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The Learned Intermediary Doctrine in the Digital World: Off-Label Marketing and the Reasonable Innovation Rule

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— Note —

THE LEARNED INTERMEDIARY
DOCTRINE IN THE DIGITAL WORLD:
OFF-LABEL MARKETING AND THE
REASONABLE INNOVATION RULE

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INTRODUCTION

In June of 2014, James McLeod went to the doctor seeking treatment for his non-life-threatening atrial fibrillation (“AFib”) and was prescribed amiodarone tablets.¹ After over a year of treatments, McLeod noticed that he had not only failed to see any improvements in his condition, but instead felt that his symptoms were worsening.² He began to feel a shortness of breath, wheezing, and coughing among other physical ailments until he was eventually admitted to a local

1. *McLeod v. Sandoz, Inc.*, No. 16-CV-01640, 2017 WL 1196801, at *2 (D.S.C. Mar. 31, 2017).

2. *Id.*

hospital in March of 2015.³ It was then that he discovered that his physical condition had deteriorated so drastically due to amiodarone toxicity.⁴ After being prescribe amiodarone just two years prior, McLeod developed Chronic Obstructive Pulmonary Disease, known as COPD.⁵

McLeod subsequently discovered that his prescription was for an “off-label” use of amiodarone.⁶ In the everyday practice of medicine, physicians are tasked with treating a diverse body of patients. Typically, physicians can follow standard treatment protocols because they are treating the average patient with a given condition. But physicians may also be faced with patients who have unique needs that cannot be treated with ordinary methods. In these circumstances, physicians must use their expertise and discretion to innovatively develop treatment plans for the unique needs of their patients. Often, physicians will do so by prescribing a drug for an off-label use.⁷

When the Food and Drug Administration (“FDA”) reviews new drugs for market approval, it only grants approval based on “label” uses, which are specific uses for certain patient populations (among other criteria).⁸ When a physician prescribes a drug for an off-label use, the physician is still prescribing an FDA-approved drug, only the FDA did not approve the drug for that specific use.⁹ As such, the drug did not go through efficacy trials for the off-label use as it would for an approved, label use, and its prescription does not include information about side effects and risks.¹⁰ As in McLeod’s case, physicians often do not tell their patients that they prescribed the drug for an off-label use,

3. *Id.*

4. *Id.*

5. *Id.*

6. *Id.*

7. See Katrina Furey & Kirsten Wilkins, *Prescribing “Off-Label”: What Should a Physician Disclose?*, 18 *AMA J. ETHICS* 587, 588–89 (2017); see also *Understanding Unapproved Use of Approved Drugs “Off Label,”* U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label> [<https://perma.cc/XC68-5REX>] (last updated Feb. 5, 2018).

8. See *Understanding Unapproved Use of Approved Drugs “Off Label,” supra* note 7.

9. 2 JAMES T. O’REILLY & KATHARINE A. VAN TASSEL, *FOOD AND DRUG ADMINISTRATION* § 15:59 (4th ed. 2020).

10. Furey & Wilkins, *supra* note 7, at 588–90.

partly because off-label drug use is common.¹¹ It is estimated that as many as one in five prescriptions are for an “off-label” use of a drug.¹²

Here, McLeod’s doctors prescribed amiodarone, the generic version of Cordarone. Cordarone is manufactured and distributed by Wyeth as a first line of therapy for ventricular fibrillation.¹³ Since amiodarone is the generic version of a brand-name drug, the FDA requires that the label is identical to the label of its brand equivalent.¹⁴ This means that the generic drug manufacturer can only provide label information (e.g., a description of the drug, warnings, adverse side effects) that is consistent with its brand equivalent.¹⁵ Additionally, the label can include only the FDA-approved uses of the drug.¹⁶ Therefore, the brand drug company is prohibited from advertising or distributing information (including risks) about an off-label use of a drug and as a result the generic equivalent is effectively restricted from distributing warnings about any off-label uses.

In this case, the manufacturer of the brand drug, Wyeth, received FDA approval only for Cordarone’s use “as a drug of ‘last resort’ for patients suffering from documented recurrent life-threatening ventricular fibrillation and ventricular tachycardia.”¹⁷ But Wyeth used a promotional campaign to market the off-label use of Cordarone as a first line of therapy for anti-arrhythmic benefits.¹⁸ This off-label promotion is how McLeod came to be prescribed amiodarone since, when he first sought treatment, he was able to manage his AFib and did not need amiodarone for the label use of last-resort medical treatment.¹⁹ Instead, McLeod’s prescription of amiodarone was for the off-label use as a first

11. *Id.* at 588, 590.

12. Elizabeth Richardson, *Health Policy Brief: Off-Label Drug Promotion*, HEALTH AFFS., June 30, 2016, at 1, https://www.healthaffairs.org/doi/10.1377/hpb20160630.920075/full/healthpolicybrief_159.pdf [<https://perma.cc/DG9X-Q3AF>].

13. *McLeod v. Sandoz, Inc.*, No. 16-CV-01640, 2017 WL 1196801, at *1 (D.S.C. Mar. 31, 2017).

14. *Generic Drug Facts*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/drugs/generic-drugs/generic-drug-facts> [<https://perma.cc/P9UU-K6MQ>] (last updated June 1, 2018).

15. *Drugs@FDA: What’s in a Drug Product Label?*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/drugs/drug-approvals-and-databases/drugs-fda-whats-drug-product-label> [<https://perma.cc/25AY-92Y2>] (last updated May 6, 2016).

16. *See* 2 O’REILLY & VAN TASSEL, *supra* note 9, § 15:19.

17. *McLeod*, 2017 WL 1196801, at *1.

18. *Id.*

19. *Id.*

line of therapy.²⁰ As a result of his injuries from the off-label use, McLeod sued the manufacturer of amiodarone for allegedly causing him to develop COPD.²¹

Despite his injuries, McLeod and others similarly situated face an uphill battle when litigating against pharmaceutical manufacturers. Across the country, plaintiffs struggle to hold drug manufacturers liable for injuries either caused by the manufacturer's promotion of a drug for an off-label use or deceptive marketing practices that misled consumers about the risks inherent to the drug.²² In part, this is because of the learned intermediary doctrine, a decades-old legal doctrine that helps shield drug manufacturers from liability.²³

The potential holes in liability created by the learned intermediary doctrine illustrate a larger issue in physician prescribing practices for off-label uses. Namely, that physicians are not held accountable for collecting patient data when they use reasonable innovation and prescribe a treatment off-label.²⁴ This absence of data has multiple implications. First, if the patient suffers an adverse outcome from using the drug off-label, the physician has no risk data that could help the patient substantiate a case against the prescription drug manufacturer. Relatedly, since manufacturers do not have their own risk data for off-label uses available because of FDA requirements, they can escape liability by claiming they had no knowledge of the risks involved.²⁵ Further, when physicians prescribe a drug off-label for all of their patients with a certain condition without registering with an Institutional Review Board ("IRB") and tracking the results, they are engaged in illegal human experimentation.²⁶

20. *Id.* at *1–2.

21. *Id.* at *1.

22. See 2 O'REILLY & VAN TASSEL, *supra* note 9, §§ 15:69, 26:1–2. Plaintiffs must show that a defendant manufacturer actually marketed and promoted a drug for its off-label use in violation of FDCA. *Carson v. Depuy Spine, Inc.*, 365 F. App'x 812, 815 (9th Cir. 2010).

23. See *infra* Part II.

24. See Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J. LAW MED. ETHICS 476, author manuscript at 6 (2009), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2836889/pdf/nihms-180818.pdf> [<https://perma.cc/VQF5-RFNP>]; see also C. Lee Ventola, *Off-Label Drug Information: Regulation, Distribution, Evaluation, and Related Controversies*, 34 PHARMACOLOGY & THERAPEUTICS 428, 432 (2009) (underscoring that physicians often fail to implement evidence-based strategies when prescribing off-label).

25. See Ventola, *supra* note 24, at 431 (describing avenues through which prescription drug manufacturers evade conducting renewed clinical research for off-label uses).

26. See Todd W. Rice, *How to do Human-Subjects Research if You do not Have an Institutional Review Board*, 53 RESPIRATORY CARE 1362, 1363 (2008),

To better protect patients, physicians should have access to a coordinated system of data collection for off-label prescriptions. If physicians are going to be prescribing off-label anyway, the best practice is to track information throughout the process. This data collection can be executed by implementing patient registries. To use patient registries, physicians must obtain the patient's informed consent, both to the off-label treatment and to submitting the patient's health information to the registry. This registry can then alert physicians of trends in adverse patient outcomes, which the physicians can then timely disclose to their patients. The registry can also send this patient data to the FDA for label change considerations. Further, the increased reliance on patient registries will diminish a drug manufacturer's ability to circumvent FDA regulations by claiming the risk information was not knowable because the registries are collecting it for them.

This Note will first address the regulatory and legal doctrines at play when a plaintiff attempts to recover from injuries caused by a prescription drug manufacturer: Part II examines the learned intermediary doctrine, Part III considers direct-to-consumer marketing, and Part IV reviews "off-label" drug promotion. In Part V, this Note recommends implementing patient registries whenever physicians are prescribing a drug off-label. The data collected by patient registries can protect patients without disrupting or adding an exception to the learned intermediary doctrine.

II. LEARNED INTERMEDIARY DOCTRINE

Under the regime for defective products liability, the Restatement (Third) of Torts outlines the potential liability for harm caused by prescription drug manufacturers. "A manufacturer of a prescription drug . . . who sells or otherwise distributes a defective drug . . . is subject to liability for harm to persons caused by the defect. A prescription drug . . . is one that may be legally sold or otherwise distributed only pursuant to a health-care provider's prescription."²⁷ A prescription drug manufacturer can avoid liability by invoking the learned intermediary doctrine ("LID"). According to the LID, if a manufacturer communicates the risks of a drug to the prescribing physician, then the manufacturer has no duty to warn the patient

<http://www.rcjournal.com/contents/10.08/10.08.1362.pdf> [<https://perma.cc/DT3B-873P>]; see Ventola, *supra* note 24, at 439.

27. RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6(a) (AM. L. INST. 1998).

directly.²⁸ The healthcare provider is then considered a “learned intermediary” between the manufacturer and the consumer.²⁹

A. *Liability Under the Learned Intermediary Doctrine*

The LID is based on the presumption that healthcare providers are the ones best suited to evaluate and weigh the attendant risks and benefits of a given drug for each individual patient.³⁰ This presumption thereby creates a duty for the healthcare provider to relay relevant information to the patient so the patient can make informed treatment decisions.³¹ Through the LID, prescription drug manufacturers effectively discharge their duty to give warnings to the consumer by providing warnings to the healthcare provider. “A prescribing physician who has been adequately warned about a drug’s risks breaks ‘the causal link between the manufacturer and the plaintiff, thereby insulating the manufacturer from tort liability for harm caused by the drug.’”³² If a manufacturer fulfills its duty to warn the prescribing physician, then the manufacturer has a strong defense against liability³³ because “[t]he learned intermediary doctrine precludes a tort plaintiff from recovering for any injuries sustained from use of the drug unless she can show that the warnings were inadequate as to prescribing physicians.”³⁴

If a plaintiff can persuade a court that her injuries were caused by the manufacturer’s failure to adequately warn the learned intermediary, then the manufacturer may be held liable.³⁵ Conversely, if the manufacturer provided adequate warnings to the intermediary, but the intermediary failed to adequately communicate these risks to the patient, then the patient can only make a claim against the healthcare

28. See 2 O’REILLY & VAN TASSEL, *supra* note 9, § 15:25.

29. See RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6 reporters’ note to cmt. d (AM. L. INST. 1998).

30. *Id.* § 6 cmt. b.

31. *Id.* There may be some limited circumstances when drugs will be administered to patients without prior evaluation by a healthcare provider (e.g., mass vaccinations administered in clinics); thus, it will be appropriate for the manufacturer to warn the patient directly in some instances. See *id.* § 6(d)(2) & cmt. e.

32. 2 O’REILLY & VAN TASSEL, *supra* note 9, § 26:52 (quoting *Zanzuri v. G.D. Searle & Co.*, 748 F. Supp. 1511, 1515 (S.D. Fla. 1990)).

33. DAN B. DOBBS, PAUL T. HAYDEN & ELLEN M. BUBLICK, *DOBBS’ LAW OF TORTS* § 466 (2d ed. 2020).

34. 2 O’REILLY & VAN TASSEL, *supra* note 9, § 26:52.

35. See *id.*; see also *Simon v. Wyeth Pharm., Inc.*, 989 A.2d 356, 375–76 (Pa. Super. Ct. 2009) (finding that the plaintiff satisfied the causation requirement by presenting evidence that her doctor would not have prescribed a hormone-replacement drug had its manufacturer informed doctor of the risk of breast cancer).

provider who acted as the intermediary, not the manufacturer.³⁶ The manufacturer satisfies its duty under the LID once it has provided information about the risks to the physician; “[w]hether the physician in fact reads the warning, or passes its contents along to the recipient of the drug is irrelevant.”³⁷

A prescription drug manufacturer’s duty to warn of the risks of its drug is limited to the risks that are reasonably foreseeable at the time of sale.³⁸ From a public policy perspective, courts do not want to impose liability for unforeseeable risks at the expense of discouraging the development and sale of new drugs into the market.³⁹ Drug manufacturers are still responsible for performing reasonable tests for risks before their drug goes to market, but it would be impossible for manufacturers to accurately insure against unknowable risks.⁴⁰ Accordingly, the LID provides a broad shield of protection for prescription drug manufacturers from injured consumers.

Traditionally, drug manufacturers have been held liable only for harm caused by their products in two situations: (1) when their drug contains a manufacturing defect; and (2) when their drug is sold without the manufacturer supplying adequate warnings to the prescribing physician.⁴¹ Of particular import in this discussion is the more recent practice of imposing liability for “defectively designed” products. Unlike other forms of product liability, courts have relied upon the LID to shield drug manufacturers from tort liability, in part, because of the unique characteristics inherent in prescription drugs, i.e., a drug that may cause harm to one patient may be beneficial to another.⁴² Because of this, the Restatement characterizes a drug as a “defective[ly] design[ed]” product only when the risk of harm is so great in comparison to the potential benefits that no “reasonable health-care provider[], knowing of such foreseeable risks and therapeutic benefits, would . . . prescribe the drug . . . for any class of patients.”⁴³ Put another way, even if a drug is harmful to some patients, it is not

36. DOBBS ET AL., *supra* note 33, § 466.

37. *Guarino v. Wyeth, LLC*, 719 F.3d 1245, 1250 (11th Cir. 2013) (quoting *E.R. Squibb & Sons, Inc. v. Farnes*, 697 So. 2d 825, 827 (Fla. 1997)).

38. RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6 cmt. g (AM. L. INST. 1998).

39. *See id.*

40. *Id.*

41. *Id.* cmt. a. Note that non-prescribing healthcare providers, for example doctor’s assistants, must also be warned if they interact with the patient in a decision-making capacity. *Id.* reporters’ note to cmt. d (citing *McEwen v. Ortho Pharm. Corp.*, 528 P.2d 522, 529 (Or. 1974)).

42. *Id.* cmt. b.

43. *Id.* § 6(c).

considered defectively designed if it is an effective treatment for any other class of patients.⁴⁴ If a plaintiff can meet this high bar and prove that a prescription drug was defectively designed, then the manufacturer will be held liable for the harm caused by the negligent design.⁴⁵

Over the past few decades, state courts across the country have cited a myriad of reasons to support their reliance on the LID.⁴⁶ Most notably, courts have cited the lack of feasibility for manufacturers to communicate warnings directly to consumers,⁴⁷ the marked interference such warnings could have on the doctor-patient relationship,⁴⁸ the concern that warnings would “drive some patients to hysteria,”⁴⁹ and the presumption that the manufacturer can reasonably rely on the intermediary to communicate risks to the patient and that the patient will correspondingly rely on the intermediary’s advice.⁵⁰ In response, critics of the courts’ continued invocation of the LID assert that healthcare providers cannot be reasonably relied upon to communicate

44. *Id.* cmt. b.

45. *Marroquin v. Pfizer, Inc.*, 367 F. Supp. 1152, 1163–64 (E.D. Cal. 2019); RESTATEMENT (SECOND) OF TORTS, § 402A cmt. k (AM. L. INST. 1965) (“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.”).

46. DOBBS ET AL., *supra* note 33, § 466 (“Courts have asserted several reasons for the learned-intermediary rule.”).

47. *Id.* (“They have said for example that warnings to the consumer are not feasible . . .”).

48. *In re Certified Questions*, 358 N.W.2d 873, 883 (Mich. 1984) (Boyle, J., dissenting) (expressing the concern that, in some instances, directly warning the patient “could potentially cause undue interference with the doctor-patient relationship [and] cause patient confusion”).

49. DOBBS ET AL., *supra* note 33, § 466.

50. *Id.* (citing *Larkin v. Pfizer, Inc.*, 153 S.W.3d 758, 763–64 (Ky. 2004); *MacDonald v. Ortho Pharm. Corp.*, 394 N.E.2d 131, 136 (Mass. 1985)); *see also* *West v. Searle & Co.*, 806 S.W.2d 608, 613–14 (Ark. 1991) (reasoning that the provider is the best at assessing risks and benefits); *Brown v. Superior Court*, 751 P.2d 470, 478–79 (Cal. 1988) (expressing the concern that increasing manufacturer liability would increase drug prices and make them less available); *Niemiera v. Schneider*, 555 A.2d 1112, 1118 n.3 (N.J. 1989) (relying on the FDA’s existing regulatory framework as an already incredibly detailed system to set and control standards for safety, efficacy and labeling); *Gravis v. Parke-Davis & Co.*, 502 S.W.2d 863, 870 (Tex. App. 1973) (relying on the system of drug and healthcare administration to hold those in such professions accountable).

drug risks to patients.⁵¹ Those scholars have argued that the high-pressure and time-crunched schedules of physicians may actually make them unreliable intermediaries, consequently making it much less reasonable for drug manufacturers to rely upon physicians to pass on adequate risk information to consumers.⁵² If this rationale is assumed, it would undermine the presumption that the prescribing physician is a reliable intermediary, which is critical to the logic of the LID.

An essential rationale for the LID is that prescribing physicians have specialized knowledge.⁵³ In *Tutwiler v. Sandoz, Inc.*,⁵⁴ the Eleventh Circuit's decision turned on the important distinction between a manufacturer's failure to warn the physician and the physician's failure to change her prescribing behavior based on a manufacturer's warning. "The adequacy of the manufacturer's warning is 'measured by its effect on the physician . . . to whom it owed a duty to warn, and not by its effect on the consumer.'"⁵⁵ In *Tutwiler*, the plaintiff suffered pulmonary complications after taking amiodarone for her non-life-threatening atrial fibrillation.⁵⁶ The plaintiff alleged that because she did not receive the manufacturer's Medication Guide from her physician, she was not fully aware of the risks of the drug.⁵⁷ The court dismissed the plaintiff's claims by applying the LID, reasoning that it is not enough for the plaintiff to argue that she herself would have acted differently if she had received different information; rather, plaintiffs must present evidence that the prescribing physician would have made a different treatment decision had the physician been made aware of additional warnings.⁵⁸

B. *Exceptions to the Learned Intermediary Doctrine*

Courts have held that the LID does not apply—and thus liability attaches for a drug manufacturer's failure to warn the consumer

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51. DOBBS ET AL., *supra* note 33, § 466 (citing Teresa Moran Schwartz, *Consumer-Directed Prescription Drug Advertising and the Learned Intermediary Rule*, 46 FOOD DRUG COSM. L.J. 829, 831 (1991)).
 52. *See* Teresa Moran Schwartz, *Consumer-Directed Prescription Drug Advertising and the Learned Intermediary Rule*, 46 FOOD DRUG COSM. L.J. 829, 831 (1991).
 53. *Cf.* RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6 cmt. b (AM. L. INST. 1998) ("The rationale supporting this 'learned intermediary' rule is that only health-care professionals are in a position to understand the significance of the risks involved . . .").
 54. 726 F. App'x 753 (11th Cir. 2018).
 55. *Id.* at 756 (quoting *Wyeth, Inc. v. Weeks*, 159 So. 3d 649, 673 (Ala. 2014)).
 56. *Id.* at 754.
 57. *Id.*
 58. *Id.* at 757.

directly—in three circumstances: vaccine administration in mass-vaccination settings,⁵⁹ the prescription of contraceptives,⁶⁰ and the use of marketing campaigns that directly target consumers.⁶¹ In mass-inoculation settings, the healthcare providers are not in a position to relate the risks of the drug to each individual patient. Therefore, the law requires that the manufacturer warn the patient directly, so long as feasible and effective means for doing so are available.⁶² With contraceptives, the FDA requires that manufacturers include a package insert that contains patient warnings with each set of pills.⁶³ When executing mass advertising campaigns for a drug directly to the consumer, the manufacturer is required by federal regulations to accurately convey the risks associated with a drug in the advertisement.⁶⁴

More recently, courts have started applying a fourth exception for pharmacists. The exception for pharmacists is grounded in the distinction between the duty to communicate general risks about drug side effects and the duty to communicate specific risks that are known to the pharmacist.⁶⁵ Such specific risks uniquely knowable by the pharmacist may, for example, be if an excessive quantity of a particular drug is being filled or if the FDA has recently withdrawn the drug from the market.⁶⁶ Additional exceptions to the LID may be recognized at the state level, but the Restatement leaves the application of additional

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59. *See, e.g.*, *Davis v. Wyeth Laboratories, Inc.*, 399 F.2d 121, 131 (9th Cir. 1968).
60. *See, e.g.*, 1 O'REILLY & VAN TASSEL, *supra* note 9, § 14:53 (4th ed. 2020).
61. *See* RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6 reporters' note to cmt. e (AM. L. INST. 1998).
62. *Id.*; DOBBS ET AL., *supra* note 33, § 466.
63. RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6 cmt. e (AM. L. INST. 1998); 21 C.F.R. § 310.501 (2019). *But see* *West v. G.D. Searle & Co.*, 879 S.W.2d 412, 414 (Ark. 1994) (stating that no direct warning to the consumer was given, but, nevertheless, the defendant complied with the regulatory requirements); *Martin v. Ortho Pharm. Corp.*, 661 N.E.2d 352, 354–57 (Ill. 1996).
64. RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6 cmt. e (AM. L. INST. 1998). *But see* *Watts v. Medicis Pharm. Corp.*, 365 P.3d 944, 949–51 (Ariz. 2016) (declining to adopt the marketing exception by acknowledging that no other courts have adopted it and that the Restatement Third's "different exception"—under which a warning to a patient is required "when the manufacturer knows or has reason to know that health-care providers will not be in a position to reduce the risks of harm in accordance with the instructions or warnings"—served a similar function (quoting *id.* § 6(d))).
65. DOBBS ET AL., *supra* note 33, § 466; *see* *Downing v. Hyland Pharmacy*, 194 P.3d 944, 949 (Utah 2008) (holding that the LID did not preclude a negligence action against a pharmacy for filling prescriptions for a drug that the FDA had withdrawn from the market).
66. DOBBS ET AL., *supra* note 33, § 466.

exceptions up to “developing case law.”⁶⁷ Even in light of these exceptions, the LID grants significant protection to prescription drug manufacturers, thereby making redress for injured patients more challenging.

III. DIRECT-TO-CONSUMER MARKETING

Under the LID framework, a prescription drug manufacturer has no duty to directly warn the patient of risk information if the manufacturer gives an adequate warning to the prescribing physician. However, the popularization of direct-to-consumer (“DTC”) marketing has changed the way patients receive information about their treatments. DTC marketing is advertising by a pharmaceutical company that targets consumers directly.⁶⁸ This direct line of communication between the manufacturer and consumer disrupts many presumptions of the LID, including that the manufacturer lacks an effective means of communication with the consumer and that the physician is the only party directly receiving risk-benefit information within the physician-patient relationship.⁶⁹ The potential that the harms of DTC may outweigh the benefits has called the attention of the FDA and courts, and this scrutiny is discussed in turn.

A. *FDA Regulation of Direct-to-Consumer Marketing*

In the 1962 amendments to the Food, Drug and Cosmetic Act (“FDCA”), Congress granted the FDA the authority to regulate prescription drug advertising.⁷⁰ The FDA has comprehensive jurisdiction over pharmaceutical advertising, “includ[ing] advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems.”⁷¹ In response to the rise of DTC advertising, the FDA has promulgated regulations to control and mitigate the risk that consumers will be misled by drug advertisements.⁷² The FDA primarily evaluates a manufacturer’s use of DTC

67. RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6 reporters’ note to cmt. e (AM. L. INST. 1998).

68. 1 CHARLES S. ZIMMERMAN, PHARMACEUTICAL AND MEDICAL DEVICE LITIGATION § 3:2 (2018).

69. See 2 O’REILLY & VAN TASSEL, *supra* note 9, § 15:25.

70. See 21 U.S.C. § 352 (2018); James L. Zelenay Jr., *The Prescription Drug User Fee Act: Is a Faster Food and Drug Administration Always a Better Food and Drug Administration?*, 60 FOOD & DRUG L.J. 261, 266 (2005).

71. 21 C.F.R. § 202.1(l)(1) (2019).

72. Victor E. Schwartz, Cary Silverman, Michael J. Hulka & Christopher E. Appel, *Marketing Pharmaceutical Products in the Twenty-First Century: An Analysis of the Continued Viability of Traditional Principles of Law in*

marketing through the “major statement rule.”⁷³ The major statement rule “requires the manufacturer to present a major statement that represents a ‘fair balance of risks and benefits’ as well as lists any side effects or contraindications of the drug.”⁷⁴ The FDA attempts to protect consumers against misleading marketing campaigns by requiring that such advertisements “provide information that is truthful, balanced, and accurately described.”⁷⁵ The manufacturer will also be subject to penalties if the advertisements are false, do not fairly balance the benefits of the drug against the side effects, or are otherwise misleading.⁷⁶

Research by the FDA indicates that DTC advertisements tend to give consumers “an exaggerated sense of . . . benefits” while simultaneously only providing part of the picture when it comes to the risks of a drug.⁷⁷ Proponents of DTC marketing argue that drug advertisements help bolster a patient’s right to be informed about new treatments,⁷⁸ and manufacturers purport that these advertisements encourage consumers to take a more active role in their healthcare.⁷⁹ Conversely, critics argue that DTC advertisements interfere with the doctor-patient relationship and encourage the overprescribing of medications, among other issues.⁸⁰ Concerns ranging from the downplaying of potential product side effects to ads influencing consumers to demand unnecess-

the Age of Direct-to-Consumer Advertising, 32 HARV. J.L. & PUB. POL’Y 333, 344–46 (2009).

73. Y. Tony Yang & Brian Chen, *Legal Considerations for Social Media Marketing by Pharmaceutical Industry*, 69 FOOD & DRUG L.J. 39, 44 (2014).

74. *Id.*

75. *Background on Drug Advertising*, FOOD & DRUG ADMIN., <https://www.fda.gov/drugs/prescription-drug-advertising/background-drug-advertising#:~:text=FDA%20Authority%20Over%20Advertising,-We%20serve%20the&text=Our%20authority%20is%20based%20on,be%20accurate%20and%20not%20misleading> [<https://perma.cc/7682-TPRJ>] (last updated June 19, 2015).

76. 21 C.F.R. § 202.1(e)(5)–(7) (2008).

77. Anna Wilde Mathews, *FDA to Review Drug Marketing to Consumers*, WALL ST. J. (Aug. 2, 2005), <https://www.wsj.com/articles/SB112294184051402127> [<https://perma.cc/38E4-TQQL>]; KATHRYN J. AIKIN, JOHN L. SWASY & AMIE C. BRAMAN, PATIENT AND PHYSICIAN ATTITUDES AND BEHAVIORS ASSOCIATED WITH DTC PROMOTION OF PRESCRIPTION DRUGS—SUMMARY OF FDA SURVEY RESEARCH RESULTS 107 (2004), <https://www.fda.gov/media/112016/download> [<https://perma.cc/QBD4-JS68>].

78. ZIMMERMAN, *supra* note 68, § 3:2.

79. *Id.*

80. *Id.*

ary prescriptions have prompted heavy scrutiny of the practice from not only the FDA but Congress as well.⁸¹

In addition to FDA regulations, the Federal Trade Commission (“FTC”) imposes similar enforcement mechanisms to protect consumers from unfair and deceptive trade practices.⁸² While the FDA has the primary responsibility for regulating advertising of prescription drugs specifically, the FTC “has primary responsibility with respect to the regulation of the truth or falsity of all advertising (other than labeling) of foods, drugs, devices, and cosmetics.”⁸³ FTC guidance on drug advertising has purposes similar to those of the FDA: “(1) to ensure advertising is truthful and non-misleading, and (2) that prior to releasing an advertisement on a product, any objective product claims have been substantiated.”⁸⁴ Allegations of deceit or fraud on the part of the manufacturer have particular relevance when scrutinizing labeling issues.⁸⁵

B. The Effect of Direct-to-Consumer Marketing on Application of the Learned Intermediary Doctrine

The Restatement (Third) does not explicitly advise whether courts should allow an exception to the LID for manufacturers that advertise directly to consumers.⁸⁶ In one respect, the use of DTC marketing may call into question the continued application of the LID by altering the underlying presumption that “drug manufacturers do not participate in the patient-physician decision.”⁸⁷ Even so, courts may still find that DTC marketing should have little to no effect on the application of the LID, taking the Fifth Circuit’s stance that “as long as a physician-

81. Mathews, *supra* note 77; AIKIN, SWASY & BRAMAN, *supra* note 77, at 107.

82. *See* 15 U.S.C. § 45 (2018).

83. *Memorandum of Understanding Between the Fed. Trade Comm’n and the Food & Drug Admin.*, U.S. FOOD & DRUG ADMIN. (April 27, 1971), <http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm115791.htm> [<https://perma.cc/9NQD-XQNG>].

84. Megan Smith-Mady, *Celebrity Drug Endorsements: Are Consumers Protected?*, 43 AM. J.L. & MED. 139, 152 (2017).

85. 2 O’REILLY & VAN TASSEL, *supra* note 9, § 15:18.

86. RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6 reporters’ note to cmt. e. (AM. L. INST. 1998); *see In re Norplant Contraceptive Prods. Liab. Litig.*, 215 F. Supp. 2d 795, 815–16 (E.D. Tex. 2002); *Watts v. Medicis Pharm. Corp.*, 342 P.3d 847, 855 (Ariz. Ct. App. 2015), *vacated*, 365 P.3d 944 (Ariz. 2016); *Perez v. Wyeth Laboratories*, 734 A.2d 1245, 1257 (N.J. 1999).

87. Yang & Chen, *supra* note 73, at 45.

patient relationships exists, the learned intermediary doctrine applies.”⁸⁸

Since the duty to warn in DTC advertising cases is government mandated, if a court finds that a manufacturer has complied with relevant federal regulations, then the court may subsequently hold that any related state tort claims are federally preempted.⁸⁹ In *Perez v. Wyeth Laboratories*,⁹⁰ the New Jersey Supreme Court became the first state high court to recognize DTC marketing as an exception to the LID.⁹¹ In *Perez*, the plaintiffs experienced complications after having the Norplant contraceptive implanted. The plaintiffs asserted that the manufacturer should be held liable for their injuries because Wyeth executed a mass advertising campaign that was both directed at consumers and did not provide adequate warnings about the inherent dangers in using Norplant.⁹² In this landmark opinion, the New Jersey Supreme Court held that the LID did not shield the manufacturer from liability when the manufacturer sought to influence patients through targeted marketing campaigns.⁹³

As support for its decision to adopt a DTC marketing exception, the *Perez* court cited the ways in which the administration of healthcare has changed since the LID was first adopted.⁹⁴ Specifically, the court noted that when the LID was first adopted, medical advice was primarily received at the doctor’s office, prescriptions were filled at neighborhood pharmacies, and “the prevailing attitude of law and medicine was that the ‘doctor knows best.’”⁹⁵ By the time of this opinion, and even more so today, the landscape of healthcare administration has changed dramatically.⁹⁶ The court reasoned that the rise of managed care organizations, the increased accessibility of prescription

88. *In re Norplant Contraceptive Prods. Liab. Litig.*, 165 F.3d 374, 379 (5th Cir. 1999).

89. RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6 reporters’ note to cmt. e (AM. L. INST. 1998).

90. 734 A.2d 1245 (N.J. 1999).

91. Corey Schaecher, “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, 438 (2007).

92. *Perez*, 734 A.2d at 1248.

93. *Id.* at 1264.

94. *Id.* at 1246–47, 1263.

95. *Id.* at 1246–47 (quoting *Logan v. Greenwich Hosp. Ass’n*, 465 A.2d 294, 299 (Conn. 1983)).

96. *Id.*; Aaron George, *The Physician-Patient Relationship Has Changed*, MED. ECON. (Feb. 25, 2020), <https://www.medicaleconomics.com/view/physician-patient-relationship-has-changed> [https://perma.cc/6DQ9-6JZ3].

drugs, and the pervasiveness of mass marketing campaigns have changed the context within which the LID is applied and warranted rethinking the application of the LID in the DTC context.⁹⁷

Since the decision in *Perez*, only a few other courts have considered applying a DTC exception to the LID.⁹⁸ In *In re Norplant Contraceptive Products Liability Litigation*,⁹⁹ a federal district court in Texas considered a case that also involved injuries sustained from Norplant.¹⁰⁰ The court acknowledged *Perez*, but because “no other court in any jurisdiction ha[d] directly addressed an advertising exception to the learned intermediary doctrine, making New Jersey the only jurisdiction to recognize this exception,” it declined to extend the DTC exception.¹⁰¹

A few other courts have called the LID into question based on DTC marketing, but *Perez* remains the only court to formally recognize a DTC exception. In *State ex rel. Johnson & Johnson Corp. v. Karl*,¹⁰² the decedent was prescribed a heartburn medication by her primary care physician and died unexpectedly just three days after she began taking the drug.¹⁰³ The Supreme Court of Appeals of West Virginia held that prescription drug manufacturers have the same duty to warn as other product manufacturers, thereby rejecting the LID.¹⁰⁴ However, this decision has since been superseded by a West Virginia statute that adopted the LID.¹⁰⁵

In light of the pervasiveness of DTC marketing campaigns, the Arizona Supreme Court held “that the learned intermediary principle is inconsistent with the state’s later-implemented comparative fault tort system because it allows a prescribing physician to bear all the responsibility for an inadequate warning given to a consumer, even if a manufacturer played a part in making the warning insufficient.”¹⁰⁶ In

97. *Id.* at 1255–56, 1263.

98. DIANE FENNER & JAMES A. MORRIS, JR., 5 LITIGATING TORT CASES § 60:35 (2019).

99. 215 F. Supp. 2d 795 (E.D. Tex. 2002).

100. *Id.* at 800.

101. *Id.* at 812. The *Norplant* court also noted that, at the time of the case, 48 states, the District of Columbia, and Puerto Rico all had either applied or recognized the LID without any relevant exceptions for Norplant. *Id.* at 806.

102. 647 S.E.2d 899 (W. Va. 2007).

103. *Id.* at 901.

104. *Id.* at 914.

105. W. VA. CODE § 55-7-30 (2016); J.C. *ex rel. Michelle C. v. Pfizer, Inc.*, 814 S.E.2d 234, 238 n.9 (W. Va. 2018).

106. 2 O’REILLY & VAN TASSEL, *supra* note 9, § 15:25 (footnote omitted).

this case, *Watts v. Medicis. Pharmaceutical Corp.*,¹⁰⁷ the plaintiff suffered from drug-induced lupus after taking acne medication.¹⁰⁸ The plaintiff argued that the manufacturer advertised the drug under false pretenses by omitting material risks in order to influence consumers to buy the product.¹⁰⁹ The Arizona Court of Appeals refused to apply the LID, in part because of the manufacturer's use of DTC marketing, which the court reasoned had both misled consumers and changed the nature of the relationship between the consumer and the "learned intermediary."¹¹⁰ The decision in *Watts* was ultimately vacated by the Arizona Supreme Court, which declined to recognize a DTC exception to the LID.¹¹¹ Instead of creating a DTC exception to protect consumers from deceptive marketing practices, the Court relied on section 6(d)(2) of the Third Restatement of Torts.¹¹² This Restatement section requires that prescription drug manufacturers provide information on risks directly to consumers "when the manufacturer knows or has reason to know that health-care providers will not be in a position to reduce the risks of harm in accordance with the instructions or warnings."¹¹³

Even when pharmaceutical manufacturers launch extensive promotional campaigns, plaintiffs must prove the prescribing physician was actually misled by the advertisements.¹¹⁴ In *Dean v. Eli Lilly & Co.*, the Second Circuit declined to extend an LID exception even though the manufacturer extensively promoted the drug at issue.¹¹⁵ In *Dean*, the plaintiff asserted a failure-to-warn claim under state law, alleging that he developed diabetes from his schizophrenia medication.¹¹⁶ The court rejected the plaintiff's claims because of his failure to cite any evidence that the overpromotion actually induced his physician to prescribe the medication.¹¹⁷ Even though the court acknowledged that "the record reflect[ed] a vigorous sales campaign," it found the lack of evidence demonstrating that the manufacturer's marketing campaign had

107. 342 P.3d 847 (Ariz. Ct. App. 2015), *vacated*, 365 P.3d 944 (Ariz. 2016).

108. *Id.* at 849.

109. *Id.* at 849–50.

110. *Id.* at 855–56.

111. *Watts*, 365 P.3d at 953.

112. *Id.* at 950.

113. *Id.* at 950 (quoting RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6(d)(2) (AM. L. INST. 1998)).

114. *Dean v. Eli Lilly & Co.*, 387 F. App'x. 28, 30 (2d Cir. 2010).

115. *Id.* at 30.

116. *Id.* at 29.

117. *Id.* at 30.

actually misled the plaintiff's physician about the link between the drug and the development of diabetes to be fatal to the plaintiff's claims.¹¹⁸

The courts' failure to extend a DTC exception to the LID comes in stark contrast to the pervasiveness of DTC advertising in the prescription drug industry. A 2005 study reported that, in just the previous year, Pfizer had spent \$668 million on DTC advertising, Merck had spent \$348 million, and Johnson & Johnson had spent \$335 million.¹¹⁹ Interestingly, only two developed countries, the United States and New Zealand, allow drug companies to advertise through mass media marketing campaigns.¹²⁰ Nevertheless, as long as drug manufacturers remain compliant with relevant federal regulations, precedent indicates that the large majority of state courts will continue to apply the LID despite the harmful effects DTC marketing campaigns may have on the consumer.

IV. OFF-LABEL DRUG USE AND PROMOTION

The FDA has distinct regulatory requirements for a manufacturer's promotion of a drug for an off-label use. An "off-label" use of a drug refers to the use of a drug for something other than that for which the FDA has approved the drug.¹²¹ The "off-label use of drugs" can also describe the prescription of drugs "for indications and in dosages other than those expressly approved by the FDA."¹²² As long as a drug is approved by the FDA for some purpose, a physician can prescribe that drug for an off-label use without violating any FDA regulations or federal laws.¹²³ Physicians must be diligent, however, in their off-label prescribing practices in order to remain compliant with FDA standards. When a physician needs to deviate from customary care and prescribe a drug for an off-label use, the physician must only use reasonable innovation to do so.¹²⁴ The reasonable innovation rule allows physicians to deviate from the norm and prescribe off-label based on the unique needs of the patient without running afoul of FDA regulations.¹²⁵

118. *Id.*

119. 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> [<https://perma.cc/A8LB-4MU9>].

120. Yang & Chen, *supra* note 73, at 41.

121. 2 O'REILLY & VAN TASSEL, *supra* note 9, § 15:59.

122. *Id.* § 15:66.

123. *Id.*

124. *See* Brook v. St. John's Hickey Mem'l Hosp., 380 N.E.2d 72, 76 (Ind. 1978) (applying the reasonable innovation rule in practice).

125. *Id.*

A. *FDA Regulation of Off-Label Use*

1. FDA Label Approval Process

As a regulatory matter, the FDA recognizes both that physicians prescribe off-label and that the FDCA does not place limitations on how a physician may use an approved drug.¹²⁶ By permitting physicians to prescribe drugs off-label, regulators allow physicians to exercise some degree of creativity in the way they treat each individual patient. “Once the FDA has cleared a device for introduction into the stream of commerce, physicians may use the device in any manner they determine to be best for the patient, regardless of whether the FDA has approved the device for this usage.”¹²⁷ “Off-label use does not violate federal law or FDA regulations because the FDA regulates the marketing and distribution of drugs in the United States, not the practice of medicine, which is the exclusive realm of individual states.”¹²⁸ “Once a product has been approved for marketing, a physician may choose to prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling.”¹²⁹

The FDA conducts its approval process for new drugs by reviewing the proposed labeling for the drug. A drug’s label includes all proposed claims about the drug’s risks and benefits and adequate directions for use.¹³⁰ The FDA will approve a drug only if the uses approved by the FDA mirror the label uses.¹³¹ The approval process additionally entails reports by the manufacturer on the safety and efficacy of their drug.¹³² All in all, from development to approval, getting a new drug on the market takes considerable time and money. Estimates indicate that it takes an average of approximately fifteen years for a drug to go from the early stages of research to approval by the FDA.¹³³ It is additionally

126. *Foreword to the 62nd Edition of PHYSICIANS’ DESK REFERENCE* (62d ed. 2008).

127. *Cooper v. Smith & Nephew, Inc.*, 259 F.3d 194, 197 (4th Cir. 2001).

128. 2 O’REILLY & VAN TASSEL, *supra* note 9, § 15:66.

129. *Foreword to the 62nd Edition of PHYSICIANS’ DESK REFERENCE* (62d ed. 2008).

130. *See* 21 U.S.C. § 355 (2018).

131. 2 O’REILLY & VAN TASSEL, *supra* note 9, §§ 15:18–19.

132. *Id.* § 15:18.

133. *See* Richard J. Findlay, *Originator Drug Development*, 54 *FOOD & DRUG L.J.* 227, 228 (1999).

estimated that the average monetary investment in a newly approved drug is over \$1 billion dollars.¹³⁴

Since the FDA's approval process is narrowly tailored to the factors (such as dose and patient population) studied for a specified use, any additional on-label use of that drug will require separate approval from the FDA.¹³⁵ This means that if a manufacturer wants to change the label of its drug or wants to market the drug for an off-label use, then the manufacturer has to conduct additional clinical trials, among other steps, to obtain FDA approval for that additional use.¹³⁶ On top of the extra time and expense required to conduct more clinical trials, drug manufacturers have incentives for *not* trying to gain approval for a new use of a market drug. For one, the manufacturer already enjoys the profits of the drug since it is already on the market. Since physicians have the freedom to prescribe the drug for an off-label use, there is little monetary incentive for the manufacturer to conduct trials for additional uses. Moreover, FDCA regulations prohibit manufacturers from disseminating risk-benefit information about off-label uses anyway.¹³⁷ Therefore, even if the manufacturer were to conduct trials to gather this risk-benefit information, it would be prohibited from distributing the results.

2. FDA Regulations on the Promotion of Off-Label Uses

In general, the FDA's narrow label approvals resulted in a vast growth of off-label prescribing.¹³⁸ As noted in Section III, the FDA employs an expansive regulatory scheme that prohibits drug manufacturers from advertising their drug in a way that deceives or misleads the consumer.¹³⁹ In addition, the FDA prohibits prescription drug manufacturers from marketing their drugs for uses that do not have FDA approval, i.e., off-label uses.¹⁴⁰ "Permitting manufacturers to promote off-label uses of a new drug would completely undermine the

134. Peter Landers, *Cost of Developing a New Drug Increases to About \$1.7 Billion*, WALL ST. J. (Dec. 8, 2003, 12:01 AM), <https://www.wsj.com/articles/SB107083909136415400> [<https://perma.cc/573S-AHZM>].

135. Santosh V. Coutinho, *License to Promote, or Just What the Doctor Ordered? The New FDA Guidance on Dissemination of Off-Label Reprints by Pharmaceutical Companies*, 28 TEMP. J. SCI. TECH & ENV'T L. 279, 287–88 (2009).

136. *Id.* at 288.

137. *See* 21 U.S.C. § 352 (2020).

138. Sandra H. Johnson, *Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims Regarding Off-Label Prescribing*, 9 MINN. J.L. SCI. & TECH. 61, 68 (2008).

139. Schwartz et al., *supra* note 72, at 344–46.

140. Coutinho, *supra* note 135, at 281.

government's interest in subjecting off-label uses to the FDA evaluation process as well as the government's interest in preserving the integrity of the FDCA's new drug approval process."¹⁴¹

In fact, manufacturers are restricted from sharing any information about an off-label use of their drug, truthful or otherwise.¹⁴² These regulations come with the caveat that the FDA prohibits manufacturers from promoting their drugs for off-label uses, but does not prohibit healthcare providers from prescribing drugs for off-label uses.¹⁴³ There are both monetary and public health incentives for manufacturers to promote off-label uses of their drugs and courts have repeatedly held that off-label uses can be acceptable treatment options.¹⁴⁴ However, drug manufacturers can face substantial civil and criminal liability when marketing their drugs for off-label uses, as this promotion can amount to a violation of the FDCA.¹⁴⁵ For example, Genentech Inc., "one of the world's largest biotechnology corporations, paid \$50 million in criminal and civil fines in 1999 to settle charges that it illegally promoted the growth hormone Protropin for unapproved uses."¹⁴⁶

This web of federal regulations creates a challenging dilemma in that these regulations pit the provider's desire to obtain information about the benefits and risks of off-label drug therapies against the manufacturer's desire to avoid subjecting themselves to years of lawsuits. This tension played out in the FDA's regulation of pedicle screw spinal systems.¹⁴⁷ The "pedicle screw" had become widely utilized by physicians for one of its off-label uses, and in the process had also become widely litigated.¹⁴⁸ As a result, the FDA decided to review the

141. 2 O'REILLY & VAN TASSEL, *supra* note 9, § 15:61.

142. Christopher M. Wittich, Christopher M. Burkle & William L. Lanier, *Ten Common Questions (and Their Answers) About Off-label Drug Use*, 87 MAYO CLINIC PROC. 982, 988 (2012).

143. Coutinho, *supra* note 135, at 281.

144. Richard C. Ausness, "There's Danger Here, Cherie!": *Liability for the Promotion and Marketing of Drugs and Medical Devices for Off-Label Uses*, 73 BROOK. L. REV. 1253, 1255 & n.15 (2008) (citing Bristol-Meyers Squibb Co. v. Shalala, 91 F.3d 1493, 1500 (D.C. Cir. 1996); Ortho Pharm. Corp. v. Cosprophar, Inc., 32 F.3d 690, 692 (2d Cir. 1994); Upjohn Co. v. MacMurdo, 562 So. 2d 680, 683 (Fla. 1990)).

145. *Id.* at 1322.

146. 2 O'REILLY & VAN TASSEL, *supra* note 9, § 15:37.

147. *See* Orthopedic Devices: Classification and Reclassification of Pedicle Screw Spinal Systems, 63 Fed. Reg. 40,025, 40,033 (Jul. 27, 1998) (to be codified at 21 C.F.R. pt. 300).

148. John Schwartz & Benjamin Weiser, *The Tangled Path of FDA Review*, WASH. POST (March 29, 1996), <https://www.washingtonpost.com/archive/politics/1996/03/29/the-tangled-path-of-fda-review/3e7fe546-8f31-415e-89d6-788686a1285e/> [https://perma.cc/F6ML-E5Z7].

device again and ultimately reclassified it to include the popularized off-label use as an FDA-approved label use.¹⁴⁹ Subsequently, the FDA released guidance that addressed the issues at the heart of the pedicle screw cases.¹⁵⁰ In relevant part, former FDA Commissioner Scott Gottlieb stated that “it’s our belief that giving companies clear guidelines for . . . truthful and non-misleading information about unapproved products and unapproved uses of approved or cleared products will help facilitate communications that can allow . . . coverage for these new products and new uses more quickly after FDA approval or clearance.”¹⁵¹

From the perspective of physicians, prescribing off-label affords them the freedom to offer patients new treatment options based on the latest clinical research.¹⁵² A 2006 study estimated that approximately 21% of prescriptions for commonly used medications were written for an off-label use.¹⁵³ This number is projected to be even higher in some sub-populations. For example, one study found that 78.7% of children were prescribed at least one drug for an off-label use after being discharged from a pediatric hospital.¹⁵⁴ Other sources report that off-label drug use is often the most common and effective treatment for cancer patients.¹⁵⁵ This practice is not without risk as off-label uses are

149. *Id.*

150. U.S. FOOD & DRUG ADMIN., DRUG AND DEVICE MANUFACTURER COMMUNICATIONS WITH PAYORS, FORMULARY COMMITTEES, AND SIMILAR ENTITIES—QUESTIONS AND ANSWERS 16–22 (2018).

151. *Statement from FDA Commissioner Scott Gottlieb, M.D., on new efforts to advance medical product communications to support drug competition and value-based health care*, U.S. FOOD & DRUG ADMIN. (June 11, 2018), <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-efforts-advance-medical-product-communications> [<https://perma.cc/H2WM-UYQU>].

152. See Sandeep Kumar Gupta & Roopa Prasad Nayak, *Off-label Use of Medicine: Perspective of Physicians, Patients, Pharmaceutical Companies and Regulatory Authorities*, 5 J. PHARMACOLOGY & PHARMACOTHERAPEUTICS 88, 88 (2014).

153. David C. Radley, Stan N. Finkelstein & Randall S. Stafford, *Off-label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1023, 1025 (2006).

154. Samir S. Shah, Matthew Hall, Denise M. Goodman, Pamela Feuer, Vidya Sharma, Crayton Fargason, Jr., Daniel Hyman, Kathy Jenkins, Marjorie L. White, Fiona H. Levy, James E. Levin, David Bertoch & Anthony D. Slonim, *Off-label Drug Use in Hospitalized Children*, 161 ARCHIVES PEDIATRICS & ADOLESCENT MED. 282, 283 (2007).

155. Coutinho, *supra* note 135, at 288; see also William L. Christopher, *Off-Label Drug Prescription: Filling the Regulatory Vacuum*, 48 FOOD & DRUG L.J. 247, 248–49 (1993).

typically backed by little, if any, formal scientific evidence.¹⁵⁶ Critics argue that promoting the off-label use of drugs undermines the FDA's role in ensuring the safety of drugs on the market, discouraging manufacturers from performing safety and efficacy studies, and relatedly encouraging manufacturers to seek FDA approval for the narrowest and easiest to support use of their drugs.¹⁵⁷ Yet prescribing a drug off-label allows physicians to give patients the opportunity to try experimental treatment options or try new treatments when all of the available FDA-approved therapies have failed. Additionally, an off-label use may be the only treatment available for rare diseases that do not have any FDA-approved treatment options.¹⁵⁸ Often, it is the patients' own demand for alternative treatment options when the standard procedures have failed that influences a physician's decision to experiment with off-label therapies.¹⁵⁹ Thus, both physicians and patients benefit from the prescription of off-label medications.

B. Reasonable Innovation Rule

The FDA has recognized that the practice of medicine necessarily involves physicians prescribing some drugs for off-label uses.¹⁶⁰ But if a physician does not follow proper protocols when prescribing off-label, her prescribing behaviors can move away from innovation and encroach on illegal human experimentation. This distinction is rooted in the reasonable innovation rule. Generally, physicians are making treatment decisions based on the average person with that illness and can treat using the customary standard of care. Customary care is evidence-based, using "population level data on the safety and efficacy of medical interventions in order to produce generalizable knowledge with which to guide clinical decisionmaking."¹⁶¹ But when a physician needs to deviate from customary care to treat a patient with unique needs, she may use reasonable innovation to do so.¹⁶²

Courts have generally recognized the need for physicians to innovate when such care is reasonable under the circumstances. As early as

156. Radley et al., *supra* note 153, at 1023.

157. Maxwell J. Mehlman, *Off-Label Prescribing*, THE DOCTOR WILL SEE YOU NOW (May 1, 2005), <http://www.thedoctorwillseeyounow.com/content/bioethics/art1971.html> [<https://perma.cc/DX27-9495>].

158. Coutinho, *supra* note 135, at 289.

159. Gupta & Nayak, *supra* note 152, at 90.

160. *Foreword to the 62nd Edition of PHYSICIANS' DESK REFERENCE* (62d ed. 2008).

161. Anna B. Laakman, *When Should Physicians be Liable for Innovation?*, 36 CARDOZO L. REV. 913, 918 (2015).

162. *Id.*

1935, the Supreme Court of Michigan in *Fortner v. Koch*¹⁶³ recognized that “if the general practice of medicine and surgery is to progress, there must be a certain amount of experimentation carried on.”¹⁶⁴ In *Brook v. St. John’s Hickey Memorial Hospital*,¹⁶⁵ the Supreme Court of Indiana reasoned that physicians are “presumed to have the knowledge and skill necessary to use some innovation to fit the peculiar circumstances of each case.”¹⁶⁶

Under the reasonable innovation rule, physicians may deviate from the “norm” by providing reasonable care under the circumstances based on the unique needs of the patient.¹⁶⁷ “A physician provides standard treatment when she uses routine methods to treat patients, and she provides innovative treatment when she deliberately deviates from established practices in an attempt to improve patient outcomes.”¹⁶⁸ “Physician innovation includes performing novel medical and surgical procedures and prescribing drugs and devices for uses with unknown safety and efficacy.”¹⁶⁹ Therefore, a physician may use reasonable innovation to prescribe a drug off-label for *one* of her patients. However, when a physician prescribes a drug off-label for *all* patients with a certain condition, this practice is no longer clinical innovation, but is instead considered illegal human experimentation.¹⁷⁰ Put another way, off-label prescription by a physician constitutes human experimentation whenever the decision to prescribe off-label is not based on the unique needs of the patient.

Regulations concerning research involving human subjects are promulgated by the FDA and the Department of Health and Human Services.¹⁷¹ For any clinical investigation, such as a physician trying an

163. 261 N.W. 762 (Mich. 1935).

164. *Id.* at 765.

165. 380 N.E.2d 72 (Ind. 1978).

166. *Id.* at 76.

167. Stephanie M. Mehle, *Protecting Patients: A Proposal For Codifying the Reasonable Innovation Rule*, 48 AKRON L. REV. 419, 421 (2015).

168. Laakman, *supra* note 161, at 938.

169. *Id.* at 915.

170. Myrisha S. Lewis, *Halted Innovation: The Expansion of Federal Jurisdiction over Medicine and the Human Body*, 2018 UTAH L. REV. 1073, 1089–90 (2018).

171. 21 C.F.R. § 56.101–124 (2018); 45 C.F.R. § 46.101–124 (2018). *See also* Bonnie M. Lee, *Comparison of FDA and HHS Human Subject Protection Regulations*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/science-research/good-clinical-practice-educational-materials/comparison-fda-and-hhs-human-subject-protection-regulations> [<https://perma.cc/4GDH-YZFV>] (last updated Mar. 13, 2018) (detailing the scope of FDA regulations, the

off-label treatment on a group of patients, the FDA requires that the physician acquire approval for the treatment from an IRB.¹⁷² In practice, however, the FDA does not exercise strong oversight over all clinical trials and IRB-approved studies.¹⁷³ The Office of the Inspector General has recognized these weaknesses, underscoring both that the FDA does not have a system in place to track all human trials and that it “lacks a comprehensive database for tracking its inspections of clinical trials.”¹⁷⁴ This lack of organized data collection is a flaw repeated by physicians. By prescribing drugs off-label to patient groups without registering with an IRB and tracking the results, physicians are in actuality conducting illegal human experiments.

V. RECOMMENDATION

Deficits in the organization and dissemination of patient data regarding off-label drug uses leave patients vulnerable, both at the clinical stage as they accept the risks of their treatment, and further down the road if the patients suffer harm from their treatment and attempt to sue. Taken together, the restrictions on a manufacturer’s promotion of off-label risks, coupled with the practice of physicians prescribing drugs off-label and the reluctance of courts to recognize exceptions to the LID, leave patients at a disadvantage. Overall, the goal of this regulatory system should be, first and foremost, to protect patients. At the same time, the continued promotion of physician innovation through off-label prescribing is vital to providing patients access to the most effective treatment options for their needs. Because physicians are prescribing drugs off-label (and we want to encourage them to continue to), the best practice is to implement a comprehensive system for tracking this patient data.

circumstances in which IRB review is mandated, waivers of FDA IRB requirements, and lesser administrative actions available to the agency).

172. *Institutional Review Boards Frequently Asked Questions*, U.S. FOOD & DRUG ADMIN. (Jan. 1998), <https://www.fda.gov/regulatoryinformation/guidances/ucm126420.htm> [<https://perma.cc/9MM2-CGYG>].

173. *OIG Releases Report of FDA’s Oversight of Clinical Trials, Concludes Improvement of Information Systems and Processes is Needed*, DEP’T OF HEALTH & HUMAN SERVS. (Sept. 28, 2007), <https://oig.hhs.gov/publications/docs/press/2007/FDAClinicalTrials3.pdf> [<https://perma.cc/L225-6QF3>].

174. *Id.* In 2007, the FDA created the Sentinel System to surveil electronic health records for post-market safety concerns. While this did increase the FDA’s surveillance ability, the system was not very successful at identifying problems; rather, it allowed the FDA to verify the existence of problems, but only once those problems had been separately brought to the attention of the FDA. *See* W. Nicholson Price II, *Drug Approval in a Learning Health System*, 102 MINN. L. REV. 2413, 2424–25 (2018).

A. *Patient Registries in the Physician-Patient Relationship*

Aggregate and timely treatment data can be collected through patient registries. “A patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure”¹⁷⁵ To include a patient in the patient registry, the prescribing physician must obtain that patient’s informed consent.¹⁷⁶ Additionally, the physician will be subject to a duty to timely disclose adverse patient outcomes identified by the registry to their own patients. This continuous disclosure of patient outcomes across a nationwide pool gives the patient the ability to provide renewed consent based on updated risk information. Thus, to properly prescribe off-label using reasonable innovation without conducting an illegal human experiment, physicians must *both* use a patient registry, with the patient’s informed consent, *and* monitor patient progress by timely disclosing adverse effects reported in the registry.

For off-label treatments included in a registry, a patient’s informed consent is obtained during two phases of treatment: consent to the treatment itself and consent to having the patient’s health data made available through the registry. For the patient, this process will take place entirely in the clinical setting.¹⁷⁷ After diagnosis of a condition of interest for the registry, the physician may recommend prescribing a drug off-label. As a best practice to ensure the physician is engaging in reasonable innovation and not conducting a human experiment,¹⁷⁸ the physician will also recommend the patient be included in the registry. This way, the consent process takes place entirely within the scope of the physician-patient relationship.¹⁷⁹ Importantly, a patient’s refusal to consent to inclusion in the registry is not a bar to receiving the off-label treatment. Rather, a patient’s denial of consent to the registry requires

175. 1 AGENCY FOR HEALTHCARE RSCH. & QUALITY, REGISTRIES FOR EVALUATING PATIENT OUTCOMES: A USER’S GUIDE 13 (Richard E. Gliklich, Nancy A. Dreyer & Michelle B. Leavy eds., 3d ed. 2014).

176. Leslie P. Francis & Michael Squires, *Patient Registries and Their Governance: A Pilot Study and Recommendations*, 16 IND. HEALTH L. REV. 43, 55 (2018).

177. *Id.* at 63.

178. *See generally* Laakman, *supra* note 161, at 916–17 (“Transforming an individual from a patient into a research subject fundamentally alters her role in the medical decisionmaking process and the goals of the intervention. By enrolling in a randomized clinical trial, an individual forfeits decisional autonomy over her ultimate treatment course. And while the goal of a medical intervention in the treatment setting is to further the patient’s interests, the goal in the research setting is to expand generalizable knowledge, with the individual subject’s interests acting as a side constraint.”).

179. Francis & Squires, *supra* note 176, at 63.

the prescribing physician to take separate precautions in order to adhere to the reasonable innovation rule when not safeguarded by the procedural protections created by the registry system.

Importantly, with the increased digitization of medicine and patient records, any physician in the country who is prescribing the same treatment can enroll her patients in the same registry.¹⁸⁰ The registry can then facilitate the identification of patterns across a nationwide dataset. If the registry shows a trend in adverse patient outcomes, it can promptly notify all physicians with patients in the registry, who must subsequently disclose this information to their patients. This notification requirement helps patients assess the risks of their off-label treatment on a continuous basis and, in the worst case, gives them an opportunity to timely withdraw if experiencing the same adverse effects as others in the registry in an attempt to mitigate potential harm. Even though the registry notification system imposes an additional duty on physicians, “[p]hysicians who recommend innovative care are [already] subject to heightened disclosure duties.”¹⁸¹ If the physician fails to timely disclose, then she will have breached her duty of informed consent to the patient and will be subject to existing liability regimes in tort to the patient.¹⁸²

B. Patient Registries and the FDA

Patient registries can also be used to mitigate weaknesses at the regulatory level. The use of patient registries for off-label treatments can supply the FDA with data to monitor post-market safety of off-label uses.¹⁸³ The patient data collected by registries is commonly referred to as real-world evidence (“RWE”).¹⁸⁴ RWE “is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of” patient health data.¹⁸⁵ In 2017, the FDA approved a label change based on RWE for the first time.¹⁸⁶ This

180. For a list of registries operating at the national level, see *List of Registries*, NAT’L INST. HEALTH, <https://www.nih.gov/health-information/nih-clinical-research-trials-you/list-registries> [<https://perma.cc/D37A-U9FC>] (last updated June 17, 2020).

181. Laakman, *supra* note 161, at 940.

182. See 4A AMERICAN LAW OF TORTS § 15:72 (Stuart M. Speiser, Charles F. Krause, Alfred W. Gans & Monique C.M. Leahy eds., 2020).

183. See *Real-World Evidence*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence> [<https://perma.cc/RNZ4-CY2L>] (last updated Nov. 30, 2020).

184. *Id.*

185. *Id.*

186. Jeffrey Shuren & Bram Zuckerman, *How Creative FDA Regulation Led to First-in-the-World Approval of a Cutting-Edge Heart Valve*, FDA VOICE

change was for an artificial transcatheter heart valve, initially approved by the FDA in 2011 to treat patients with a life-threatening heart problem.¹⁸⁷ After the drug was put on the market, the manufacturer started tracking the use of its device, including the off-label use that led to the new indication in 2017.¹⁸⁸ After reviewing approximately 600 records relating to the off-label use from the manufacturer's product registry, the FDA approved the off-label procedure without requiring a separate clinical trial.¹⁸⁹ This FDA milestone was accomplished at approximately the same time Congress passed the 21st Century America Cures Act ("Cures Act").¹⁹⁰ Pursuant to the Cures Act, the FDA "created a framework for evaluating the potential use of [RWE] to help support the approval of a new indication for a drug already approved . . . or to help support or satisfy drug postapproval study requirements."¹⁹¹ Accordingly, the widespread adoption of patient registries can further the legislative goal of the Cures Act by providing the FDA with data for label change considerations.

In addition to monitoring patient registry data for label changes, the FDA can utilize this data to hold manufacturers more accountable for the risks associated with their market drugs. With off-label risk information accessible through patient registries, manufacturers can no longer circumvent FDCA regulations by claiming the risk-benefit information for off-label uses of their drug was not available. The risks collected through patient registries and communicated to the FDA then become known risks that the manufacturer must communicate to the learned intermediary.¹⁹² The data collected by the registries thereby serves to better protect patients by increasing the accountability of manufacturers to prescribing physicians—the intermediary—and places a higher burden on the manufacturer to dispel its duty to warn under the LID.

(June 14, 2017), <https://www.fdanews.com/ext/resources/files/2017/06/06-15-17-FDABlog.pdf?1497644513> [<https://perma.cc/4QW7-SN7B>].

187. *Id.*

188. Neil A. Belson, *FDA's Historical Use of "Real World Evidence"*, FOOD & DRUG L. INST., <https://www.fdpi.org/2018/08/update-fdas-historical-use-of-real-world-evidence/> [<https://perma.cc/7Y9V-8LVQ>] (last visited Dec. 15, 2020).

189. *Id.*

190. 21st Century Cures Act, Pub. L. No. 114-255, § 3022, 130 Stat. 1033, 1096-98 (2016).

191. U.S. FOOD & DRUG ADMIN., FRAMEWORK FOR FDA'S REAL-WORLD EVIDENCE PROGRAM 3 (2018) (footnote omitted), <https://www.fda.gov/media/120060/download> [<https://perma.cc/DN46-S7ZJ>].

192. Prescription drug manufacturers have a duty to warn about knowable risks. RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6 cmt. g (AM. L. INST. 1998).

CONCLUSION

Through the implementation of patient registries, patients can be better protected against the infliction of harm in the first place, alleviating the pressure on courts to remedy these harms through the LID. The coordination of patient data among physicians, the FDA, and drug manufacturers increases transparency and accountability in off-label treatment programs. The use of nationwide patient registries also acknowledges the vital role technology now plays in the administration of healthcare. This sentiment has been recognized by courts for decades. In *Hall v. Hilbun*,¹⁹³ the Supreme Court of Mississippi noted that the practice of medicine has changed such that physicians attend the same universities, are subject to the same training, and then move to practice across the country, where they have the same access to evolving medical knowledge.¹⁹⁴ “Our law is not administered in isolation, any more than the physicians who practice in this state work in isolation from the rest of the country.”¹⁹⁵

The implementation of RWE systems in everyday clinical practice is nonetheless a shift away from the existing paradigm. Traditionally, “systematic learning about health care takes place principally in clinical trials, and not much in clinical care.”¹⁹⁶ However, with the adoption of patient registries for off-label treatments, there would be a shift towards a “learning health system,” where “data [is] continuously collected in ongoing clinical care” and used to benefit the patient in real time and to protect the patient in the future.¹⁹⁷

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193. 466 So. 2d 856 (Miss. 1985).

194. *Id.* at 870.

195. *Id.* at 867.

196. Price II, *supra* note 174, at 2414.

197. Rachel E. Sherman, Steven A. Anderson, Gerald J. Dal Pan, Gerry W. Gray, Thomas Gross, Nina L. Hunter, Lisa LaVange, Danica Marinac-Dabic, Peter W. Marks, Melissa A. Robb, Jeffrey Shuren, Robert Temple, Janet Woodcock, Lilly Q. Yue & Robert M. Califf, *Real-World Evidence—What Is It and What Can It Tell Us?*, NEW ENGL. J. MED. 2294 (2016).

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