” *Surveillance: Post Drug-Approval Activities*, U.S. FOOD & DRUG ADMIN. (Feb. 5, 2018) <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/default.htm>. See also Kip Viscusi & Richard Zeckhauser, *Regulating Ambiguous Risks: The Less than Rational Regulation of Pharmaceuticals*, 44 J. Legal Stud. 387, 409 (2015) (assessing response by FDA to uncertainty of risk; post-marketing surveillance “far from a perfectly rational process;” FDA, like any agency “hesitant to admit to past errors”).

³⁴ See 21 U.S.C.A. § 355(o)(3) (West 2013); GUIDANCE FOR INDUSTRY: POSTMARKETING STUDIES AND CLINICAL TRIALS—IMPLEMENTATION OF SECTION 505(o)(3) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (2011), <http://www.fda.gov/downloads/Drugs/>

information may lead to changes in the required labeling, and occasionally, but rarely, to withdrawal of a drug from the market.³⁵ Brand name manufacturers are permitted to change product labeling unilaterally if information about serious risk is discovered that would warrant additional information for prescribers to enhance public health and safety.³⁶ Generic manufacturers are not required to make label changes upon acquiring post-approval risk information as are their brand name counterparts, but they “should contact [the] FDA [which] will determine whether the labeling for the generic and listed drugs should be revised.”³⁷

At each juncture of expansion in FDA authority, the operation of the tort liability system acted as a complementary oversight mechanism while also compensating those injured as a result of adverse drug side effects. Courts have long been permitted to consider compliance with a statutory or regulatory standard as some evidence of reasonable care, but compliance is not conclusive because those statutory and regulatory standards are typically considered minimum standards of reasonableness.³⁸ Hence, liability for the injuries caused by the pharmaceutical manufacturer’s failure to warn properly or otherwise to market an unreasonably safe product could lead to liability for injuries caused by the pharmaceutical. This treatment of a statutory standard is classic tort law doctrine.³⁹ Federal legislation involving pharmaceuticals has never expressly changed this treatment of common law tort claims.⁴⁰

With the advent of strict products liability in the 1960s, which permitted a claim of liability based on the defective condition of a product without regard to the manufacturer’s unreasonable conduct in creating that condition, many scholars debated whether pharmaceutical products should be treated differently from other products.⁴¹ Professor David Owen summarizes the state of things:

GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf [hereinafter FDA, April 2011 Guidance]; see also Jennifer S. Bard, *Putting Patients First: How the FDA Could Use Its Existing Powers to Reduce Post-Market Adverse Events*, 10 IND. HEALTH L. REV. 495, 510–15 (2013) (explaining post-market information gathering process from drug companies).

³⁵ See Bard, *supra* note 34, at 506.

³⁶ See 21 C.F.R. § 314.70(c)(6)(iii)(A)–(C); see also 21 C.F.R. § 314.105(b)(2018).

³⁷ 21 U.S.C.A. § 355(j); 21 C.F.R. § 314.140(b)(10). For additional explanation, see *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 610 (2011). See also Brumfield, *supra* note 12, at 438–39.

³⁸ OWEN & DAVIS, *supra* note 14, § 14.4.

³⁹ *Id.* § 2.4; see also Mary J. Davis, *The Battle Over Implied Preemption: Products Liability and the FDA*, 48 BOSTON COLLEGE L. REV. 1089, 1090 (2009) (summarizing history of tort law reference to statutory standards).

⁴⁰ *Wyeth v. Levine*, 555 U.S. 555, 577 (2009) (describing federal regulatory scheme for branded pharmaceuticals and relationship to state tort law).

⁴¹ See DAVID G. OWEN, *PRODUCTS LIABILITY LAW* § 18.1 (3d ed. 2014) [hereinafter OWEN, *PRODUCTS LIABILITY LAW*].

The issue is complex, involving the learned intermediary doctrine, product category liability, state of the art, the battle for supremacy between the consumer expectations and risk-utility liability test for design defectiveness, the never-ending struggle between negligence and strict liability, how design and warning defect notions fit together, federal preemption, and, at bottom, whether drugs in fact are sufficiently different from other types of products to be treated differently by products liability law.⁴²

The tension comes from the recognition that many millions of lives have been saved and improved due to advances in pharmaceutical science, but these same powerful chemicals and biologics also cause suffering and death as the inevitable negative side effect results.⁴³ All prescription drugs possess substantial costs as well as benefits because all prescription drugs do inevitable harm to some number of patients while treating the ailments of others for which they are prescribed.⁴⁴ The new drug approval process is inherently incapable of determining all adverse reactions that might result from use of a drug.⁴⁵

The federal regulatory system breaks down, even today when the FDA is one of the most important federal regulatory agencies with one of the most significant budgets.⁴⁶ Yet no one would suggest that pharmaceuticals should not be marketed. The operation of the *ex post* tort system, however, has historically played an important role in discovering the extent of post-approval risks and enforcing the standards set by the regulatory scheme through the requirement to pay damages for losses suffered. Consequently, state products liability doctrines may permit a finding that reasonable care in negligence or non-defectiveness in strict liability requires something more from the manufacturer. That “something more” is usually different labeling and warning information⁴⁷ com-

⁴² *Id.* For a summary of these issues with particular focus on the Restatement (Third) of Torts: Products Liability treatment, see Lars Noah, *This Is Your Products Liability Restatement on Drugs*, 74 BROOK. L. REV. 839, 841–42 (2009).

⁴³ OWEN, PRODUCTS LIABILITY LAW, *supra* note 41, § 18.1.

⁴⁴ *Id.*

⁴⁵ See Bard, *supra* note 34, at 502–05 (“It is, however inevitable that issues will emerge over time as they are used by many more patients and by patients with characteristics different from the subjects on which the drug was tested. Indeed, subjects in drug trials are often far less sick than those patients who will eventually be taking the drug once it is on the market.”). See also Michelle Mello et al., *Ethical Considerations in Studying Drug Safety—The Institute of Medicine Report*, 367 NEW ENGLAND J. MED. 959, 961 (2012); Viscusi & Zeckhauser, *Regulating Ambiguous Risks*, *supra* note 33, at 408–09.

⁴⁶ U.S. DEP’T OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMIN., *FY 2019 FDA Budget Summary* (2019).

⁴⁷ See OWEN, PRODUCTS LIABILITY LAW, *supra* note 41, § 18.1; OWEN & DAVIS, *supra* note 14, § 5.8; RESTATEMENT (THIRD) OF TORTS, *supra* note 6, § 6 (“Failure to warn or instruct

municated to the physician, the learned intermediary, or, where required, directly to the patient-consumer.⁴⁸ As with other warning claims, whether a pharmaceutical warning is adequate is often a fact question for the jury. With pharmaceutical warnings, of course, the status of the federally-approved labeling, as well as the history behind formulation of that labeling, will play an important role in determining inadequacy.⁴⁹

Under § 402A, a prescription product with inadequate packaging, labeling, warnings, or instructions regarding the unreasonable risks of its use may be considered defective even though the risk of harm cannot be alleviated. On its face, § 402A does not differentiate between prescription products and the universe of all other products. But during the drafting of § 402A, concern was raised about application of strict liability to products with knowable but unavoidable risks, particularly pharmaceuticals. In recognition that many prescription products “are quite incapable of being made safe for their intended use,” comment *k* provides that for such products “both the marketing and the use of [the pharmaceutical] are fully justified, notwithstanding the unavoidable high risk which they involve.”⁵⁰ Such a product, comment *k* continues, “properly prepared, and accompanied by proper directions and warnings, is not defective, nor is it unreasonably dangerous.”⁵¹

is the major basis of liability for manufacturers of prescription drugs and medical devices.”); see generally James A. Henderson, Jr. & Aaron D. Twerski, *Drug Design Liability: Farewell to Comment K*, 67 BAYLOR L. REV. 521 (2015).

⁴⁸ OWEN & DAVIS, *supra* note 14, § 8.5 n.8.

⁴⁹ *Id.* See also *Wyeth*, 555 U.S., at 577–82.

⁵⁰ Comment *k* provides in its entirety:

k. Unavoidably Unsafe Products. There are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of drugs. An outstanding example is the vaccine for the Pasteur treatment of rabies, which not uncommonly leads to very serious and damaging consequences when it is injected. Since the disease itself invariably leads to a dreadful death, both the marketing and the use of the vaccine are fully justified, notwithstanding the unavoidable high degree of risk which they involve. Such a product, properly prepared, and accompanied by proper directions and warning, is not defective, nor is it unreasonably dangerous. The same is true of many other drugs, vaccines, and the like, many of which for this very reason cannot legally be sold except to physicians, or under the prescription of a physician. It is also true in particular of many new or experimental drugs as to which, because of lack of time and opportunity for sufficient medical experience, there can be no assurance of safety, or perhaps even of purity of ingredients, but such experience as there is justifies the marketing and use of the drug notwithstanding a medically recognizable risk. *The seller of such products, again with the qualification that they are properly prepared and marketed, and proper warning is given, where the situation calls for it, is not to be held to strict liability for unfortunate consequences attending their use, merely because he has undertaken to supply the public with an apparently useful and desirable product, attended with a known but apparently reasonable risk.*

RESTATEMENT (SECOND) OF TORTS § 402A cmt. k (AM. LAW INST. 1965) (emphasis added).

⁵¹ *Id.*

Debate over the meaning of comment *k* began immediately and continued for the next four decades.⁵² The confusion from comment *k* led to a variety of jurisdictional approaches to pharmaceutical liability. Virtual blanket immunity from liability for pharmaceutical design is one response, influential, in part, due to its support by California courts.⁵³ An important reason why the majority of courts, as well as most commentators, reject a strict liability standard is the perceived socially detrimental effect of inhibiting the contributions to public health made by pharmaceutical manufacturers.⁵⁴ Cases involving vaccines, which are specifically mentioned in comment *k*, were the early adopters of the comment's protections for this very reason.⁵⁵

Most jurisdictions have determined that the protections of comment *k* are only available after the court assesses, on a case-by-case basis, whether the product's benefits exceeded its risks and that it was incapable of being made safer.⁵⁶ Further, the warning on such products must be adequate, leaving the bulk of pharmaceutical liability to failure-to-warn theories. Jurisdictions that have rejected comment *k* have used alternative tests of defectiveness such as consumer expectations or an "ordinary physician" standard, which characterizes the physician as a "learned in-

⁵² See, e.g., George W. Conk, *Is There a Design Defect in the Restatement (Third) of Torts Products Liability?*, 109 YALE L.J. 1087, 1091–94 (2000); Henderson & Twerski, *supra* note 47; Joseph A. Page, *Generic Product Risks: The Case Against Comment K and for Strict Tort Liability*, 58 N.Y.U. L. REV. 853, 862–72 (1983); see generally OWEN & DAVIS, *supra* note 14, § 8.5.

⁵³ *Brown v. Superior Court*, 751 P.2d 470, 475 (Cal. 1988) (adopting presumption from comment *k* that drug designs are not subject to liability). The comment *k* presumption of non-defectiveness, according to *Brown*, obviates a case-by-case analysis of either the public health benefit or the therapeutic attributes of each ethical drug. *Id.* at 470. See also *Kearl v. Lederle Laboratories*, 218 Cal. Rptr. 452, 458–60 (Cal. Ct. App. 1985) (regarding polio vaccines; strict liability standard, arguably suited to the "vast majority of products cases," "might not be appropriate with regard to some special products that are extremely beneficial to society and yet pose an inherent and substantial risk that is unavoidable at the time of distribution."); *Feldman v. Lederle Laboratories*, 479 A.2d 374 (N.J. 1984); OWEN & DAVIS, *supra* note 14, § 8.5.

⁵⁴ See OWEN, PRODUCTS LIABILITY LAW, *supra* note 41, at 477–83 (1st ed., 2005) (discussing cases from 30 states and the District of Columbia that endorse comment *k*); see, e.g., *Woodhill v. Parke Davis & Co.*, 402 N.E.2d 194, 198–99 (Ill. 1980); *Seley v. G. D. Searle & Co.*, 423 N.E.2d 831, 836 (Ohio 1981); *Ortho Pharm. Corp. v. Chapman*, 388 N.E.2d 541, 545–46 (Ind. Ct. App. 1979).

⁵⁵ See generally *White v. Wyeth Laboratories, Inc.*, 533 N.E.2d 748 (Ohio 1988).

⁵⁶ See *Toner v. Lederle Labs.*, 732 P.2d 297, 306–10 (Idaho 1987); *Glassman v. Wyeth Labs., Inc.*, 606 N.E.2d 338, 342 (Ill. 1992); *Bennett v. Madakasira*, 821 So.2d 794, 809 (Miss. 2002); *Freeman v. Hoffman-La Roche, Inc.*, 618 N.W.2d 827, 840 (Neb. 2000); *Feldman v. Lederle Labs.*, 479 A.2d 374, 382–83 (N.J. 1984); *Brochu v. Ortho Pharm. Corp.*, 642 F.2d 652, 655 (1st Cir. 1981) (applying N.H. law); *Weiss v. Fujisawa Pharm. Co.*, No. 5:05-527-JMH, 2006 WL 3533072 (E.D. Ky. 2006); see also L. Frumer & M. Friedman, *Products Liability* §§ 8.07[5] (Supp. 2012).

termediary” between patient and pharmaceutical company.⁵⁷ The “ordinary physician” standard is a consequence of the manner in which pharmaceuticals reach patients: through a learned intermediary who is responsible for making the prescribing choice.⁵⁸ The role of such health care professionals is to ensure that the right drugs are prescribed for the right purpose in the right doses to the right patient. Consequently, pharmaceutical labeling is usually directed toward these learned intermediaries.

After three decades of § 402A and comment *k*, the Reporters for the American Law Institute’s Products Liability Restatement crafted a new approach to pharmaceutical liability doctrine.⁵⁹ Products Liability Restatement §§ 6(d)(1) & (2) separate pharmaceutical seller *warning* obligations into two settings: (1) the prescription of a drug or medical device chosen and prescribed pursuant to conventional means, which is to say, the orthodox health care provider-patient relationship; and (2) other circumstances in which the manufacturer knows or has reason to know that the health care provider may not be in a position “to reduce the risks of harm [to the patient] in accordance with the instructions or warnings.”⁶⁰ In the former situation, the Products Liability Restatement preserves the “learned intermediary” rule that permits the seller to discharge its warning duties by providing adequate warnings or instructions to the appropriate health care intermediaries. The exception to the learned intermediary rule recognized in subsection (2) has been associated with mass immunizations and certain limited physician-patient contact scenarios, such as prescriptions for birth control medicines, which may trigger a manufacturer’s obligation to provide warnings and instructional information directly to the patient.⁶¹

Section 6(c) breaks new ground in the *design* defect liability area by recognizing a limited avenue for challenging a pharmaceutical’s design.⁶² It provides near blanket immunity for pharmaceutical design features and has been strongly criticized.⁶³ A claim of manufacturer liability

⁵⁷ See, e.g., *Shanks v. Upjohn Co.*, 835 P.2d 1189, 1194 (Alaska 1992); *Allison v. Merck & Co.*, 878 P.2d 948, 954 (Nev. 1994); *Collins v. Eli Lilly Co.*, 342 N.W.2d 37, 52 (Wis. 1984).

⁵⁸ *Shanks v. Upjohn Co.*, 835 P.2d 1189, 1195 (Alaska 1992).

⁵⁹ RESTATEMENT (THIRD) OF TORTS, *supra* note 6, § 6.

⁶⁰ *Id.*

⁶¹ *Davis v. Wyeth Laboratories, Inc.*, 399 F. 2d 121, 131 (9th Cir. 1968).

⁶² RESTATEMENT (THIRD) OF TORTS, *supra* note 6, § 6(c) (“A prescription drug or medical device is not reasonably safe due to defective design if the foreseeable risks of harm posed by the drug or medical device are sufficiently great in relation to its foreseeable therapeutic benefits that reasonable health-care providers, knowing such foreseeable risks and therapeutic benefits, would not prescribe the drug or medical device for any class of patients.”).

⁶³ See generally George Conk, *The True Test: Alternative Safer Designs for Drugs and Medical Devices in a Patent-Constrained Market*, 49 UCLA L. REV. 737 (2002); see also Lars

arising from the design or formulation of a prescription drug will prevail only upon a showing that the product would be unduly dangerous for any class of patients, or specifically, when “reasonable health care providers, knowing of . . . foreseeable risks and therapeutic benefits, would not prescribe the drug or medical device for any class of patients.”⁶⁴ Most courts have rejected this test.⁶⁵ The narrow window that § 6(c) leaves open for a viable design defect claim leaves courts uneasy, as does the blanket exception for most pharmaceutical design challenges.⁶⁶

Design defectiveness has never been a favored theory of recovery for drug injuries.⁶⁷ A design defect claim in strict liability would fit awkwardly with the traditional tests of defectiveness: consumer expectations and risk-utility. The consumer expectations test would seem inapposite because, although the consumer is the patient, the consumer knows virtually nothing about the risks of harm in the prescriptions chosen for her.⁶⁸ Almost every jurisdiction shields a manufacturer from liability for unforeseeable dangers under the prevailing “state of the art” doctrine, so a patient injured by a truly unforeseeable drug risk in most jurisdictions would have no expectation of safety.⁶⁹ Yet, every patient has an expecta-

Noah, *supra* note 42, at 839. *See generally* OWEN, PRODUCTS LIABILITY LAW, *supra* note 41, § 8.10.

⁶⁴ RESTATEMENT (THIRD) OF TORTS, *supra* note 6, § 6.

⁶⁵ *Freeman*, 618 N.W.2d, at 839–40 (After noting that no precedent existed for the “reasonable physician test” for judging design defect claims, the Nebraska Supreme Court offered several reasons that militated against it. It is difficult to apply and premised on a misapprehension of what influences prescribing decisions; unjustifiably protects less essential drugs, including “cosmetic” or lifestyle drugs; and would deny plaintiffs recovery even in cases where a reasonable alternative design existed). *See also* *Bryant v. Hoffmann-La Roche, Inc.*, 585 S.E.2d 723, 727 (Ga. Ct. App. 2003) (rejecting § 6 and adopting § 402A, comment *k*); *In re Fosamax Products Liability Litig.*, 742 F. Supp. 2d 460, 471–72 (S.D.N.Y. 2010) (applying Florida law which applies § 402A and declines to adopt § 6). A few cases have endorsed § 6. *Gebhardt v. Mentor Corp.*, 191 F.R.D. 180, 185 (D. Ariz. 1999); *Madsen v. American Home Prods. Corp.*, 477 F. Supp. 2d 1025, 1037 (E.D. Mo. 2007) (applying Iowa law). On the debate about § 6, *see* Noah, *supra* note 42, at 840; James A. Henderson Jr. & Aaron Twerski, *Drug Designs are Different*, 111 YALE L.J. 151 (2001); Anita Bernstein, *Enhancing Drug Effectiveness and Efficacy through Personal Injury Litigation*, 15 J.L. & POL’Y 1051 (2007); and *Conk*, *supra* note 63. *See generally* OWEN, PRODUCTS LIABILITY LAW, *supra* note 41, § 8.10.

⁶⁶ *Freeman*, 618 N.W.2d (rejecting Products Liability Restatement blanket exception to design defect liability approach in favor of § 402A comment *k* affirmative defense).

⁶⁷ OWEN, PRODUCTS LIABILITY LAW, *supra* note 41, § 8.10.

⁶⁸ A few jurisdictions permit a consumer expectations test. *See Allison v. Merck and Co.*, 878 P.2d 948, 956 (rejecting comment *k* for consumer expectations or product malfunction theory); *see also* *Castrignano v. E.R. Squibb & Sons, Inc.*, 546 A.2d 775, 782 (R.I. 1988) (treating comment *k* as an affirmative defense that allows manufacturers to respond to consumer expectations based design defect claim with risk-utility balancing).

⁶⁹ David G. Owen, *Dangers in Prescription Drugs: Filling a Private Law Gap in the Healthcare Debate*, 43 CONN. L. REV. 733, 747 (2010).

tion of safety from pharmaceuticals taken for therapeutic effect. No one expects to be the patient on whom the risk of side effects falls.⁷⁰

Under a risk-utility test for design defectiveness, in either negligence or strict liability, a manufacturer is subject to liability for failing to adopt a particular design feature that would have prevented the plaintiff's injuries if the alternative's safety features were greater than its risks.⁷¹ Because a pharmaceutical generally has no alternative design—if it did, it would be a different pharmaceutical product—many jurisdictions resort to a design defect analysis that requires assessment of whether a pharmaceutical's inherent risks outweigh its utility, a decision arguably made by the FDA when the drug was approved for marketing. Commentators and some courts express concern regarding a jury's ability to decide that a pharmaceutical, approved by an expert federal regulatory agency, is either defective in design or fails to have an adequate warning.⁷²

Products liability theory for pharmaceuticals is complex because of the role of the federal regulatory process and the wide variety of tests jurisdictions use to assess both design and warning claims. This is not different from many other types of products, but the intensity of the regulatory approval process certainly plays a much more central role. Further, the inherent dangers in pharmaceuticals are not traditional defects; they are fundamental elements of the product that make it what it is, and give it both its' therapeutic effect and the potential for serious harm that cannot be prevented, regardless of the warning given to prescribers, or some change in design, which will carry its own risk of side effects. What is very different from other products liability contexts, however, is the dramatic impact on state tort liability from modern federal preemption doctrine in the area.

II. FEDERAL PREEMPTION OF STATE LAW PRODUCTS LIABILITY CLAIMS IN PHARMACEUTICAL LITIGATION

Federal law can preempt the operation of state law, under the Supremacy Clause of the United States Constitution, when congressional

⁷⁰ For a discussion of risk aversion and risk ambiguity in decision-making, see Viscusi & Zeckhauser, *supra* note 33, at 410.

⁷¹ *Doe v. Solvay Pharm., Inc.*, 350 F. Supp. 2d 257, 266 (D. Me. 2004); *Savina v. Sterling Drug, Inc.*, 795 P.2d 915, 924 (Kan. 1990); *Brochu v. Ortho Pharm., Corp.*, 642 F.2d 652, 655 (1st Cir. 1981) (applying N.H. law); *Bryant v. Hoffmann-La Roche, Inc.*, 585 S.E.2d 723, 729 (Ga. Ct. App. 2003) (discussing strict liability and negligent design defect are independent of FDA minimum standards; state law may impose a higher obligation of care upon a drug manufacturer).

⁷² See, e.g., James R. Copland, *Administrative Compensation for Pharmaceutical and Vaccine Related Injuries*, 8 IND. HEALTH L. REV. 275, 283–84 (2011); Owen, *Dangers in Prescription Drug*, *supra* note 69, at 773–74; *Wyeth v. Levine*, 555 U.S. 555, 574 (2009) (Alito, J. dissenting).

intent to preempt is found in federal legislation.⁷³ That intent may be expressed within the text of legislation or implied because of a conflict between the operation of state and federal law.⁷⁴ The Federal Food Drug and Cosmetic Act does *not* contain an express preemption provision.⁷⁵ Preemption of state law relating to pharmaceuticals is, therefore, based on doctrines of implied preemption. The broadest possible scope of implied preemption, that the federal regulatory scheme entirely occupies the field even though Congress did not expressly indicate such scope, has been rejected for the field of pharmaceutical regulation.⁷⁶

Because of the traditional complementary operation of state tort law alongside the regulatory scheme, state tort laws were not considered preempted by federal regulation or administrative action, particularly because congressional intent to preempt a traditional area of state law governing public health and safety was never expressed.⁷⁷ That is, state laws were not considered subject to implied preemption in the area of pharmaceutical regulation until 2009. Until then, the presumption against preemption of traditionally operating state law was in full force.⁷⁸

Since 2009, the Supreme Court has decided four cases which govern preemption under the FDCA for prescription pharmaceuticals: *Wyeth v. Levine*,⁷⁹ governing implied preemption for failure to warn claims involving brand name pharmaceutical manufacturers; *Bruesewitz v. Wyeth LLC*,⁸⁰ involving express preemption under the National Childhood Vaccine Injury Compensation Act for vaccine-related injuries; *PLIVA, Inc. v. Mensing*,⁸¹ involving implied preemption for failure to warn claims involving generic pharmaceuticals; and *Mutual Pharmaceutical Co., Inc. v. Bartlett*,⁸² involving implied preemption of design defect claims in generic pharmaceutical cases. In only one of these cases, *Wyeth v. Levine*, did the Court find state law *not* preempted, but even in *Wyeth*, the Court

⁷³ *Wyeth v. Levine*, 555 U.S. 555, 565 (2009). See generally OWEN & DAVIS, *supra* note 14, § 15.1.

⁷⁴ *Wyeth*, 555 U.S. at 576.

⁷⁵ *Id.* at 567; see also *Merrell Dow Pharm., Inc. v. Oxendine*, 649 A.2d 825 (D.C. 1994).

⁷⁶ See, e.g., *Reese v. Payless Drug Stores Northwest, Inc.*, 900 P.2d 600 (Cal. 1995); *MacDonald v. Ortho Pharm. Corp.*, 475 N.E.2d 65 (Mass. 1985). see also, Richard C. Ausness, *Federal Preemption of State Products Liability Doctrines*, 44 S.C. L. REV. 187, 219 (1993) (“[t]he regulatory history of the FDA requirements belies any objective to cloak them with preemptive effect”). Some scholars prefer it as a theory of preemption. See, e.g., Richard A. Epstein, *The Case for Field Preemption of State Law in Drug Cases*, 103 NW. UNIV. L. REV. 463 (2009).

⁷⁷ See Ausness, *supra* note 76, at 251.

⁷⁸ See Davis, *supra* note 39, at 1118–19.

⁷⁹ *Wyeth v. Levine*, 555 U.S. 555, 575–76 (2009).

⁸⁰ See generally *Bruesewitz v. Wyeth, LLC*, 562 U.S. 223 (2011).

⁸¹ See generally *PLIVA Inc., v. Mensing*, 564 U.S. 604 (2011).

⁸² See generally *Mutual Pharm. Co. v. Bartlett*, 570 U.S. 472 (2013).

opened the door for such preemption to operate in a way that had not previously been available.⁸³

In brief, the Supreme Court has held that failure-to-warn claims against brand name pharmaceutical manufacturers generally are *not* to be preempted because the regulatory framework permits those manufacturers to unilaterally change product labeling upon acquiring “reasonable evidence of an association of a serious hazard with a drug.”⁸⁴ The Court left open whether, given “clear evidence” of specific FDA action prohibiting a label change, preemption based on an impossible conflict with federal regulations may be available to brand name manufacturers as well.⁸⁵ Regarding generic pharmaceuticals, which comprise over 80% of the pharmaceuticals prescribed in this country,⁸⁶ the Supreme Court has concluded that failure-to-warn claims against generic pharmaceutical manufacturers are impliedly preempted because the manufacturer is obligated to have the same label as the brand name manufacturer and is not permitted to change it unilaterally without FDA approval.⁸⁷ In addition, the Supreme Court has concluded that design defect claims against generic drug manufacturers are impliedly preempted when the state law basis for such claims would require a challenge to the design formulation or to the warning label because generic drug manufacturers are not permitted to change the chemical formulation or label of a drug without FDA permission.⁸⁸ The Supreme Court has not directly addressed whether design defect claims against brand name manufacturers are im-

⁸³ See *Wyeth*, 555 U.S. at 555–57. The Supreme Court, in the 2018–19 term, will address this avenue for implied preemption regarding brand-name pharmaceutical failure-to-warn claims in *Merck, Sharp & Dohme Corp. v. Albrecht*, 138 S.Ct. 2705 (2018), certiorari pet. granted in *In re. Fosamax Prods. Liab. Litig.*, 852 F.3d 268 (3d. Cir. 2017).

⁸⁴ See *Wyeth*, 555 U.S. at 571. See also 21 C.F.R. § 201.80(e) (2015); Food and Drug Admin., 73 Fed. Reg. 49603, 49605 (Aug. 22, 2008) (“Manufacturers continue to have a responsibility under Federal law . . . to maintain their labeling and update the labeling with new safety information”).

⁸⁵ See generally *Wyeth*, 555 U.S. at 570. See also *Dolin v. GlaxoSmithKline L.L.C.*, 901 F.3d 803, 812 (7th Cir. 2018) (citing that clear evidence of FDA action prohibiting label change supports impossibility conflict preemption). This avenue for implied preemption, and an assessment of what constitutes “clear evidence,” are now before the Supreme Court. See *Merck, Sharp & Dohme Corp. v. Albrecht*, 138 S. Ct. 2705 (2018).

⁸⁶ In 2016, 84.6% of pharmaceuticals prescribed in the United States were generic. STATISTA, Proportion of Branded versus Generic Drug Prescriptions Dispensed in the United States from 2005 to 2016, <https://www.statista.com/statistics/205042/proportion-of-brand-to-generic-prescriptions-dispensed/> (percentage of generic prescriptions filled increased from 50% in 2005 to 84.6% in 2016).

⁸⁷ See *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 614 (2011).

⁸⁸ See *Mutual Pharm. Co. v. Bartlett*, 570 U.S. 472, 477 (2013). The Court did not address state design defect claims that parallel the federal misbranding statute. *Id.* at 487, n.4 (“The misbranding statute requires a manufacturer to pull even an FDA-approved drug from the market when it is ‘dangerous to health’ even if ‘used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof.’”); 21 C.F.R. § 314.70(b)(2)(i) (2016); 21 U.S.C.A. § 379d–4(a) (2012).

pliedly preempted,⁸⁹ but some observers consider that claim also preempted.⁹⁰

The Supreme Court had long held that where Congress has not expressly preempted state tort law claims, there exists a strong presumption against implied preemption when the area involved has traditionally been left to the states to regulate, as in the case of public health and safety.⁹¹ In the case of state common law actions against pharmaceutical product manufacturers, federal preemption had rarely been found, in large part because of the longstanding role of state tort law in enforcing standards of due care and because the FDA has historically considered its drug labeling regulations to set minimum standards.⁹² That traditional approach has changed dramatically.⁹³ The following discussion explains the pharmaceutical preemption cases to illustrate what little remains of state tort law.

A. *Implied Impossibility and Obstacle Preemption under the FDCA*

The Court's landmark opinion in *Wyeth v. Levine*, involved a plaintiff seriously injured by the use of the anti-nausea drug Phenergan, manufactured by Wyeth Pharmaceuticals, which was administered to her while she was in the emergency room.⁹⁴ Plaintiff claimed that the defendant inadequately warned medical care providers of the risk of developing gangrene from the IV-push method of administering the drug used on plaintiff. The plaintiff alleged that the FDA-approved labeling was inadequate and that the defendant had an obligation to seek an improved warning from the FDA when it acquired additional information of the seriousness of the risk.⁹⁵ Defendant responded that the FDA had ordered it to use the warning language in question, and thus it would be impossible for it to satisfy both the state law warning obligation proposed by plaintiff and the FDA's command.⁹⁶ In addition, the defendant argued

⁸⁹ See generally *Mutual Pharm. Co.*, 570 U.S. at 472–73.

⁹⁰ See Aaron D. Twerski, *The Demise of Drug Design Litigation: Death by Federal Preemption*, 68 AM. U. L. REV. 281, 281 (2018).

⁹¹ See, e.g., *Hillsborough Cty. v. Automated Med. Labs, Inc.*, 471 U.S. 707, 715, 718 (1985) (citing a presumption against preemption endorsed. No occupation of the field preemption by FDA regulations. “We will seldom infer, solely from the comprehensiveness of federal regulations, an intent to preempt in its entirety a field related to health and safety.”). See also *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996) (noting a presumption against preemption consistent with federalism concerns and historic primacy of state regulation of matters of health and safety). See Davis, *supra* note 39, at 1141–44.

⁹² See *Caraker v. Sandoz Pharm. Corp.*, 172 F. Supp. 2d 1018, 1038–39 (S. D. Ill. 2001); *Merrell Dow Pharm. Inc., v. Oxendine*, 649 A.2d 825, 828 (D.C. 1994).

⁹³ See OWEN, PRODUCTS LIABILITY LAW, *supra* note 41, § 14.4 (3d ed. 2015). See generally Davis, *supra* note 39.

⁹⁴ *Wyeth v. Levine*, 555 U.S. 555, 555–57 (2009).

⁹⁵ See *id.* at 558–59.

⁹⁶ See *id.* at 560–61.

that the FDA's regulatory scheme and its authority over pharmaceutical labeling would be frustrated by a state common law tort claim that would substitute a lay jury's verdict about drug labeling for the expert judgment of the FDA.⁹⁷ The jury found for the plaintiff and the Vermont Supreme Court affirmed.⁹⁸

The United States Supreme Court reiterated that "the purpose of Congress" is the ultimate touchstone of preemption jurisprudence, and that the historic police powers of the States were not to be superseded by a federal act absent "clear and manifest" evidence of that purpose.⁹⁹ Throughout the history of the FDCA, Congress took care to preserve state law.¹⁰⁰ The Court noted "through many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market."¹⁰¹ Indeed, the FDA did not have the authority to require a manufacturer to change a drug label based on after-market acquired safety information until Congress amended the Act in 2007.¹⁰²

The Court found that neither implied impossibility conflict preemption nor implied obstacle conflict preemption were supported by the evidence.¹⁰³ The Court paved the way for future challenges based on impossibility preemption, however, by noting that if Wyeth had produced evidence that the FDA would have rejected a label change, that might have made it impossible for Wyeth to comply with both federal regulations and a state common law verdict requiring a different label.¹⁰⁴ Even though the Court stated that impossibility preemption is "a demanding defense,"¹⁰⁵ and it had not before found impossibility preemption established under the FDCA,¹⁰⁶ it created a roadmap for brand manufacturers to establish impossibility preemption that has become the new battleground in preemption.¹⁰⁷ The Court may have recognized the

⁹⁷ See *id.* at 563–64.

⁹⁸ *Id.* at 562.

⁹⁹ See *id.* at 565.

¹⁰⁰ *Id.* at 567; see also *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 333 (Ginsburg, J., dissenting) (discussing the history of FDCA pharmaceutical regulation and the complementary treatment of state tort litigation).

¹⁰¹ *Wyeth*, 555 U.S. at 570–71.

¹⁰² *Id.* at 571.

¹⁰³ See *id.* at 572.

¹⁰⁴ See *id.* at 571 ("absent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements.").

¹⁰⁵ *Id.* at 572.

¹⁰⁶ See, e.g., *Hillsborough Cty. v. Automated Med. Labs., Inc.*, 471 U.S. 707, 707 (1985).

¹⁰⁷ See *Merck Sharp & Dohme Corp. v. Albrecht*, 138 S. Ct. 2705 (2018), *cert. granted*, 86 U.S.L.W. 3647 (June 28, 2018) (No. 17-290) (granting petition for *In Re Fosamax* from the

“central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times,”¹⁰⁸ but it nevertheless created an opportunity to use impossibility preemption in a way that had not been considered viable before.

Once the Court rejected the impossibility conflict preemption argument, it was an easy step to conclude that the defendant had not established implied obstacle preemption. Wyeth contended that the FDA regulations establish both a floor and a ceiling for drug labeling regulation.¹⁰⁹ The Court disagreed: “The most glaring problem with this argument is that all evidence of Congress’ purposes is to the contrary Congress did not provide a federal remedy for consumers harmed by unsafe or ineffective drugs in the 1938 statute or in any subsequent amendment. Evidently, it determined that widely available state rights of action provided appropriate relief for injured consumers. It may also have recognized that state-law remedies further consumer protection by motivating manufacturers to produce safe and effective drugs and to give adequate warnings.”¹¹⁰ After *Wyeth*, the primary avenue for implied preemption is based on impossibility.¹¹¹

B. *Implied Preemption for Generic Pharmaceuticals*

After *Wyeth v. Levine*, the issue of implied preemption when generic pharmaceuticals were involved came to the fore. Manufacturers argued that, based on a different FDA approval and regulatory framework, they were prohibited from unilaterally changing the labels on their drugs because federal law prohibited it and, thus, *Wyeth* did not control the implied preemption analysis. *PLIVA, Inc. v. Mensing*¹¹² brought this issue to the Supreme Court. The Court agreed with the manufacturers and held that the plaintiff’s failure-to-warn claims involving generic

Third Circuit); *Dolin v. GlaxoSmithKline L.L.C.*, 901 F.3d 803, 812 (7th Cir. 2018) (finding impossibility preemption on clear evidence of FDA refusal to permit a labeling change).

¹⁰⁸ *Wyeth*, 555 U.S. at 555–58.

¹⁰⁹ *Id.* at 573.

¹¹⁰ *See id.* at 572–76 (“If Congress thought state-law suits posed an obstacle to its objectives, it surely would have enacted an express pre-emption provision at some point during the FDCA’s 70-year history. Its silence on the issue, coupled with its certain awareness of the prevalence of state tort litigation, is powerful evidence that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness.”).

¹¹¹ *See, e.g., Lefair v. KV Pharm. Co.*, 636 F.3d 935, 939 (8th Cir. 2011); *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 390 (7th Cir. 2010); *Wimbush v. Wyeth*, 619 F.3d 632, 643 (6th Cir. 2010) (applying Ohio law); *Dorsett v. Sandoz Inc.*, 699 F. Supp. 2d 1142, 1155 (C.D. Cal. 2010). For a discussion of pharmaceutical litigation post-*Wyeth*, see Richard C. Ausness, *The Impact of Wyeth v. Levine on FDA Regulation of Prescription Drugs*, 65 FOOD & DRUG L. J. 247, 265 (2010).

¹¹² *PLIVA, Inc. v. Mensing*, 546 U.S. 604 (2011).

pharmaceuticals were preempted under principles of implied impossibility conflict.¹¹³

In spite of having defined impossibility preemption as “a demanding defense,” the Court applied the doctrine expansively in *Mensing*.¹¹⁴ It was persuaded by several important differences in the two cases. First, the generic drug regulatory scheme prohibits generic manufacturers from using labeling that is not identical to the brand name equivalent. Previously, the FDA had taken the position that generic manufacturers, unlike brand name manufacturers, were not permitted to change drug labels unilaterally based on evidence of increased risk.¹¹⁵ Plaintiffs, and the FDA in the litigation, asserted that manufacturers had a different avenue for changing generic drug labels such that it was not impossible to adequately satisfy both federal regulatory requirements and the state law tort duties to warn.¹¹⁶ According to the FDA, manufacturers could have proposed—indeed were required to propose—stronger warning labels to the agency if they believed such warnings were needed. This obligation harkened back to *Wyeth’s* recognition that drug manufacturers bear the ultimate responsibility for the content of their drug labels at all times.¹¹⁷

The Court stated that this “possibility” of complying with both federal and state law did not defeat a finding of impossibility conflict.¹¹⁸ The Court found that the federal duty to seek a labeling change from the FDA would not have satisfied the state law duty to warn, and, the manufacturers were not required to prove that they would have been prohibited from making a labeling change if they had asked the FDA for permission to do so in order to establish impossibility preemption.¹¹⁹ The Court explained:

This raises the novel question whether conflict pre-emption should take into account these possible actions by the FDA and the brand-name manufacturer. Here, what federal law permitted the Manufacturers to do could have changed, even absent a change in the law itself, depending on the actions of the FDA and the brand-name manufacturer. Federal law does not dictate the text of each generic drug’s label, but rather ties those labels to their brand-name counterparts. Thus, federal law would permit the Manufacturers to comply with the state

¹¹³ *Id.* at 604–08.

¹¹⁴ *Id.* at 626–27.

¹¹⁵ *Id.* at 614.

¹¹⁶ *Id.* at 615–16.

¹¹⁷ *Id.*

¹¹⁸ *Id.* at 619–23.

¹¹⁹ *Id.* at 619.

labeling requirements if, and only if, the FDA and the brand-name manufacturer changed the brand-name label to do so.¹²⁰

The plaintiffs argued that the manufacturers could not establish impossibility preemption because they did not even start the process for seeking a label change.¹²¹ The Court disagreed: “The question for ‘impossibility’ is whether the private party could independently do under federal law what state law requires of it . . . [a]ccepting [Plaintiffs’] argument would render conflict pre-emption largely meaningless because it would make most conflicts between state and federal law illusory.”¹²² The Court thus found that impossibility conflict preemption had been established: “To decide these cases, it is enough to hold that when a party cannot satisfy its state duties without the Federal Government’s special permission and assistance, which is dependent on the exercise of judgment by a federal agency, that party cannot independently satisfy those state duties for pre-emption purposes.”¹²³

After *Mensing*, courts split on whether all claims against generic drug manufacturers were preempted.¹²⁴ The Supreme Court resolved this question in favor of preemption in *Mutual Pharmaceutical Co. v. Bartlett*.¹²⁵ Karen Bartlett was prescribed Clinoril, a non-steroidal anti-inflammatory (“NSAID”) for shoulder pain. Her pharmacist filled the prescription with a generic, “sulindac,” manufactured by Mutual Pharmaceutical. She soon developed an acute case of toxic epidermal necrolysis, which caused 65% of her body surface to deteriorate, burn off, or turn into an open wound. This side effect occurred in a small number of patients and was not described on the labeling when Bartlett was prescribed the drug but was subsequently required by the FDA.¹²⁶

Bartlett sued Mutual Pharmaceutical asserting both failure-to-warn and design defect claims. The failure-to-warn claim was dismissed—her physician admitted not reading the warning that was given, so causation could not be established.¹²⁷ A jury awarded her \$21 million based on the design defect claim. The First Circuit affirmed, concluding that the design defect claims were not preempted under *Mensing* because “the ge-

¹²⁰ *Id.* at 620.

¹²¹ *Id.*

¹²² *Id.*

¹²³ *Id.* at 623–24.

¹²⁴ *Demahy v. Shwarz Pharma, Inc.*, 702 F.3d 177, 186 (5th Cir. 2012).

¹²⁵ *Mutual Pharmaceutical Co., Inc. v. Bartlett*, 570 U.S. 472 (2013).

¹²⁶ *Id.* at 472–77.

¹²⁷ *Bartlett v. Mutual Pharmaceutical Company, Inc.*, 760 F. Supp. 2d 220, 229 (D. N.H. 2011).

neric maker can avoid . . . design defect lawsuits by not making the drug.”¹²⁸

Bartlett argued that the design defect cause of action in New Hampshire was compensatory, not regulatory, and did not impose affirmative duties on the defendant, and thus it was possible for the defendant to comply with both federal and state law.¹²⁹ The Court disagreed, finding that New Hampshire law is not an “absolute liability” regime, but a “strict liability” regime, which “signals the breach of a duty.”¹³⁰

Because it was impossible to re-design the drug, the Court found the plaintiff’s design defect claim essentially to be a failure-to-warn claim in disguise, and thus preempted because it was impossible to comply with both federal and state law under *Mensing*.¹³¹ The Court preserved the possibility of some design defect claims when it specifically excluded from its holding “design defect claims that parallel the federal misbranding statute.”¹³² Such claims are surely rare, because a generic that complies with the labeling for the branded pharmaceutical cannot be misbranded.

The Court also rejected the First Circuit’s rationale that Mutual Pharmaceutical could choose not to make sulindac at all, finding “this ‘stop-selling’ rationale as incompatible with . . . pre-emption jurisprudence.”¹³³ The Court explained, “[o]ur pre-emption cases presume that an actor seeking to satisfy both his federal- and state-law obligations is not required to cease acting altogether in order to avoid liability. Indeed, if the option of ceasing to act defeated a claim of possibility, impossibility pre-emption would be ‘all but meaningless.’”¹³⁴ Continuing, the

¹²⁸ *Bartlett*, 678 F.3d 30, at 38 (1st Cir. 2012).

¹²⁹ 570 U.S. 472 at 480.

¹³⁰ *Id.* at 481. The Court importantly noted: “We can thus save for another day the question whether a true absolute-liability state-law system could give rise to impossibility pre-emption. As we have noted, most common-law causes of action for negligence and strict liability do not exist merely to spread risk, but rather impose affirmative duties.” *Id.* at 518 n.1. The Court also failed to understand the nature of strict, non-fault liability, which does not “signal a breach of a duty.” *Id.* at 481. *See generally* Brief of Torts Professors as Amici Curiae Supporting Respondents, 570 U.S. 472; *see also* Henderson & Twerski, *supra* note 47.

Justice Sotomayor, dissenting, explained that compensation for harm done under a strict, non-fault, basis of liability, is entirely consistent with “the limitations of *ex ante* regulatory review in this context. On its own, even rigorous preapproval clinical testing of drugs is ‘generally . . . incapable of detecting adverse effects that occur infrequently, have long latency periods, or affect sub-populations not included or adequately represented in the studies . . .’ [m]oreover, the FDA, which is tasked with monitoring thousands of drugs on the market and considering new drug applications, faces significant resource constraints that limit its ability to protect the public from dangerous drugs.” *Mutual Pharm.*, 570 U.S. at 500 (Sotomayor, J., dissenting).

¹³¹ *Id.* at 486–97.

¹³² *Id.* at 518 n.4.

¹³³ *Id.* at 488.

¹³⁴ *Id.*

Court firmly rejected the “stop-selling” rationale for future cases by commenting that adopting that rationale would mean that “the vast majority—if not all—of the cases in which the Court has found impossibility pre-emption, were wrongly decided. Just as the prospect that a regulated actor could avoid liability under both state and federal law by simply leaving the market did not undermine the impossibility analysis in *PLIVA*, so it is irrelevant to our analysis here.”¹³⁵

Whether state law design defect claims for pharmaceuticals will “always create an automatic conflict between . . . federal premarket review requirements,”¹³⁶ is the arguable end-game of federal preemption doctrine as it applies to pharmaceuticals.¹³⁷

C. *Express Preemption under the FDCA*

Congress has expressly preempted state law on very few occasions in the FDCA.¹³⁸ In 1986, Congress enacted the National Childhood Vaccine Injury Act and created a no-fault compensation program to both stabilize the vaccine market which had been adversely affected by an increase in vaccine-related tort litigation, and to facilitate compensation to claimants who found pursuing legitimate vaccine-inflicted injuries too costly and difficult.¹³⁹ The Act created a vaccine injury claims-compensation system that was intended to provide fast, informal adjudication for covered vaccines and identified injuries. No showing of causation is necessary.¹⁴⁰ The quid pro quo for this system was the provision of significant tort-liability protections.¹⁴¹ The Act contains an express preemption provision clearly based on a comment *k*-type of protection for unavoidable risks.¹⁴²

The preemptive effect of this provision was the subject of *Bruesewitz v. Wyeth, LLC*,¹⁴³ in which the Court was asked to determine whether this provision preempted a claim by the family of a young girl who had been injured by the DPT vaccine and who had been denied her claim in the Vaccine Court.¹⁴⁴ She alleged that the DPT vaccine she was given was defectively designed because an alternative formulation was

¹³⁵ *Id.* at 489–90.

¹³⁶ *Id.* at 517.

¹³⁷ *Id.* at 517–18 (Sotomayor, J., dissenting) (a result that Justice Sotomayor described as “frankly astonishing.”)

¹³⁸ *See, e.g.*, Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 26 (codified as amended in sections of 21 U.S.C. § 301).

¹³⁹ *See generally* *Bruesewitz v. Wyeth*, 562 U.S. 223 (2011).

¹⁴⁰ *Id.* at 223–28; *see also* Petitions for Compensation, 42 U.S.C. § 300aa-11(a)(1) and Vaccine Injury Table, 42 C.F.R. § 100.3.

¹⁴¹ *Bruesewitz*, 562 U.S. at 223.

¹⁴² Standards of Responsibility, 42 U.S.C. § 300aa-22(b)(1).

¹⁴³ *Bruesewitz*, 562 U.S. at 223.

¹⁴⁴ *Id.* at 230–32.

available that would have prevented her seizure disorder.¹⁴⁵ Not surprisingly, the Court held her claims were expressly preempted.¹⁴⁶ The Court paid scant attention to the legislative history which indicated that the “unavoidable” language from comment *k* meant that an “unavoidable” risk was one for which no alternative product design was available.¹⁴⁷ The Court concluded that even vaccines that might have alternative formulations, as was alleged with the DTP vaccine in issue, contained “unavoidable” risks because “the language of the provision thus suggests that the *design* of the vaccine is a given, not subject to question in the tort action.”¹⁴⁸ Thus, express preemption provisions, like implied preemption doctrines, are construed broadly.

Federal preemption of state product liability laws has dramatically limited the ability of consumers injured by pharmaceuticals to recover for those injuries in the context of vaccine-related harms, generic pharmaceuticals for both failure to warn and design flaw cases, and for brand name pharmaceutical cases that involve clear evidence that the FDA would not permit a labeling change for a post-approval risk.¹⁴⁹ Some argue that no design flaw case remains for a branded pharmaceutical either.¹⁵⁰ It appears that only cases that involve a failure to comply with federal requirements, also called parallel claims, and product contamination cases survive federal preemption. Very little tort liability remains.¹⁵¹

III. RECENT TRENDS IN PHARMACEUTICAL USE AND MANUFACTURER PRACTICES AFFECTING THE LIABILITY LANDSCAPE

The astounding pace with which federal preemption doctrine devoured state tort law claims has occurred while adverse drug events are increasing and the influence of the pharmaceutical industry on the provision of medical care grows. Changes in reporting requirements regarding payments by pharmaceutical companies to prescribers, broader sharing

¹⁴⁵ *Id.* at 224–32.

¹⁴⁶ *Id.* at 224.

¹⁴⁷ *Id.* at 234–35 (discussing the history of § 402A, cmt. *k*). The Justices disagreed on the importance of the comment *k* derivation of the express preemption provision and on the treatment comment *k* has had in the courts. *See id.* at 244–47 (Breyer, J., concurring); *id.* at 254–568 (Sotomayor, J., dissenting).

¹⁴⁸ *Id.* at 232. The Court discussed the history of comment *k* and its impact on design defect litigation generally.

¹⁴⁹ The Seventh and Third Circuit Courts of Appeal have rendered conflicting opinions on the issue; *compare* *In Re: Fosamax (Alendronate Sodium) Prod. Liab. Litig.*, 852 F.3d 268 (3d Cir. 2017) *with* *Dolin v. GlaxoSmithKline LLC*, 901 F.3d 803 (7th Cir. 2018). The Court will decide the issue in the 2018–19 term. *Merck Sharp & Dohme Corp. v. Albrecht*, 852 F.3d 268 (3d Cir. 2017), *cert. granted*, 86 U.S.L.W. 3647 (U.S. June 21, 2018) (No. 17-290).

¹⁵⁰ Henderson & Twerski, *supra* note 47.

¹⁵¹ Marc A. Rodwin, *Compensating Pharmaceutical Injuries in the Absence of Fault*, 69 FOOD AND DRUG L.J. 442, 448 (2014).

of information about the number and scope of adverse events, and widespread understanding of the influence of pharmaceutical marketing on prescribing practices has also occurred over the last ten years.¹⁵² These trends support a reconsideration of non-fault liability for pharmaceutical injuries. Part III chronicles those trends.

A. *Increased Incidence of Adverse Events*

In a study of the magnitude of the impact of adverse drug events (ADEs),¹⁵³ the United States General Accounting Office concluded that it was difficult to assess the impact because of uncertainty in the underlying data.¹⁵⁴ Nevertheless, it observed that between one-half and three-quarters of ADEs are not due to the fault of medical care providers or pharmaceutical manufacturers, but rather, are inherent in the use of the product.¹⁵⁵ The uncertainty in data is largely the result of a failure by regulators to keep official statistics on deaths and injuries due to ADEs as they keep statistics for automobile accidents, cancer and other diseases, and crime.¹⁵⁶

In a recent review of the literature on the impact of ADEs, Dr. Marc Rodwin evaluated the most authoritative studies and concluded:

Prescription drug injuries cause 5.1 percent of hospital admissions, according to a systematic review of thirty-six studies in 1993. The estimates of injuries varied between three percent and 28 percent with most studies estimating between three and 11 percent. If we extrapolate nationally from these studies using the low three percent estimate, that means about one million people are hospitalized for drug injuries each year.¹⁵⁷

Dr. Rodwin's review also indicates that ADEs increase hospital costs by \$5.2 billion annually; this amount does not take into consideration the cost of outpatient care, lost income, and household production.¹⁵⁸

¹⁵² 42 U.S.C. § 1320a-7h(a)(1)(A). See also Corey Schneider, "Ask Your Doctor if this Product is Right for You": *Perez v. Wyeth Laboratories, Inc., Direct-to-Consumer Advertising and the Future of the Learned Intermediary Doctrine in the Face of the Flood of Vioxx Claims*, 26 ST. LOUIS U. PUB. L. REV. 421, 421 (2007); 21 U.S.C. § 355(o)(3)(E)(ii).

¹⁵³ Adverse drug events include both medical interventions related to a drug and adverse reactions related to a drug. For a description of these differences, see David W. Bates et al., *Incidence of Adverse Drug Events and Potential Adverse Drug Events: Implications for Prevention*, 274 J.A.M.A. 1, 29 (1995). See also Rodwin, *supra* note 151, at 447.

¹⁵⁴ UNITED STATES GENERAL ACCOUNTING OFFICE, ADVERSE DRUG EVENTS: THE MAGNITUDE OF HEALTH RISK IS UNCERTAIN BECAUSE OF LIMITED INCIDENCE DATA, REPORT TO CONGRESSIONAL REQUESTERS, B-2810822, 2, 4-5 (Jan. 2000) [hereinafter GAO REPORT].

¹⁵⁵ GAO REPORT, *supra* note 154, at 2. See also Rodwin, *supra* note 151, at 449.

¹⁵⁶ *Id.* at 450.

¹⁵⁷ *Id.* at 450-51 (footnotes omitted).

¹⁵⁸ *Id.* at 451. Other studies estimated higher costs. *Id.* at n.21-23.

The studies reviewed by Dr. Rodwin all took place before Congress adopted the Food and Drug Administration Amendments Act of 2007 (the FDAAA).¹⁵⁹ The FDAAA amended § 505 of the Federal Food, Drug, and Cosmetic Act¹⁶⁰ to enhance the FDA's authority to require pharmaceutical manufacturers to do post-market studies and clinical trials, as well as require risk evaluation and mitigation strategies, or REMS.¹⁶¹ The FDAAA also required manufacturers to monitor ADEs post-marketing.¹⁶² Until § 505(o) was amended, the FDA did not require that pharmaceutical manufacturers gather and report data on the incidence of adverse events in the use of their products. The only post-marketing adverse event reporting came from reports of such events by medical care providers in the field on a voluntary basis.¹⁶³ A study of the incidence of adverse drug reactions (or ADRs) worldwide concluded that estimates of under-reporting based on voluntary reporting systems range between 80% and 95%.¹⁶⁴

After the FDAAA, the FDA instituted a number of mechanisms to gather information about ADEs, and has been working to correct a backlog of post-marketing studies required by the 2007 legislation.¹⁶⁵ The

¹⁵⁹ Food and Drug Admin. Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007). For an explanation of the wide variety of components of the Act and changes to the FDCA, see James T. O'Reilly and Katherine A. VanTassel, *FOOD AND DRUG ADMIN. § 3:13* (2018). See also Von Eschenbach, *The FDA Amendments Act of 2007*, 63 *FOOD AND DRUG L.J.* 579 (2008).

¹⁶⁰ Section 505 of the FDCA is codified at 21 U.S.C.A. § 355.

¹⁶¹ 21 U.S.C.A. § 355(o)(3)(B). Section 505(o) provides that the FDA may require post-marketing studies and clinical trials for any or all of three purposes: (1) to assess a known serious risk related to the use of the drug involved; (2) to assess signals of serious risk related to the use of the drug; and (3) to identify an unexpected serious risk when available data indicates the potential for a serious risk. *Id.*

¹⁶² 21 U.S.C.A. § 355(o)(3), which adds section 505(o)(3) to the Federal Food, Drug and Cosmetic Act (FDCA) Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301-399d (2006)). In 2011, the FDA issued guidance to the pharmaceutical industry as to how it would implement its new authority. FDA, April 2011 Guidance, *supra* note 34; *About the Center for Biologics Evaluation and Research (CBER)*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cber/> (last visited Sept. 25, 2018); *About the Center for Drug Evaluation and Research*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/> (last visited May 1, 2019); U.S. DEP'T. OF HEALTH AND HUMAN SERVICES, <https://www.hhs.gov/> (last visited May 1, 2019); see generally, Barbara J. Evans, *The Ethics of Postmarketing Observational Studies of Drug Safety Under Section 505(o)(3) of the Food, Drug, and Cosmetic Act*, 38 *AM. J.L. & MED.* 577, 578 (2012) (describing the FDA's new powers and expressing concerns about pharmaceutical companies conducting their own post-market research).

¹⁶³ See Rodwin, *Compensating Pharmaceutical Injuries*, *supra* note 151, at 450. See also GAO REPORT, *supra* note 154, at 4-5, 10.

¹⁶⁴ L. Hazell & S.A. Shakir, *Under-Reporting of Adverse Drug Reactions: A Systematic Review*, 29 *DRUG SAFETY* 385 (2006) (evidence of significant and widespread under-reporting of ADRs to spontaneous, or voluntary, reporting systems).

¹⁶⁵ REPORT TO SENATE COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS AND THE HOUSE COMMITTEE ON ENERGY AND COMMERCE: REPORT ON THE FOURTH REVIEW OF THE

incidence of ADEs must be reported before post-marketing studies or trials are required, and the limitations on gathering the data and assessing it are substantial.¹⁶⁶

The potential for harm from ADEs propelled the United States Senate to create a Federal Interagency Task Force in 2012 to “identify common, preventable, and measurable . . . ADEs that may result in significant patient harm” and align federal agencies to reduce those harms.¹⁶⁷ In 2014, the Department of Health and Human Services devised an Action Plan for Adverse Drug Event Prevention based on the Task Force’s recommendations.¹⁶⁸ That Action Plan provided the following summary of the magnitude of adverse drug events in this country:

In 2006, 82 percent of the United States population reported using at least one prescription medication, over-the-counter medication, or dietary supplement, and 29 percent reported using five or more prescription medications. Among older adults (65 years of age or older), 57–59 percent reported taking five to nine medications and 17–19 percent reported taking 10 or more over the course of that year. Given the U.S. population’s large and ever-increasing magnitude of medication exposure, the potential for harms from ADEs constitutes a critical patient safety and public health challenge.¹⁶⁹

Other studies confirm the Action Plan’s conclusions. The Federal Adverse Event Reporting System, or FAERS, is the world’s largest database of voluntary, spontaneous reports of adverse drug reactions and medications errors.¹⁷⁰ It has been in operation since 1998. Using the

BACKLOG OF POSTMARKETING REQUIREMENTS AND COMMITMENTS BY THE FOOD AND DRUG ADMINISTRATION (2012). That backlog continues to exist though the FDA reports that it is making progress. *What’s New in GCP?: FDA Reports Most Required Post-Approval Studies are on Schedule*, 14 J. CLINICAL RESEARCH BEST PRACTICES 1, 1–2 (2018), https://firstclinical.com/journal/2018/1802_New115.pdf (stating that an average of 261 post-marketing requirements (PMRs) established each year since 2010; 29 percent of open PMRs were considered off-schedule).

¹⁶⁶ See Bard, *supra* note 34 at 510–24 (explaining limits on acquiring information about ADEs and exploring ways that FDA could use its improved authority to assess ADEs).

¹⁶⁷ *National Action Plan for Adverse Drug Event Prevention*, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES OFFICE OF DISEASE PREVENTION AND HEALTH PROMOTION (2014), <https://health.gov/hcq/pdfs/ADE-Action-Plan-508c.pdf> [hereinafter National Action Plan].

¹⁶⁸ *Id.*

¹⁶⁹ *Id.* at 5.

¹⁷⁰ *Id.* See also *Questions and Answers on FDA’s Adverse Event Reporting System (FAERS)*, U.S. FOOD AND DRUG ADMIN., <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm> (last visited May 1, 2019). There are also mandatory reporting requirements for manufacturers and other regulated industries. These are facilitated through the FDA’s MedWatch system. *MedWatch: The FDA*

FAERS, one study of all serious ADEs from 1998 to 2005 found that serious adverse events increased 2.6-fold and fatal adverse events increased 2.7-fold.¹⁷¹ Reported serious events increased four times faster than the total number of outpatient prescriptions during that period.¹⁷² Other studies have confirmed the increased incidence of ADEs.¹⁷³ ADEs are increasingly common, in part, because of the increased use of pharmaceuticals. Between 2011 and 2014, 91 percent of U.S. adults aged 65 years and older reported use of a prescription drug within the past 30 days, as compared to 74 percent between 1988 and 1994.¹⁷⁴ Many use more than one pharmaceutical on a daily basis.¹⁷⁵

Certain patient populations may be especially vulnerable to ADEs such as the very young, older adults, individuals with lower socioeconomic status, those with low health literacy, those with limited access to health care services, and certain minorities or ethnic groups.¹⁷⁶ These populations are also least likely to have the financial resources or insurance to manage the personal costs of ADEs, such as lost current and future income, cost of post-inpatient care, and other losses that result from inadequate access to health care in underserved, at-risk communities. The National Action Plan recognized that the full economic impact of ADEs has been inadequately studied.¹⁷⁷

During the premarketing approval process, there are limits on the number of clinical studies that can be conducted, and, therefore, limits on

Safety Information and Adverse Event Reporting Program, U.S. FOOD AND DRUG ADMIN., <https://www.fda.gov/Safety/MedWatch/default.htm> (last visited May 1, 2019).

¹⁷¹ Moore et al., *Serious Adverse Drug Events Reported to the Food and Drug Administration, 1998–2005*, 167(16) ARCH. INTERN. MED 1752 (2007).

¹⁷² *Id.*

¹⁷³ Weiss et al., *Adverse Drug Events in U.S. Hospitals, 2010 versus 2014*, AGENCY FOR HEALTH CARE RESEARCH AND QUALITY 2018 (Jan. 2018), <https://www.hcup-us.ahrq.gov/reports/statbriefs/sb234-Adverse-Drug-Events.jsp> (citing the number of hospital stays involving ADEs that originated during the stay decreased 27%, but those involving ADEs present at admission increased 11%). See also Rodwin, *supra* note 151, at 450–51.

¹⁷⁴ Rodwin, *supra* note 151 (quoting Poudel et al., *Burden of Hospitalizations Related to Adverse Drug Events in the USA: A Retrospective Analysis from Large Inpatient Database*, 26 PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 635–41 (2017)). See also U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, HEALTH UNITED STATES 2016: WITH CHARTBOOK ON LONG-TERM TRENDS ON HEALTH 3 (2017), available at <https://www.cdc.gov/nchs/data/hus/hus16.pdf>; INSTITUTE OF MEDICINE, ETHICAL AND SCIENTIFIC ISSUES IN STUDYING THE SAFETY OF APPROVED DRUGS, 29 (2012).

¹⁷⁵ Weiss et al., *supra* note 173, at 1.

¹⁷⁶ National Action Plan, *supra* note 167, at 7. A number of factors contribute to ADEs. Some of them are related to the patient profile: age, use of multiple pharmaceuticals, multiple chronic conditions, health literacy, and accessibility to health care. The National Action Plan proposes a number of interventions including enhanced surveillance, research, and prevention approaches in response to the variety of contributing factors. *Id.* at 18.

¹⁷⁷ *Id.* at 6.

what those studies show.¹⁷⁸ As mentioned, the FDA has the authority to require post-marketing requirements and other commitments to assess after-market risk information. In 2012, there were 1,637 post-marketing requirements underway that had been backlogged since 2007.¹⁷⁹ Because the FDA's post-marketing requirements authority has been in existence only since 2008, it is difficult to assess whether this number of post-marketing studies is significant.

As a way to assess whether the number of post-marketing requirements is significant, it may be helpful to know more about the number of drugs approved over the years and the approval rate of new drug applications. From its inception to 2012, the FDA had approved 1,524 drugs considered "new molecular entities," or NMEs. These include structurally unique, active ingredients that have never before been marketed, however this does not include any "me, too" drugs—those which build off of a prior NME.¹⁸⁰ The pace of New Drug Approvals (NDAs) slowed around the time of the changes in the approval process implemented by the 1962 amendments to the FDCA, which required proof of efficacy as part of approval.¹⁸¹ The approval rate peaked in 1996, when the agency approved 53 NMEs.¹⁸²

The increase of NME approvals in the 1990s stems from adoption of the Prescription Drug User Fee Act (PDUFA) in 1992.¹⁸³ The PDUFA authorizes the FDA to collect fees from pharmaceutical companies to expedite the drug approval process. Congress authorized this expedited approval system because of concerns over how long it was taking to obtain new drug approvals, particularly in relation to approval times in the European Union.¹⁸⁴ Since PDUFA was enacted, median drug approval

¹⁷⁸ See Bard, *supra* note 34, at 502–06 (noting that most adverse events are discovered after approval because of the limitations of pre-approval clinical trials and sponsor practices that limit the likelihood that adverse events will be identified). See also GAO REPORT, *supra* note 154, at 10–11.

¹⁷⁹ See REPORT TO SENATE COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS AND THE HOUSE COMMITTEE ON ENERGY AND COMMERCE: REPORT ON THE FOURTH REVIEW OF THE BACKLOG OF POSTMARKETING REQUIREMENTS AND COMMITMENTS BY THE FOOD AND DRUG ADMINISTRATION, *supra* note 165.

¹⁸⁰ U.S. FOOD AND DRUG ADMIN., SUMMARY OF NDA APPROVALS & RECEIPTS, 1938 TO THE PRESENT, <https://www.fda.gov/about-fda/histories-product-regulation/summary-nda-approvals-receipts-1938-present> (last visited May 1, 2019).

¹⁸¹ See Merrill, *supra* note 12, at 1764–77 (explaining purposes and impact of the 1962 Amendments to the FDCA).

¹⁸² *Id.*

¹⁸³ Prescription Drug User Fee Act, Pub. L. No. 102-571, 106 Stat. 4491 (1992) (current version at 21 U.S.C. 379(h) (2012)).

¹⁸⁴ Cassie Frank et al., *Era of Faster Drug Approval Has Also Seen Increased Black-Box Warnings and Market Withdrawals*, 33 HEALTH AFFAIRS No. 8, 1 (2014) (citing Kramer and Kesselheim, *User fees and beyond—the FDA Safety and Innovation Act of 2012*, 367 N. ENGL. J. MED. 1277 (2012)). See also Merrill, *supra* note 12, at 1792–96.

times for NMEs have decreased by 52 percent.¹⁸⁵ The FDA has hailed the Act as increasing patient access to over 1,500 new drugs and biologics.¹⁸⁶

A variety of studies have attempted to determine whether the faster approval process has had an impact on safety.¹⁸⁷ A recent study observed an increase in use of black-box warnings, warnings required for the most serious side effects, and market withdrawals since the PDUFA was first adopted.¹⁸⁸ Studies have drawn differing conclusions about whether drug safety has been compromised since the enactment of PDUFA. One reason is that no comprehensive source of information on black-box warnings or drug withdrawals is available to researchers or the public.¹⁸⁹ It is clear that drugs approved after the enactment of PDUFA were more likely to receive a black-box warning or be withdrawn from the market post-approval.¹⁹⁰

The time it takes to obtain a new drug approval in the United States averages between eight¹⁹¹ and twelve years.¹⁹² New drug applications typically fail, according to a recent retrospective review of FDA documents, because of inadequate drug performance and inadequate information submitted to the FDA.¹⁹³ That retrospective study concluded that 54 percent of NDAs failed on first pass because of safety deficiencies, and efficacy deficiencies accounted for 76 percent of first-pass failures.¹⁹⁴ Seventy-five percent of these NDAs were ultimately approved.¹⁹⁵ Safety concerns represented by serious adverse events, inadequate clinical data,

¹⁸⁵ Frank et al., *supra* note 184, at 1.

¹⁸⁶ *Id.*, *supra* note 184 at 5, n.27 (quoting *FDA User Fee Agreements: Strengthening FDA and the Medical Products Industry for the Benefit of Patients: Hearing Before the Sen. Comm. on Health, Educ., Lab., and Pensions*, 112th Cong. (2012) (statement of Janet Woodcock, Dir., Ctr. for Drug Evaluation & Res., Food and Drug Admin.)).

¹⁸⁷ Frank et al., *supra* note 184, at 1–2 (summarizing study results and limitations on evaluating data; most studies that review long-term data, where available, have found evidence of increased drug safety problems following enactment of PDUFA).

¹⁸⁸ *Id.* (“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.”).

¹⁸⁹ *Id.* at 3.

¹⁹⁰ *Id.* at 4–5 (“One theory is that PDUFA-imposed deadlines may have caused rushed approvals, resulting in an increase in safety problems that were recognized only after a drug was already in use. PDUFA was the most prominent in a series of initiatives designed to speed the drug approval process. . . . Another theory is that faster approvals following the enactment of PDUFA may have compromised the quality of clinical trial evidence that underlies such approvals . . .”).

¹⁹¹ 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 (2014)

¹⁹² DRUGS.COM, NEW DRUG APPROVAL PROCESS, <https://www.drugs.com/fda-approval-process.html> (last visited May 1, 2019).

¹⁹³ Sacks et al., *supra* note 191.

¹⁹⁴ *Id.* at 379–80.

¹⁹⁵ *Id.*

and improper dose selection are the reasons that NDAs do not obtain approval.¹⁹⁶ The study notes that the “life-cycle” approach to drug regulation is critical to maintaining an understanding of the drug experience because “even very large drug development programs may lack the power to identify serious rare adverse events.”¹⁹⁷

Given the concerns for pharmaceutical safety widely expressed, the National Action Plan for ADE Prevention includes a number of components to improve the quality of health care: safer care, informed patient and family engagement, communication and care coordination, and science driven prevention and treatment.¹⁹⁸ Surveillance is required to implement these, or any, efforts to reduce the incidence of ADEs.¹⁹⁹ Surveillance for medication errors is complicated by a number of factors. Determination of error is often subjective, dependent on voluntary reporting. The nature of claims data is therefore limited.²⁰⁰ The federal systems that currently conduct ADE surveillance are labyrinthine: (1) active systems through Medicare and Medicaid Services and the Centers for Disease Control; (2) passive system through FAERS; and (3) administrative claims captured through the Healthcare Cost and Utilization Report, and other agencies.²⁰¹ Many complications exist in assessing this mass of data that may confound the link between a drug and a certain outcome.²⁰² ADEs have many contributing factors and assessing them takes time. The 1,637 post-marketing requirement studies backlog identified earlier seems a significant number, in light of the decrease in approval times and increase in approval rates, the difficulty recognizing and assessing ADEs, and the limits in the reporting system.

The National Action Plan’s complexity illustrates the difficulty health care providers face addressing the problem of ADEs and the patients they serve. Many years may elapse between approval and sufficient understanding of problems with a drug before FDA oversight is triggered.²⁰³ The limitations of current surveillance methods necessary to document such knowledge are evident: the primary depository of the in-

¹⁹⁶ *Id.* at 381–82. For a critique of the efficacy standard and its limitations, see Jonathan J. Darrow, *Pharmaceutical Efficacy: The Illusory Legal Standard*, 70 WASH. & LEE. L. REV. 2073 (2013).

¹⁹⁷ *Id.* at 383.

¹⁹⁸ National Action Plan, *supra* note 167, at 17.

¹⁹⁹ Another term for post-marketing surveillance is pharmacovigilance, a phrase used by the World Health Organization for this subject, https://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en.

²⁰⁰ *Id.* at 23–26

²⁰¹ *Id.* at 27.

²⁰² *Id.* at 28.

²⁰³ Frank et al., *supra* note 184, at 2 (quoting R. Rodriguez-Monguio et al., *Examination of risk evaluation and mitigation strategies and drug safety in the US*, 10(1) RES. SOCIAL ADMIN. PHARM. 232 (2014)).

formation about post-marketing adverse reactions is in the hands of the manufacturer, if it exists anywhere.²⁰⁴ The passive reporting from medical providers and patients that provides a manufacturer with information about ADEs contains enormous amounts of noise—the type of reporter, the sophistication of the reporting method, the quality of the manufacturer’s call center instructions about how to obtain information from the caller, and other variables in the information itself are likely to swamp, and possibly mask, the information of pharmaceutical risk.²⁰⁵ Coordinating the passive reporting from FAERS with the information from the federal databases is similarly likely to require a combination of disparate information—different sources and types of information that may mask a connection between a pharmaceutical and its hidden risks and their magnitude.

Adverse events are being reported with increasing frequency and constitute a public health crisis.²⁰⁶ The ability of the FDA, other federal agencies, and pharmaceutical manufacturers to assess reports of ADEs and determine causes has taken and will likely continue to take decades. Pharmaceutical manufacturers have been criticized for delays in sharing information of both pre- and after-market risks.²⁰⁷ Discovering a post-marketing risk, assessing its significance, engaging the FDA in determining appropriate steps to share that information, through risk mitigation strategies or changed labeling, takes substantial time. The lag time between acquisition of knowledge about risk and providing that knowledge to medical care providers to use in making prescribing choices only makes a patient’s situation more precarious.²⁰⁸ The surveillance and assessment systems in place appear structured in a way to avoid the conclusion that some ADEs are the result of inherent pharmaceutical risks that either were not known, or were under-appreciated or ignored at the time of marketing.²⁰⁹ The current state of affairs calls for greater incentives to acquire and understand pharmaceutical risks.

²⁰⁴ See *id.*

²⁰⁵ See *id.*

²⁰⁶ See National Action Plan, *supra* notes 167–71. See also Amy Kapczynski, *Dangerous Times: The FDA’s Role in Information Production, Past and Future*, 192 MINN. L. REV. 2357, 2364–65 (2018) (discussing history of Vioxx and its ultimate withdrawal from market).

²⁰⁷ See Kapczynski, *supra* note 207; see also David A. Kessler & David C. Vladek, *A Critical Examination of the FDA’s Efforts to Preempt Failure-to-warn Claims*, 96 GEO. L.J. 461, 486–91 (2009) (discussing how statutory gaps hamper post-approval data gathering).

²⁰⁸ See Kapczynski, *supra* note 206, at 2368–71 (discussing frequent failure of some new drug applications to contain full clinical trial data).

²⁰⁹ Rodwin, *supra* note 151, at 4 (citing GAO Report). See also Bard, *supra* note 34, at 506–10.

B. *Impact of Pharmaceutical Industry Marketing Techniques on Prescribing Practices*

Complicating an already complex surveillance system to identify pre- and post-approval risks is the relationship between medical care providers and pharmaceutical companies.²¹⁰ A number of changes in the marketing of pharmaceuticals have influence on that relationship and impact the legal liability landscape. Those influences include aggressive pharmaceutical marketing directly to the consumer, the impact on prescribing habits of gifts and payments made by pharmaceutical companies to medical care providers, and the increase in efforts by pharmaceutical companies to encourage off-label prescribing of pharmaceuticals. These trends are explored below.

1. Effect of Direct-to-consumer Advertising on Prescribing Practices

Patients obtain prescription pharmaceuticals through authorized prescribers, typically a physician known as the learned intermediary. Consequently, the obligation to warn a patient of risk information is satisfied by providing information to the learned intermediary physician. Labeling and other risk information are directed toward the physician who is an expert and has at least basic understanding of pharmacology. Physicians are expected to prescribe the proper medicine for a patient's needs given knowledge about the patient and knowledge about the risk profile of the alternative pharmaceutical choices for treatment.²¹¹

Scholars have discussed the rationales behind the learned intermediary doctrine, which places the legal obligation on the pharmaceutical manufacturer to warn the learned intermediary and not the patient directly, and its consequences for litigation over inadequate warning claims.²¹² Debate has intensified over the last decade, however, over the propriety of the learned intermediary doctrine in the era of increasing technology that enables patients both to search for information about drugs they think might be beneficial for what ails them, and to seek out

²¹⁰ See, e.g., Bloomberg News, *Pfizer to Detail Drugs' Risks and Consult Doctors Earlier*, N.Y. TIMES, Aug. 12, 2005, <https://www.nytimes.com/2005/08/12/business/pfizer-to-detail-drugs-risks-and-consult-doctors-earlier.html>.

²¹¹ See Schneider, *supra* note 152, at 458–59.

²¹² See, e.g., Noah, *supra* note 42, at 890–94; Owen, *Dangers in Prescription Drugs*, *supra* note 69, 774–75 (advocating for abolishing the learned intermediary rule to provide greater access to risk information for patients); Jennifer Girod, *The Learned Intermediary Doctrine: An Efficient Protection for Patients, Past and Present*, 40 IND. L. REV. 397 (2007); T.S. Hall, *Reimagining the Learned Intermediary Rule for the New Pharmaceutical Marketplace*, 35 SETON HALL L. REV. 193 (2004); Richard Ausness, *Will More Aggressive Marketing Practices Lead to Greater Tort Liability for Prescription Drug Manufacturers?*, 37 WAKE FOREST L. REV. 97 (2002). See also OWEN & DAVIS, *supra* note 14, § 9:25.

those drugs from their physicians.²¹³ Who hasn't used WebMD or a similar medical information website to search symptoms, self-diagnose a medical condition, and then ask a physician to consider a particular pharmaceutical treatment?

More often, however, consumers are prompted to ask their physicians for specific pharmaceuticals because of direct-to-consumer advertising that encourages them to do so.²¹⁴ Scholars and observers of the pharmaceutical industry recognize that direct-to-consumer advertising has changed the drug industry and the consumer market.²¹⁵ Studies show that physicians are more likely to prescribe a pharmaceutical that a patient has requested.²¹⁶ In addition, direct-to-consumer advertising and patient access to pharmaceutical information through modern technology-enhanced resources has been found to have a significant impact on the physician-patient relationship.²¹⁷ Significant concerns have been expressed about the misleading nature of these advertisements and claims of effectiveness that are, in some cases, unfounded.²¹⁸

Very few jurisdictions have adopted an exception to the learned intermediary doctrine for direct-to-consumer advertised pharmaceuti-

²¹³ See Hall, *supra* note 212, at 197.

²¹⁴ Schneider, *supra* note 152, at 442; see generally CHARLES ZIMMERMAN, PHARMACEUTICAL AND MEDICAL DEVICE LITIGATION § 3:1 (2017).

²¹⁵ See ZIMMERMAN, *supra* note 214 (“Advertising has become a huge part of a drug company’s overall production effort for a new drug. In one year, Pfizer spent approximately \$668 million on consumer advertising while Merck spend \$348 million and Johnson & Johnson a mere \$335 million.”); see also Bloomberg News, *Pfizer to Detail Drugs’ Risks and Consult Doctors Earlier*, N.Y. TIMES, Aug. 12, 2005, <https://www.nytimes.com/2005/08/12/business/pfizer-to-detail-drugs-risks-and-consult-doctors-earlier.html>.

²¹⁶ See Matthew F. Hollon, *Direct-to-Consumer Marketing of Prescription Drugs: Creating Consumer Demand*, 281 J.A.M.A. 382, 383–84 (1999); Richard L. Kravitz et al., *Influence of Patients’ Requests for Direct-to-Consumer Advertised Antidepressants: A Randomized Controlled Trial*, 293 J.A.M.A. 1995, 1999 (2005); Steven Pearlstein, *Drug Firms Take a Dose of Responsibility for Ads: FDA Survey Finds Drug Ads Influence Requests by Patients*, WALL ST. J., Jan. 14, 2003, at D5. *But see* John E. Calfee et al., *Direct-to-Consumer Advertising and the Demand for Cholesterol-Reducing Drugs*, 45 J.L. & ECON. 673, 683–86 (2002) (finding little evidence that DTCA increased short-term demand for statins but noting beneficial effects such as improved patient compliance with already prescribed treatments). For instance, it appears that the aggressive marketing of COX-2 inhibitors led to the dangerous overprescribing of these drugs. See Marc Kaufman, *New Study Criticizes Painkiller Marketing: Arthritis Drug Ads a Factor in Overuse*, WASH. POST, Jan. 25, 2005, at A1; Barry Meier et al., *Medicine Fueled by Marketing Intensified Trouble for Pain Pills*, N.Y. TIMES, Dec. 19, 2004, § 1, at 1; see generally Victor E. Schwartz et al., *Marketing Pharmaceutical Products in the Twenty-First Century: An Analysis of the Continued Viability of Traditional Principles of Law in the Age of Direct-to-Consumer Advertising*, 32 HARV. J.L. & PUB. POL’Y 333, 376 (2009); Marshall H. Chin, *The Patient’s Role in Choice of Medications: Direct-to-Consumer Advertising and Patient Decision Aids*, 5 YALE J. HEALTH POL’Y, L. & ETHICS 771, 781 n.47 (2005).

²¹⁷ See Nadia Sawicki, *Choosing Medical Malpractice*, 92 WASH. L. REV. 891, 902–05 (2018) (summarizing studies on impact of patient access to pharmaceutical information on physician prescribing practices).

²¹⁸ See Darrow, *supra* note 196, at 2116–18.

cal.²¹⁹ Most experts in the field conclude that adequate consumer labeling cannot be designed for prescription drugs.²²⁰ A patient in need of treatment for a medical condition must rely on her physician. Yet, patients who seek a particular pharmaceutical, because of the power of marketing tools, have little to no ability to assess whether that pharmaceutical is appropriate.²²¹

Physicians, expected to exercise professional judgment in an increasingly time-restrictive medical care environment, cannot be overly criticized for capitulating to a patient's request. Medical care providers also should not be overly criticized for responding to the demands on their time that may prevent a thorough assessment of the risk profile of a pharmaceutical for every patient. Many challenges from the structure of modern medical care impact the quality of prescribing decisions, which inevitably impacts the incidence of adverse drug reactions and events.²²²

2. The Effect of Pharmaceutical Payments to Medical Care Providers on Prescribing Practices

The power of advertising is widely known. So is the power of gift giving. "The pull of reciprocity is exceedingly powerful, often acting on us in ways we may not consciously appreciate."²²³ One provision of the Patient Protection and Affordable Care Act (the ACA) requires that pharmaceutical companies report payments made to medical care providers—a sunshine provision.²²⁴ On October 1, 2014, the Centers for Medicare and Medicaid Services (CMS) released the long-awaited Open Payments Database to the public, detailing financial connections between physicians and drug and device makers.²²⁵ The Open Payments database was created to increase transparency regarding financial transactions between

²¹⁹ See *Perez v. Wyeth Laboratories, Inc.*, 734 A.2d 1245, 1262 (N.J. 1999) (duty to warn consumer directly of direct-to-consumer advertised drugs; explores relationship between pharmaceutical companies and the learned intermediary physician who prescribes). See generally, OWEN & DAVIS, *supra* note 14, § 9.25.

²²⁰ See Noah, *supra* note 42, at 904.

²²¹ See Hollon, *supra* note 216, at 384.

²²² A full exploration of the effects of the changing medical care landscape due to business pressures and rapid changes in health-insurance is beyond the scope of this Article. Preliminary suggested readings can be found at the website of the American Medical Association, <https://www.ama-assn.org/practice-management/economics/business-medicine>.

²²³ Ray Fisman & Michael Luca, *Did Free Pens Cause the Opioid Crisis?*, THE ATLANTIC, Jan. 2019, at 20; see The Big Bang Theory, The Bath Item Gift Hypothesis, Season 2, Episode 11 (first aired Dec. 15, 2008) (Sheldon to Penny after the offer of a gift: "I know you think you're being generous, but the foundation of gift-giving is reciprocity. You haven't given me a gift; you've given me an obligation.").

²²⁴ See Pub. L. No. 111-148, § 6002, 124 Stat. 119, 689-96 (2010) (codified at 42 U.S.C. § 1320a-7h (2012)). See generally Richard S. Saver, *Deciphering the Sunshine Act: Transparency Regulation and Financial Conflicts in Health Care*, 43 AM. J.L. & MED. 303 (2017).

²²⁵ See generally Medicare, Medicaid, Children's Health Insurance Programs; Transparency Reports and Reporting of Physician Ownership or Investment Interests, 78 Fed. Reg.

pharmaceutical companies and medical care providers.²²⁶ In 2014, doctors and hospitals received \$6.49 billion from the pharmaceutical industry.²²⁷ For comparison's sake, prescription drug spending in 2014 totaled approximately \$424 billion.²²⁸

Professor Lars Noah has recently studied the impact of payments by the drug industry on the prescribing practices of physicians.²²⁹ The comprehensive study assessed the data available on the subject of the corrupting influence of such payments on doctors' choices of which pharmaceuticals to prescribe. Professor Noah explains all the ways that the pharmaceutical industry gives to doctors, and the effect of that giving.²³⁰ He reports all studies that have documented the link.²³¹ He concludes that gifts to prescribers "unmistakably influence treatment choices, and even fairly trivial gifts can have an impact."²³²

For example, a recent study found that simply receiving one free meal from a drug company can increase the incidence of a doctor prescribing a medication from that company.²³³ Another study found that even small amounts of payments led to a change in prescribing practices.²³⁴ Ethical codes have limited impact on these practices, and the federal government has no power to regulate gifts.²³⁵ Professor Noah also observes that while the Open Payments Database provides important information, "far more serious conflicts of interest largely remain hidden from view."²³⁶

Whether the influence of gift giving to prescribers increases the incidence of adverse drug events is unknown. A number of reports detail

9458 (Feb. 8, 2013) (codified as amended at 42 C.F.R. pt. 403(I) (2018)). The database appears at www.cms.gov/openpayments.

²²⁶ See *id.* at 9458–59.

²²⁷ Peter Loftus & Joseph Walker, *Drug and Medical-Device Makers Paid \$6.49 Billion to Doctors, Hospitals in 2014*, WALL ST. J., June 30, 2015, at B3.

²²⁸ See *A Look at Drug Spending in the US*, PEW (Feb. 27, 2018), <https://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2018/02/a-look-at-drug-spending-in-the-us>. Total U.S. prescription sales in 2017 were \$455.9 billion and expected to increase to over \$500 billion in 2018. Glen T. Schumock et al., *National Trends in Prescription Drug Expenditures and Projections for 2018*, 75 AM. J. HEALTH-SYS. PHARMACY 1023 (2018).

²²⁹ Lars Noah, *Doctors on the Take: Aligning Tort Law to Address Drug Company Payments to Prescribers*, 66 BUFF. L. REV. 855 (2018).

²³⁰ *Id.* at 872–73.

²³¹ *Id.* at 873–74.

²³² *Id.* at 872–73.

²³³ DeJong et al., *Pharmaceutical Industry–Sponsored Meals and Physician Prescribing Patterns for Medicare Beneficiaries*, 176(8) JAMA INTERNAL MED. 1114, 1117–18 (2016) (doctors who received a single meal promoting a certain brand-name drug prescribed those drugs for depression, high cholesterol and heart disease at higher rates).

²³⁴ Dusetzina et al., *Pharmaceutical Industry Payments and Oncologists' Selection of Targeted Cancer Therapies in Medicare Beneficiaries*, 178(6) JAMA INTERNAL MED. 854, (2018).

²³⁵ Noah, *supra* note 229, at 859–60, 865.

²³⁶ *Id.* at 870–71.

circumstances in which drug representatives sought to increase the number of prescriptions even though serious risks were widely known.²³⁷ The incidence of adverse drug events is unlikely to decrease when prescriptions increase.

C. *Off-label Prescribing: Permitted, Encouraged, and Increasing*

No matter how much information the pharmaceutical sponsor of a new drug knows and shares with the FDA, the magnitude of known side effects and the discovery of unknown, but inevitable risks will be discovered post-marketing. This is the result of the limitation of clinical trials,²³⁸ but also the result of off-label prescribing.²³⁹ Off-label prescribing is permitted; a physician is not limited to prescribing only for indications on a drug's labeling. Physicians are known to prescribe for off-label uses and thought to have done so for as long as there have been drugs to prescribe.²⁴⁰

Pharmaceutical companies have regularly been criticized for off-label marketing, and many such instances have led to high-profile litigation.²⁴¹ The primary problem, of course, is that pharmaceuticals are studied for certain indications for which they are determined to be safe and effective.²⁴² No other indication is approved because the drug is not known to be either safe or effective for any other purpose.²⁴³ Adverse side effects are discovered during clinical trials only for approved indications.²⁴⁴ If a drug is marketed for another use, there is a risk that more serious side effects, or a greater incidence of known side effects, will

²³⁷ Fisman & Luca, *supra* note 223, at 21 (while prescriptions of opioids dropped across the country in 2018, among physicians who continued to receive gifts from opioid makers prescriptions continued to see a modest rise); Letter to Democratic Members of the House of Representatives Government Reform Committee: The Marketing of Vioxx to Physicians (May 5, 2005), available at https://www.industrydocumentslibrary.ucsf.edu/wp-content/uploads/2014/11/waxmanmemo_vioxx.pdf.

²³⁸ Bard, *supra* note 34, at 502–05.

²³⁹ *Id.* at 503.

²⁴⁰ Bard, *supra* note 34, at 505, n.20 (“No one knows the extent to which drugs are prescribed ‘off-label’ but studies suggest it is a common practice.”). See also Radley et. al., *Off-label Prescribing among Office-Based Physicians*, 166 ARCH. OF INTERN MED., 1021–26 (2006) (“Off-label medication use is common in outpatient care, and most occurs without scientific support.”).

²⁴¹ See generally Richard C. Ausness, “*There’s Danger Here, Cherie!*”: *Liability for the Promotion and Marketing of Drugs and Medical Devices for Off-label Uses*, 73 BROOKLYN L. REV. 1253 (2008) (chronicling past examples of off-label marketing litigation and exploring liability issues).

²⁴² *Id.* at 1257.

²⁴³ *Id.*

²⁴⁴ *Off-Label Drug Use*, AMERICAN CANCER SOCIETY, <https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/chemotherapy/off-label-drug-use.html> (last revised May 1, 2019).

result.²⁴⁵ Yet physicians using drugs in different ways with patients whose conditions they know and understand can discover important uses. The patient for whom an off-label use is prescribed is being tested, and is risking serious harm while hoping for the reward of a beneficial therapy.

Off-label marketing that misleads or misrepresents the available information about a pharmaceutical has led to a significant number of lawsuits.²⁴⁶ The FDA guidelines require that a drug company responding to a request for information about a drug must provide truthful and balanced scientific information.²⁴⁷ The FDA has recently provided guidance for pharmaceutical companies relating to off-label marketing, with a view to increasing the use of pharmaceuticals for non-approved uses.²⁴⁸

The tide of increasing adverse drug events is surely coming in. All signs point to increasing pharmaceutical use, increasing incidence of adverse events, increasing influence over prescribing physicians by the pharmaceutical industry, and a decreasing ability of the FDA to exercise oversight over all its regulatory obligations.²⁴⁹ If the regulatory system had the ability to shield patients from unknown risks, or adequately inform patients and medical care providers of the severity of known risks, medical outcomes would improve. It is a laudable goal and many have identified ways to enhance the likelihood of better outcomes.²⁵⁰ But pa-

²⁴⁵ *Id.*

²⁴⁶ See Viscusi & Zeckhauser, *supra* note 17, at 392 (listing settlements for substantial sums arising out of allegations of improper off-label marketing).

²⁴⁷ *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012)

²⁴⁸ DRUG AND DEVICE MANUFACTURER COMMUNICATIONS WITH PAYORS, FORMULARY COMMITTEES, AND SIMILAR ENTITIES—QUESTIONS AND ANSWERS, GUIDANCE FOR INDUSTRY AND REVIEW STAFF, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory-Information/Guidances/UCM537347.pdf>; Medical Product Communications that are Consistent with the FDA-Required Labeling—Questions and Answers, Guidance for Industry, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537130.pdf>. See John Gever, *FDA Loosens Reins (Slightly) on Pharma-Doc Communication*, MEDPAGE TODAY (June 12, 2018), <https://www.medpagetoday.com/publichealthpolicy/generalprofessionalissues/73449>; Jill Wechsler, *FDA Clears Pathway for Off-Label Economic Communications*, PHARMEXEC.COM (June 25, 2018), <http://www.pharmexec.com/fda-clears-pathway-label-economic-communications>; Emily Field, 4 Takeaways from the FDA’s Info-Sharing Guidance, LAW360 (June 25, 2018) (“The FDA has been hitting the brakes on prosecuting off-label cases, and the guidance indicates that this trend will continue.”).

²⁴⁹ See Noah, *supra* note 229, at 857; *Increase Seen in Prescription Drug Use in United States*, SCIENCE DAILY (Nov. 3, 2015) <https://www.sciencedaily.com/releases/2015/11/151103134804.htm>; Michael McCarthy, *Off-Label Drug Use is Associated with Raised Risk of Adverse Events, Study Finds*, THE BMJ (Nov. 4, 2015), <https://www.bmj.com/content/351/bmj.h5861>; Thomas Sullivan, *FDA Regulatory Requirements, Enforcement Activity Have Increased Despite Agency Acknowledging the Strain on Small Companies*, POL’Y & MED., <https://www.policymed.com/2014/11/fda-regulatory-requirements-enforcement-activity-have-increased-despite-agency-acknowledging-the-str.html> (last updated May 6, 2018).

²⁵⁰ See Philip M. Rosoff & Doriane L. Coleman, *The Case for Legal Regulation of Physicians’ Off-Label Prescribing*, 86 NOTRE DAME L. REV. 649, 656 (2013); Barbara J. Evans & David A. Flockhart, *The Unfinished Business of US. Drug Safety Regulation*, 61 FOOD & DRUG L.J. 45 (2006); Bard, *supra* note 34, at 49; Noah, *supra* note 229, at 858.

tients seeking therapy for illness and disease who suffer from adverse drug events are also suffering the unpreventable consequences of the system. Strict, non-fault liability was intended to respond to just such circumstances.²⁵¹

IV. STRICT LIABILITY FOR PHARMACEUTICALS RE-IMAGINED

A. *Historic Calls for Strict Liability for Pharmaceuticals*

Calls for more robust tort liability, including strict, non-negligence-based liability, are not often expressed anymore.²⁵² As described in Part II, the move away from strict products liability to a more purely negligence-based system happened rather quickly after the adoption of strict products liability, both through changes from state statutory reform efforts and through the Products Liability Restatement project.²⁵³ Nevertheless, calls for strict tort liability for pharmaceuticals have been regularly made. In 1973, Professor Richard Merrill extensively explored the case to be made for a system of no-fault liability to place the injury costs from adverse drug reactions on the manufacturer.²⁵⁴ Professor Merrill's article identifies comprehensively the reasons why strict tort liability is appropriate for pharmaceuticals: information-forcing effect, risk reduction, and loss allocation to the party best able to bear the inevitable loss from pharmaceutical side effects.²⁵⁵ Professor Merrill's analysis of the need for strict tort liability for pharmaceuticals made a compelling case based on inevitable regulatory failure and limited FDA resources, physician and patient inability to assess product risk, and ability of industry firms to accommodate the cost and respond to the risk information disclosed through litigation.²⁵⁶ Yet, it did not hold sway.

²⁵¹ See Rosoff & Coleman, *supra* note 251, at 655.

²⁵² Bernstein, *supra* note 65, at 1051 (Professor Bernstein elegantly describes the efforts over recent decades to “trumpet[t] the dire effects of personal injury litigation on the supply of useful prescription drugs.”).

²⁵³ Richard L. Cupp, *Rethinking Conscious Design Liability for Prescription Drugs: The Restatement (Third) Standard vs. a Negligence Approach*, 63 GEO. WASH. L. REV. 76, 88 (1994).

²⁵⁴ Richard A. Merrill, *Compensation for Prescription Drug Injuries*, 59 VA. L. REV. 1 (1973). See also Paul D. Rheingold, *Products Liability—The Ethical Drug Manufacturer's Dilemma*, 20 FOOD DRUG COSM. L. J. 328 (1965).

²⁵⁵ Merrill, *supra* note 254, at 87–88. Professor Merrill's article was written during a time of significant transformation in the pharmaceutical industry: approximately a decade after changes to the FDCA required safety and efficacy for pharmaceutical approval, less than a decade after the ALI endorsed § 402A, and before comment *k* had become the baseline approach to, and significant limitation on, pharmaceutical liability.

²⁵⁶ *Id.* (“Most reactions are the by-product of what amounts to government approved medical experimentation, conducted ostensibly to advance society's interest in having available a broad range of prescription medications.”). Drug manufacturers, physicians and the FDA have greater power than consumers and patients to reduce these drug risks. The consumer is

Ten years later, Professor Joseph Page argued against the confusion that section 402A and comment *k* had produced and called for a fuller assessment of strict tort liability for unavoidably dangerous products.²⁵⁷ Professor Page, like Professor Merrill, articulated a compelling case for strict tort liability for pharmaceuticals, analogizing to strict liability for product defectiveness based on construction flaws, those whose risk cannot be alleviated with a warning, and that defeats consumers' expectations of safety.²⁵⁸ Professor Page grounded his theory in the products liability concepts of defectiveness, admitting the theoretical hurdles that theory presented.²⁵⁹

The 1980s brought widespread use of comment *k* to immunize pharmaceutical manufacturers from design defect liability and to ground liability in a warning failure.²⁶⁰ Only branded pharmaceuticals were subject to such claims because there were no generic pharmaceuticals until permitted by federal legislation in 1984.²⁶¹ The Products Liability Restatement furthered protection from design flaw liability, emphasizing failure-to-warn claims.²⁶² These applications of tort doctrine assumed that failure-to-warn claims might be available grounded in negligence even in the face of robust federal approval mechanisms that endorsed safety and effectiveness. During this time, the complementary role of state tort law with the federal regulatory system was not challenged.

The early calls for strict tort liability for pharmaceutical side effects were occasionally renewed after adoption of the Products Liability Restatement.²⁶³ The pharmaceutical industry came under scrutiny in the mid-2000s for certain excesses²⁶⁴ as well as some high-profile litigation involving failures to warn about serious side effects in widely prescribed

virtually helpless to guard against most severe or sudden risks that she cannot understand until too late. *Id.* at 93.

²⁵⁷ Joseph A. Page, *Generic Product Risks: The Case Against Comment k and for Strict Tort Liability*, 58 N.Y.U. L. REV. 853, 857 (1983).

²⁵⁸ *Id.* at 882–89 (exploring policies underlying strict liability in construction defect cases to justify liability for generic product risks: full recovery, encouraging safety and accident avoidance).

²⁵⁹ *Id.* at 889–90.

²⁶⁰ *See id.* at 855.

²⁶¹ *See* C. Scott Hemphill & Mark A. Lemley, *Earning Exclusivity: Generic Drug Incentives and the Hatch-Waxman Act*, 77 ANTITRUST L. J. 947 (2011).

²⁶² *See supra* notes 255–60 and accompanying text. *See also* Cupp, *supra* note 253.

²⁶³ *See* Barry R. Furrow, *Enterprise Liability for Bad Outcomes from Drug Therapy: The Doctor, the Hospital, the Pharmacy, and the Drug Firm*, 44 DRAKE L. REV. 377, 433 (1996) (summarizing purposes behind enterprise liability for pharmaceuticals and advocating that drug manufacturers be liable for all drug reactions not the result of physician, pharmacist, or patient negligence; noting that such “absolute strict liability with limited affirmative defenses” has the advantage of certainty over then-current tests of defectiveness).

²⁶⁴ *See generally* MARCIA ANGELL, *THE TRUTH ABOUT DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT* (2004) (criticizing the drug industry and calling for structural reforms in the regulatory arena).

products as Vioxx and FenPhen.²⁶⁵ Nevertheless, calls for strict liability for the inevitable side effects of pharmaceutical products were not widely made.²⁶⁶

The common rationales expressed against tort liability for pharmaceuticals, much less strict liability, are well-known: potential liability deters innovation and will reduce the availability of socially useful therapies, federal regulation thoroughly regulates the field and balances risks and benefits of drugs, and injured plaintiffs are better off assessing risk through personal choice and obtaining insurance, among others.²⁶⁷ Enterprise liability, based on an allocation of losses to the enterprise that can control the risk and better bear it, was advocated for in the 1970s through the 1990s as a basis for strict products liability, but did not take root.²⁶⁸

B. *Expanded Federal Preemption of State Tort Law*

Perhaps the tort liability structure for pharmaceuticals, based in failure-to-warn with limited design defect litigation, was inevitable given the influence of the Restatement (Second) project and its Reporter Dean Prosser, as well as widespread industry support for comment *k* as a limitation on potentially broad strict liability.²⁶⁹ At that time, state tort law was expected to act as a parallel complement to the federal regulatory structure, and gave common-sense support to an emphasis on failure-to-warn claims.²⁷⁰ Federal preemption doctrine has since been applied to defeat essentially all state tort law claims for generic pharmaceuticals, the most widely prescribed pharmaceuticals, and significantly strengthened the doctrine of impossibility preemption for brand name pharmaceuticals. This application has had such an effect that even those who advocated for comment *k* and for the Products Liability Restatement are alarmed at the prospect for the demise of state tort law to redress pharmaceutical injuries.²⁷¹

Mutual Pharmaceuticals v. Bartlett and *PLIVA, Inc. v. Mensing*, which immunize generic pharmaceutical manufacturers from virtually all

²⁶⁵ See David G. Owen, *Inherent Product Risks*, 93 KY. L. J. 377, 410 (2004).

²⁶⁶ See Bernstein, *supra* note 65, at 1055–57 (noting that “not since the litigation-has-tened demise of the very dangerous Dalkon Shield IUD has any pharma product demonstrated that personal injury liability can be a source of social utility”; arguing that most law review commentators “either condemn this corner of personal injury law or ignore it”). See also Owen, *Dangers in Prescription Drugs*, *supra* note 69, 770.

²⁶⁷ See Owen, *Inherent Product Risks*, *supra* note 265, at 771.

²⁶⁸ Steven P. Croley & Jon D. Hanson, *Rescuing the Revolution: The Revived Case for Enterprise Liability*, 91 MICH. L. REV. 683, 706–12 (1993). See also Guido Calabresi, *Some Thoughts on Risk Distributions and the Law of Torts*, 70 YALE L. J. 499 (1961).

²⁶⁹ Page, *supra* note 257, at 861–63.

²⁷⁰ See Twerski, *supra* note 90, at 15.

²⁷¹ See *id.*

tort liability, have changed the game of pharmaceutical liability.²⁷² These two cases so broadly apply implied impossibility preemption that the only claims that survive are contamination cases and cases involving failure of the generic pharmaceutical to comply with the brand name labeling, both of which are rare.²⁷³ *Mutual Pharmaceuticals v. Bartlett* leaves open the possibility that a viable claim may be available against generic pharmaceutical manufacturers if the state law tort claim is based purely on a compensation-type theory that allocates loss to the actor who creates the risk—a classic no-fault strict tort liability theory.²⁷⁴ What is the basis for such a theory?²⁷⁵

C. Trends in Pharmaceutical Marketing Increase Risk of Adverse Drug Events

This Article grounds the basis for a strict liability theory in the convergence of the trends in pharmaceutical marketing described in Part III, with the drastically limited role of common law tort litigation to act as a vehicle for compensation for losses from pharmaceutical injuries described in Part II. The reduction in new-drug approval times intended to speed products to market, the increase in adverse drug events chronicled since the FDA was given authority to require post-marketing reporting, and the yearly increase in spending on pharmaceuticals coupled with aggressive pharmaceutical marketing and external influences on prescribing practices all point to an inevitable rise in injuries from pharmaceuticals. It must be emphasized that 63 percent of recent drug approvals are for generics for which state tort liability is preempted.²⁷⁶ The federal regulatory structure is, therefore, the only thing standing between patients and the inevitable injuries from pharmaceuticals they are prescribed. The federal regulatory system is struggling to comprehend and address the scope of the adverse drug event problem.²⁷⁷

²⁷² See *Mutual Pharm. Co. v. Bartlett*, 570 U.S. at 472. See *supra* notes 125–37 and accompanying text.

²⁷³ See Eric Lindenfeld, *Brand Name Preemption: The New Frontier in Pharmaceutical Product Liability Litigation*, 72 *FOOD & DRUG L.J.* 636, 637 (2017).

²⁷⁴ See *id.* at 501–02.

²⁷⁵ See generally Amalea Smirniotopoulos, *Bad Medicine: Prescription Drugs, Preemption and the Potential for a No-fault Fix*, 35 *N.Y.U. REV. L. & SOC. CHANGE* 793 (2011). Other scholars have expressed modern support for strict liability for pharmaceuticals, using the classic explanations of allocation of loss and fairness. See Rodwin, *supra* note 151.

²⁷⁶ Compare U.S. Food & Drug Admin., *Novel Drug Approvals for 2017*, FDA (Feb. 2, 2018), <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm537040.htm>, with U.S. Food & Drug Admin., *First-Time Generic Drug Approvals 2017*, FDA (Feb. 20, 2018), <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ANDAGenericDrugApprovals/ucm597322.htm>.

²⁷⁷ U.S. Food & Drug Admin., *What is a Serious Adverse Event?*, FDA (Feb. 1, 2016), <https://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm>. (discussing that a serious

If we are to rely on prescribers to be properly informed by the pharmaceutical industry and to act as a first-line-of-defense to reduce the incidence of adverse drug events, prescribers must properly prescribe drugs and monitor patients for potential side effects. For prescribers to prescribe properly and monitor patients on drug treatment, the information they use should be unadulterated. However, as the influence of payments by pharmaceutical companies on doctors' prescribing habits is now widely known, the likelihood that prescribers are fully and fairly informed is reduced.²⁷⁸ This influence may not necessarily mean that pharmaceuticals are prescribed improperly, but the potential is certainly present, and at least in some cases likely. Patients are expected to rely on the learned intermediary to make an appropriate prescribing choice, without improper influence and based only on what is best for the patient. Adverse drug reactions are inevitable, both those known and those unknown, but which will be discovered only after the pharmaceutical is in wide use.²⁷⁹ The combination of potentially excessive prescribing based on influences unrelated to best prescribing practices increases the likelihood of adverse drug reactions with no corresponding benefit to the patient.

Further pressure on medical care providers comes from pharmaceutical companies marketing to patients directly, which is intended to influence prescribing habits.²⁸⁰ Advertising directed at consumers is known to complicate prescribing decisions, impose an increased burden on prescribers to access and evaluate labeling information data, and creates a scenario in which information about known side effects may be under

adverse event is "any undesirable experience associated with the use of a medical product in a patient," such as death, hospitalization, permanent damage, etc.); 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, 461–64, (2008) (discussing generally the problem the FDA has faced with the adverse drug event problem, failure-to-warn cases, and pre-emption).

²⁷⁸ See Klaus Lieb & Armin Scheurich, *Contact Between Doctors and the Pharmaceutical Industry, Their Perceptions, and the Effects on Prescribing Habits*, PLOS One, (Oct. 16, 2014), <https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0110130&type=printable>); See also Aaron Cohen et al., *The More Opioids Doctors Prescribe, The More Money They Make*, CNN (Mar. 12, 2018), <https://www.cnn.com/2018/03/11/health/prescription-opioid-payments-eprise/index.html>; see also Elaine K. Howley, *Do Drug Company Payments to Doctors Influence Which Drugs They Prescribe?*, CNN (Aug. 31, 2018), <https://health.usnews.com/health-care/patient-advice/articles/2018-08-31/do-drug-company-payments-to-doctors-influence-which-drugs-they-prescribe>.

²⁷⁹ See John Toon, *Study Suggests Drug Side Effect Are Inevitable: Basic Physics Enabled Early Biochemistry*, Georgia Institute of Technology News Center (May 20, 2013), <https://phys.org/news/2013-05-protein-drug-side-effects-inevitable.html>; see Jeffrey Skolnick & Mu Gao, *Interplay of Physics and Evolution in the Likely Origin of Protein Biochemical Function*, PNAS (Apr. 23, 2013), <http://www.pnas.org/content/pnas/110/23/9344.full.pdf>.

²⁸⁰ See C. Lee Ventola, *Direct-to-Consumer Pharmaceutical Advertising: Therapeutic or Toxic?*, 36 PHARMACY & THERAPEUTICS 669, 681 (2011).

appreciated.²⁸¹ The daily pressures of a medical practice are very different in 2019 than they were when the “learned intermediary” doctrine became widely adopted in the 1950s and 1960s. The potential for a failure of important risk information to be properly evaluated before prescribing is very real. This risk is magnified in the in-patient setting where the medical care providers may know little about a patient’s background medical issues.

The final trend explained in this Article that weighs in favor of a re-assessment of strict liability for pharmaceutical injuries is the influence of off-label promotion practices of pharmaceutical companies. Physicians have long been known to prescribe off-label; this is one of the hallmarks of federal drug regulation.²⁸² Medical care is not regulated by the FDCA; pharmaceutical products are.²⁸³ If a physician wants to prescribe a pharmaceutical for an entirely different use than that approved, she may.²⁸⁴ The risk in such cases is entirely on the patient who may or may not be benefitted, but who will be the only one who may suffer serious injuries or illness.²⁸⁵ Recent FDA policy and guidance is more favorable to off-label marketing.

These trends, all of which increase risk to the patient in circumstances where the patient is wholly without the ability to reduce that risk, coupled with the significant limitations on existing tort law theories of warning and design defect liability, support a thoughtful re-consideration of a strict liability theory based on inherently dangerous pharmaceutical risk. This theory would not require that an injured consumer establish a defect under comment *k* of § 402A or an inadequate warning under negligence or strict liability. The theory would be based on a state law tort doctrine that does not conflict with any FDA requirement or prohibition, but rather, permits the conclusion that injuries caused by an FDA-approved pharmaceutical’s inherent risks are compensable notwithstanding FDA judgment that the product is safe and effective for use under the prescribed conditions. Strict products liability theory does not supply the sole basis for this theory.²⁸⁶

²⁸¹ *Id.* at 681.

²⁸² Katherine T. Adams, *The Off-Label Conundrum*, 3 BIOTECHNOLOGY HEALTHCARE 27, 27–28 (2006); see generally, Christopher M. Wittich et al, *Ten Common Questions (and Their Answers) About Off-Label Drug Use*, 87 MAYO CLINIC PROCEEDINGS 982 (2012) (discussing general background on off-label drug use).

²⁸³ See *id.* at 27–28.

²⁸⁴ Katrina Furey & Kirsten Wilkins, *Prescribing “Off-Label”: What Should a Physician Disclose?*, 18 AMA J. OF ETHICS 587, 588–90 (2016).

²⁸⁵ *Freeman v. Hoffman-La Roche, Inc.*, 618 N.W.2d 827, 840 (Neb. 2000).

²⁸⁶ For cases that adopt a design defect liability theory based on a similar concept, see *supra* notes 56 and accompanying text (discussion of *Freeman v. Hoffmann-LaRoche*).

D. Theoretical Support for Strict Liability for Pharmaceutical Injuries

Strict tort liability for inherent pharmaceutical side effects can be supported if one constructs the argument based on classic ultra-hazardousness: the pharmaceutical contains a risk of serious harm that will fall, indiscriminately, on an unsuspecting patient who has no control over that risk, and essentially no ability to avoid it. Liability for risks of this type is not unheard of, and the Restatement (Third) of Torts: General Principles returns to this concept in lieu of the “abnormally dangerous activities” categorical liability of the Restatement (Second) of Torts.²⁸⁷ The author does not rely on either of these doctrines exclusively because the ubiquitous nature of pharmaceutical use renders harm from them neither unnatural nor unusual. That is precisely the concern, however: harm from pharmaceutical use is inevitable, unavoidable, substantially unexpected by those harmed, and becoming more frequent.

Part III illustrates how both pre- and post-approval pharmaceutical risks are discovered, assessed by the FDA, and shared with medical care providers. It also describes the features of the pre- and post-approval marketing structure that prevent serious side effects from becoming discovered and fully appreciated. The efficiency of the post-marketing adverse event reporting system is critical to full understanding and disclosure of risk, yet the current system is neither comprehensive nor robust. Many holes in the adverse event reporting mechanisms exist preventing medical care providers from learning about those risks. In addition, the ubiquitous presence of pharmaceuticals in advertising and social and other media influences prescribing practices, which likely results in ill-informed-prescribing choices, thus results in poor health outcomes. These limitations have produced an untenable situation for injured consumers that strict tort liability for the inherent risks of pharmaceuticals can address, at least in part. Such liability will also lead to the societal benefit of increased risk information sharing, enhancing the ability of medical care providers to prescribe appropriately, and potentially reducing unnecessary adverse events.

State law tort liability that compensates for such side effects does not challenge the risk-benefit calculus that the FDA has made for a pharmaceutical and thus should not suffer from federal preemption of state tort laws. In this instance, state law is choosing to compensate injured consumers because of a more basic notion that civil redress for harm done is necessary because of the seriousness and inevitability of the risk to a certain population that has no ability to control or choose exposure to that risk. The thrust of this liability is the fundamental idea that serious

²⁸⁷ RESTATEMENT (THIRD) OF TORTS, *supra* note 6, § 24.

risk from therapeutic treatments should not fall on the person seeking relief from illness or disease; rather, persons seeking medical care should not be expected to make a choice between the risk of an adverse event and the greater opportunity for relief from pain, illness, or disease. This is particularly salient given that patients often do not know, and so cannot choose to accept, the risk of the pharmaceuticals they take. A state could support treatment choices for its citizens that have both a chance of success and a risk of a serious side effects, known or unknown, by not imposing the suffering of the side effect without assistance or recompense for the additional harm suffered because of it.²⁸⁸ This is more so true given the inadequacies of the regulatory system for discovering and addressing the risk of serious adverse events and the influences on prescribing practices described above. A state could conclude that its community's public policy supports persons in need of medical treatment who should not be asked to make these kinds of Hobson's choices, whether with or without all relevant information about them. The fact that our medical care providers make these choices for us need not insulate the pharmaceutical manufacturer from the inevitable harms that result to patients from otherwise beneficial products.

A critique of this proposal is that the FDA is the expert and best arbiter of pharmaceutical risks and benefits and any alternate system that evaluates its choices is wasteful and unnecessary, particularly one that employs the adversarial method and lay juries as decision-makers. Observers have described the "challenging times" for the FDA.²⁸⁹ Its tasks have expanded but "it has been given no significant new tools to ensure that companies produce adequate data after a drug enters the market."²⁹⁰ Concerns of regulatory agency capture also loom in the background.²⁹¹ Better risk and efficacy assessment can result from requiring producers to bear the costs of its products and aid in the FDA's information-forcing role.²⁹² A pharmaceutical industry actor who is made responsible for

²⁸⁸ Recent scholars have noted the increase in state regulatory activity given perceived areas of FDA inefficiency and under-regulation of certain features of the pharmaceutical system. See, e.g., Catherine M. Sharkey, *States v. FDA*, 83 GEO. WASH. L. REV. 1609 (2016); (relevant state interests important in realm of food and drug laws; state regulation may fit within the federal regulatory scheme); Patricia J. Zettler, *Pharmaceutical Federalism*, 92 IND. L.J. (2017) (states regulate to force policies to be respected and force federal attention to state interests).

²⁸⁹ Amy Kapczynski, *Dangerous Times: The FDA's Role in Information Production, Past and Future*, 192 MINN. L. REV. 2357, 2357 (2018).

²⁹⁰ *Id.*

²⁹¹ For a comprehensive treatment of the relationship between the FDA and the pharmaceutical industry, see Daniel Carpenter, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA, 38-43 (2010).

²⁹² Kapczynski, *Dangerous Times*, at 2358 ("The core function of the FDA as a drug regulator . . . is not to make choices for the public, or to certify the truth, but to generate and validate information about medicines.").

losses stemming from known risks of products may be expected to seek to understand more fully the likelihood and nature of those risks, and at the very least to inform prescribers about them at the earliest possible opportunity and to do so clearly and effectively. If information regarding adverse side effects exists, no-fault liability may create an incentive to advise the FDA and physicians sooner rather than later to reduce the incidence of those side effects. There will be no reason to delay informing about the risks, in fact, quite the contrary. Manufacturers who are in control of this information may be encouraged to share this information more quickly so that those risks can be minimized. If it does not, we will be no less informed about the incidence and risks of serious adverse events than we are now, and no challenge to the FDA's regulatory choices is involved. The effect of strict liability will be to compensate for losses caused without judgment of a failure in labeling adequacy.

Torts scholars have explained and debated the various theories that serve as a foundation for tort law.²⁹³ Some are based in instrumental goals of deterrence, others in ideas of corrective or social justice. An enterprise liability notion, based in notions of distributive justice, supports strict products liability, according to many academics,²⁹⁴ with which the author is in general agreement. Many scholars have similarly supported the argument that loss allocation to the producer leads to fair compensation for the injured consumer.²⁹⁵ The author generally supports the distributive rationale for products liability because fairness to consumers, who after all are benefactors for, not just beneficiaries of, the manufacturers whose products they use, is an important value. Recent tort scholarship recognizes that tort theory grounded in notions of civil recourse and upholding community values have an opportunity to revitalize the role of tort law.²⁹⁶

This Article advocates for strict liability for pharmaceuticals based on more than a fairness or justice rationale, however. Classic ultra-hazardous activity theory—compensating for the inevitable risk of serious

²⁹³ An introductory source to the many theoretical bases for tort law is John C.P. Goldberg, *Twentieth Century Tort Theory*, 91 GEO. WASH. L. J. 513 (2003).

²⁹⁴ Scholars have recently renewed calls for enterprise liability in the case of autonomous vehicles. Kenneth S. Abraham & Robert L. Rabin, *Automated Vehicles and Manufacturer Liability for Accidents: A New Legal Regime for New Era*, 105 VA. L. REV. (forthcoming 2019).

²⁹⁵ For an application of enterprise liability theory to pharmaceuticals, see Furrow, *supra* note 263.

²⁹⁶ See George W. Conk, *Will the Post-911 World be a Post-Tort World?*, 112 PENN. ST. L. REV. 175 (2007) (calling for a defense and revitalization of tort and embracing the Civil Recourse theory of Professors John Goldberg and Benjamin Zipursky); Christina C. Tilley, *Tort Law Inside Out*, 126 YALE L.J. 1320 (2017) (arguing that tort law is not primarily concerned with efficiency or morality as instrumentalists have contended, but rather with community, and that tort operates as vehicle through which communities perpetually re-examine and communicate their values).

harms from valuable but uncommon activities—coupled with a more contemporary notion of recognizing and enforcing community values of care and responsibility support a State’s choice to provide recourse to persons whose harm is caused in the course of seeking treatment for existing physical or mental ailments. The three undeniable features of the pharmaco-legal landscape identified in this Article have converged to exacerbate a problem of serious adverse events that befall patients: (1) the realities of the limitations of the federal regulatory system to identify the risks, both pre- and post-approval, from the use of pharmaceuticals and to act effectively to reduce them; (2) the realities of the pharmaceutical marketplace that influence prescribing and consuming practices in a way that increases the use of pharmaceuticals while reducing the likelihood that choices will be fully informed about potential risks; and (3) the restrictive application of federal preemption doctrine that has displaced long-standing state tort liability from its traditional role as a complementary regulatory and compensatory mechanism. These three features increase the risk of the hazardousness of the pharmaceutical choices being made for patients who are the bearers of both the burdens and benefits of drugs produced and marketed in a system structured to make full information of those risks undiscoverable.

Classic ultra-hazardous danger impacts a member of the community who cannot realistically be said to have assumed the risk because that risk is unusual or uncommon, and members of the community have no choice or power to prevent the risk from happening. Because of the importance and beneficial nature of pharmaceuticals, no one would suggest that consumers would not want such products to be available: we all expect to receive the benefit of drugs and no one expects to be the bearer of the negative side effects that may exist.²⁹⁷ The uncommonness of the activity is not a necessary condition for strict liability, however, simply a typical one.²⁹⁸ Liability attaches, more importantly, because of the lack of choice and inability to avoid the inevitable risk, as with the use of pharmaceuticals.

A liability rule that creates a disincentive to research and development of pharmaceuticals should be avoided. There is scant support for the proposition that liability rules have any effect on pharmaceutical de-

²⁹⁷ There are certainly circumstances when the risk of side effects is known and the consumer would choose to accept those in the hope for a positive outcome, such as with cancer patients.

²⁹⁸ Recent scholarship has questioned the value of the uncommonness element of ultrahazardous strict liability. See Steve Shavell, *The Mistaken Restriction of Strict Liability to Uncommon Activities*, J. of Legal Analysis (forthcoming 2019), available at SSRN: <https://ssrn.com/abstract=3298135>.

velopment, however.²⁹⁹ The current regulatory system has been shown to contain incentives to increase the approval of pharmaceuticals while failing to identify the full extent of risks that occur during the “life-cycle” of the drug after marketing. The role of a rule of liability is, in part, to seek out knowledge of such risks. The current regulatory system is failing in this regard, particularly regarding widely prescribed pharmaceuticals.

This Article proposes that the traditional tort liability system operate based on a strict no-fault liability basis that imposes liability on causation and damage alone. The criticisms of such a strict liability approach to pharmaceutical injuries falls into several categories. The tort liability system is expensive and inefficient to operate. Juries are unfair to corporate actors and only see an injured patient. Adverse drug events are often the result of a combination of factors that may involve medical negligence, or other causal contributors—how can liability be assessed fairly to the pharmaceutical company in such a circumstance?³⁰⁰ The piling-on of large numbers of unmeritorious or *de minimus*, claims will inevitably result. A litigation discovery system is no more likely to disclose the nature of an adverse drug event under a no-fault scheme than under the current litigation and regulatory system. There may be others. This Article advocates that strict tort liability is the proper basis for assessing responsibility: the mechanism for implementing that basis of liability will require additional discussion.

This Article makes the case that a fresh look at strict liability for pharmaceuticals is overdue. It takes a first pass at describing the justification in the current pharmaco-legal landscape for such a theory as well as noting grounding in tort scholarship for it. It does not answer all the questions that may arise. It does not quarrel with those who have advocated for no-fault compensation schemes to address pharmaceutical injuries.³⁰¹ It does, however, pose the question whether a state could choose to compensate someone like Karen Bartlett, who took a prescription pain medication for shoulder pain and was the one person who did not know

²⁹⁹ See Steven Garber, *Economic Effects of Product Liability and Other Litigation Involving the Safety and Effectiveness of Pharmaceuticals*, RAND INST. FOR CIV. JUST., xv (2013), <https://www.rand.org/pubs/monographs/MG1259.html> (There is little direct empirical evidence concerning the economic effects of product liability on pharmaceutical companies.); Furrow, *supra* note 263, at 417.

³⁰⁰ V. Jylha, K. Saranto & D. W. Bates, *Preventable Adverse Drug Events and Their Causes and Contributing Factors: The Analysis of Register Data*, 23 *INTERNAT'L J. FOR QUALITY IN HEALTH CARE* 187, 187–97 (2011).

³⁰¹ There have been many. See, e.g., Rodwin, *supra* note 151; Smirniotopoulos, *supra* note 275; James R. Copland, *Administrative Compensation for Pharmaceutical- and Vaccine-related Injuries*, 8 *IND. HEALTH L. REV.*, 275 (2011); Catherine T Struve, *The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation*, 5 *YALE J. HEALTH POL'Y, L. & ETHICS* 587 (2005); Yi-Chen Su, *Revisiting Factor VIII Cases: Is it Time for Agency Adjudication System?*, 63 *FOOD & DRUG L.J.* 943 (2008).

of the possibility of suffering a flesh-eating disease that covered 65 percent of her body.³⁰² It poses the question: when a cancer drug causes a serious side effect about which the patient is informed, should the patient be permitted to choose the cancer treatment and still be compensated for the harms from the side effect, if they occur? A state could, and based on the analysis presented in this Article, should conclude based on the inevitability and seriousness of the risk and on the community's values that the answer to both is "yes." Ultimately, the question remains: should every patient who suffers an adverse side effect be recognized as having suffered an injury in law? This Article suggests that the answer a state could, and should, give to this question is "Yes."

CONCLUSION

The pharmaceutical industry has its advocates and its detractors. Lives are saved and healed; lives are not saved and not healed. It is a trillion-dollar industry in the U.S. alone; it is largely in control of what it produces and chooses to market. Depending on whom you ask, it either does or doesn't spend too much on research and development. It either does or doesn't improperly influence prescribers with its sophisticated marketing practices. Whatever one says about how it is regulated, the federal regulatory system is a substantial one.

It is also true that uncompensated pharmaceutical injuries constitute a major public health concern. Adverse drug risks are inevitable and unavoidable; drugs are not optional for those seeking relief for illness, disease and injury. The use of and cost of pharmaceuticals continues to increase, and so do the incidence of adverse drug events.

This Article has chronicled the trends in the pharmaco-legal landscape in which we now live that have fundamentally changed, increasing the likelihood of adverse drug events. It also situates that landscape within a system that now includes aggressive federal preemption doctrines that defeat the traditionally operating state tort law formerly available to compensate persons injured from pharmaceuticals. The case for strict, no-fault, tort liability as a way to respond to this changed landscape is presented for serious, renewed consideration.

³⁰² See generally, *Mutuyal Pharmaceuticals v. Bartlett*, 570 U.S. 472 (2013).