# The Opioid Epidemic: Fixing a Broken Pharmaceutical Market

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## Introduction

On September 16, 2016, President Obama issued a proclamation decrying the U.S. epidemic of opioid misuse and abuse. Describing opioid use disorders as "a disease that touches too many of our communities—big and small, urban and rural—and devastates families, all while straining the capacity of law enforcement and the health care system," he called on Congress to provide $1.1 billion for improved access to treatment.[1] The 21st Century Cures Act largely fulfilled that request. Passed by Congress and signed by President Obama in December 2016, the act issued one billion dollars to states for primary and secondary prevention measures over the next two years.[2]

Such funding is sorely needed. The American Society of Addiction of Medicine estimates that over 2.5 million Americans now have an opioid use disorder.[3] In 2015, 33,092 Americans died from an opioid-related overdose—a fourfold increase from 1999.[4]

In addition to funding evidence-based measures to combat the worsening public health crisis, policymakers should probe the root causes of the

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[1] Proclamation No. 9499, 81 Fed. Reg. 65,173, 65,173 (Sept. 22, 2016).

[2] 21st Century Cures Act, Pub. L. No. 114-255, § 1003, 130 Stat. 1033 (2016); *see also* Gregory Korte, *Obama Signs $6.3 Billion Law for Cancer Research, Drug Treatment*, USA Today (Dec. 13, 2016, 3:50 PM), http://www.usatoday.com/story/news/politics/2016/12/13/obama-signs-63-billion-law-cancer-research-drug-treadment/95382708/ [https://perma.cc/R5VE-LJTG].

[3] Am. Soc'y of Addiction Med., Opioid Addiction 2016 Facts & Figures 1 (2016), http://www.asam.org/docs/default-source/advocacy/opioid-addiction-disease-facts-figures.pdf [https://perma.cc/6L26-LNF6].

[4] Christopher Ingraham, *Heroin Deaths Surpass Gun Homicides for the First Time, CDC Data Shows,* Wash. Post (Dec. 8, 2016), https://www.washingtonpost.com/news/wonk/wp/2016/12/08/heroin-deaths-surpass-gun-homicides-for-the-first-time-cdc-data-show/ [https://perma.cc/V4L5-MUZ6].

overuse of opioids in the United States. Knowledge of these factors will help answer how the crisis could have been averted and, thus, how similar occurrences can be prevented. In this article, we argue that non-rigorous patenting standards and ineffectual policing of both fraudulent marketing and anticompetitive actions played an important role in launching and prolonging the opioid epidemic. We further show that these regulatory issues are not unique to prescription opioids but rather are reflective of the wider pharmaceutical market. We conclude by identifying practical ways in which the regulatory system can be reformed.

## I. Rise of Prescription Opioids

It is difficult to overstate the extent of opioid overuse and misuse in the United States. Over four million Americans misuse opioids each month.[5] Between 2005 and 2014, the annual number of opioid-related emergency department visits doubled.[6] Almost as many people now die from an opioid-related overdose each day as die in automobile accidents.[7]

A fundamental cause of the epidemic was—and continues to be—an over-prescription of opioids. From 2000 to 2010, the number of prescriptions for oral opioid analgesics rose 104%.[8] Greater use occurred among men and women, and across all age groups.[9] In 2015, U.S. clinicians wrote approximately three hundred million opioid prescriptions,[10] more than one for every adult in the country.[11] The societal cost of such overuse and misuse is rapidly approaching eighty billion dollars annually.[12]

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[5] *See* Substance Abuse & Mental Health Servs. Admin., Results from the 2015 National Survey on Drug Use and Health: Detailed Tables (2016).

[6] *See* Agency for Healthcare Research & Quality, Healthcare Cost and Utilization Project, Statistical Brief #219 1 (2017).

[7] *Injury Prevention & Control: Opioid Overdose*, U.S. Ctrs. for Disease Control & Prevention, https://www.cdc.gov/drugoverdose/ [https://perma.cc/QPG2-LE8G]; *see also* Stav Ziv*, 2015 Brought Biggest Percent Increase in U.S. Traffic Deaths in 50 Years*, Newsweek (Feb. 17, 2016, 3:47 PM), http://www.newsweek.com/2015-brought-biggest-us-traffic-death-increase-50-years-427759 [https://perma.cc/5PXJ-85YH].

[8] Brian D. Sites et al., *Increases in the Use of Prescription Opioid Analgesics and the Lack of Improvement in Disability Metrics Among Users*, 39 Reg. Anesthesia Pain Med. 6, 6 (2014).

[9] Cynthia I. Campbell et al., *Age and Gender Trends in Long-Term Opioid Analgesic Use for Noncancer Pain*, 100 Am. J. Pub. Health 2541, 2543 (2010).

[10] Dina Gusovsky, *Americans Consume Vast Majority of the World's Opioids*, CNBC (Apr. 27, 2016, 9:13 AM), http://www.cnbc.com/2016/04/27/americans-consume-almost-all-of-the-global-opioid-supply.html [https://perma.cc/CWP8-YPQV].

[11] *See QuickFacts from the US Census Bureau*, U.S. Census Bureau, https://www.census.gov/quickfacts/ [https://perma.cc/DUH2-45FS].

[12] *See* Curtis S. Florence et al., *The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013*, 54 Med. Care 901, 901 (2016).

### *A. Treating Pain: The Fifth Vital Sign*

The origins of the surge in prescription opioid use can be traced to increased awareness of the widespread prevalence and under-treatment of pain. In a 1986 article, for example, Marilee Donovan and colleagues found that forty-five percent of patients in medical and surgical units of a large Midwestern medical center reported experiencing excruciating pain.[13] Of those who reported any pain, less than half recalled being asked about it by their health care team.[14] These findings prompted Russell Portenoy, a leading pain specialist, to decry the lack of pain treatment in hospitals as "absolutely medieval."[15]

Of particular concern was chronic, non-malignant pain.[16] In Donovan et al.'s survey, twenty-one percent of patients reported pain that started months or years earlier.[17] Another study found that eight percent of adult enrollees in a large health maintenance organization suffered from severe and persistent pain, which "was strongly associated with . . . frequent use of ambulatory health care, unfavorable self-appraisal of health status, and psychological impairment."[18]

Such findings were harnessed to promote more aggressive pain management. In 1996, James Campbell introduced the concept of pain as the fifth vital sign in his presidential address to the American Pain Society.[19] The Joint Commission on Accreditation of Healthcare Organizations took up the idea in 1999, issuing pain management standards that hospitals and outpatient centers would have to meet for certification.[20] So too did the Department of Veterans Affairs, developing a "Pain as the 5th Vital Sign Toolkit" as part of a national pain management strategy in 2000.[21]

For chronic, non-malignant pain, prominent medical figures urged physicians to make greater use of opioids. Summarizing their review of thirty-

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[13] *See* Marilee Donovan et al., *Incidence and Characteristics of Pain in a Sample of Medical-Surgical Inpatients*, 30 PAIN 69, 71, 73 (1987).

[14] *See id.* at 73.

[15] Daniel Goleman, *Health: Patient Care; Physicians Said to Persist in Undertreating Pain and Ignoring the Evidence*, N.Y. TIMES (Dec. 31, 1987), http://www.nytimes.com/1987/12/31/us/health-patient-care-physicians-said-persist-undertreating-pain-ignoring-evidence.html [https://perma.cc/B4T5-FKDC].

[16] *See* Russell K. Portenoy, *Opioid Therapy for Chronic Non-malignant Pain: A Review of the Critical Issues*, 11 J. PAIN SYMPTOM MGMT. 203, 203 (1996). Chronic nonmalignant pain is commonly defined as non-cancerous pain lasting more than three months. *See* Matthew Hollon, *Nonmalignant Chronic Pain: Taking the Time to Treat*, 79 AM. FAM. PHYSICIAN 743, 743 (2009).

[17] *See* Donovan et al., *supra* note 13, at 72.

[18] Michael Von Korff et al., *Graded Chronic Pain Status: An Epidemiologic Evaluation*, 40 PAIN 279, 279, 289 (1990).

[19] DEP'T OF VETERANS AFFAIRS, PAIN AS THE 5TH VITAL SIGN TOOLKIT 5 (2000) ("If pain were assessed with the same zeal as other vital signs are, it would have a much better chance of being treated properly." (quoting James Campbell, Presidential Address at the Am. Pain Soc'y (Nov. 11, 1996))).

[20] JOINT COMM'N ON ACCREDITATION OF HEALTHCARE ORGS., PAIN MANAGEMENT STANDARDS: COMPREHENSIVE ACCREDITATION MANUAL FOR HOSPITALS, UPDATE 3 (1999).

[21] DEP'T OF VETERANS AFFAIRS, *supra* note 19.

eight patients who had been maintained on opioids for such pain, Portenoy and neurologist Kathleen Foley wrote in 1986 that long-term opioid use could be safe and effective.[22] Four years later, the psychologist Ronald Melzack favorably cited this view in a widely read *Scientific American* article, lamenting: "Many people suffer not because their discomfort is untreatable but because physicians are often reluctant to prescribe morphine."[23]

Many experts—in retrospect, often erroneously—downplayed the potential for opioid misuse and addiction. Portenoy referred to the risk as a medical myth,[24] while Melzack commented that development of addiction from treatment with morphine was rare.[25] Seminal to their arguments was a study by the Boston Collaborative Drug Surveillance Program, published as a one-paragraph correspondence in the *New England Journal of Medicine* in 1980.[26] In reviewing the cases of 11,882 hospitalized patients who received an opioid, program investigators found only four reported cases of addiction.[27]

In time, several influential organizations came to adopt the view that opioids posed limited danger when used for chronic, non-malignant pain. A consensus statement from the American Pain Society and the American Academy of Pain Medicine in 1997 and best practice guidance from the American Medical Association's Council on Scientific Affairs in 2000 noted that the risk of opioid addiction among patients without a history of misuse or abuse was low.[28] The Federation of State Medical Boards went further, concluding that "controlled substances, including opioid analgesics, may be essential in the treatment of . . . chronic pain, whether due to cancer or non-cancer origins."[29]

### *B. Introduction of Extended-Release Oxycodone*

Purdue Pharma successfully contributed to and capitalized on the medical establishment's changing view of pain management. Procured in 1952 by the Sacklers—three brothers, all psychiatrists—the company set its sights on developing an improved synthetic opioid.[30] This effort culminated in Food

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[22] Russell K. Portenoy & Kathleen M. Foley, *Chronic Use of Opioid Analgesics in Non-Malignant Pain: Report of 38 Cases*, 25 PAIN 171, 178 (1986).

[23] Ronald Melzack, *The Tragedy of Needless Pain*, 262 SCI. AM. 27, 27 (1990).

[24] Goleman, *supra* note 15.

[25] Melzack, *supra* note 23, at 27.

[26] Jane Porter & Hershel Jick, *Addiction Rare in Patients Treated with Narcotics*, 302 NEW ENG. J. MED. 123, 123 (1980).

[27] *Id.*

[28] *See* J. David Haddox et al., *The Use of Opioids for the Treatment of Chronic Pain*, 13 CLINICAL J. PAIN 6, 6 (1997); Barry D. Dickinson et al., *Use of Opioids to Treat Chronic, Noncancer Pain*, 172 WEST J. MED. 107, 107 (2000).

[29] FED'N OF STATE MED. BDS. OF THE U.S., INC., MODEL GUIDELINES FOR THE USE OF CONTROLLED SUBSTANCES FOR THE TREATMENT OF PAIN 1 (1998).

[30] Grant Robertson & Karen Howlett, *How a Little-Known Patent Sparked Canada's Opioid Crisis*, GLOBE & MAIL, http://www.theglobeandmail.com/news/investigations/oxycontin/article33448409/ (last updated Feb. 10, 2017, 7:22 PM) [https://perma.cc/YQ3Q-GKEW].

and Drug Administration (FDA) approval of extended-release oxycodone (OxyContin) "for the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days" in 1995.[31]

Using aggressive marketing tactics, Purdue successfully turned extended-release oxycodone into a blockbuster. Between 1996 and 2000, the company more than doubled its U.S. marketing team and created lucrative incentives and powerful tools to bolster sales.[32] In 2001, Purdue paid forty million dollars in bonuses tied to extended-release oxycodone.[33] Average bonuses among sales representatives exceeded average salaries by thirty percent.[34] Purdue also invested heavily in analytics, developing a database to identify high-volume prescribers and pharmacies to help focus their marketing resources.[35] Patients were offered starter coupons for a free initial supply of extended-release oxycodone, 34,000 of which were redeemed by 2001.[36] Finally, Purdue hosted forty all-expenses-paid pain management and speaker training conferences at lavish resorts.[37] Over five thousand clinicians attended, receiving toys, fishing hats, and compact discs while listening to sales representatives tout the alleged benefits of extended-release oxycodone over more affordable, non-extended release generic opioids for malignant and non-malignant chronic pain.[38] A degree of such activity typically accompanied new product launches. However, Purdue elevated the stakes, spending an estimated six to twelve times more promoting extended-release oxycodone than its competitor Janssen spent marketing a rival opioid.[39] Purdue's efforts paid off. Between 1996 and 2001, extended-release oxycodone generated $2.8 billion in sales.[40] From 2008 to 2014, annual sales exceeded $2 billion.[41]

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[31] U.S. Gov't Accountability Office, GAO-04-110, Prescription Drugs: OxyContin Abuse and Diversion and Efforts to Address the Problem 35 (2003).

[32] *See* Art Van Zee, *The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy*, 99 Am. J. Pub. Health 221, 222 (2009).

[33] *Id.*

[34] *See id.*

[35] *Id.*

[36] *Id.*

[37] *Id.* at 221.

[38] *Id.* at 222; *see also* Robertson & Howlett, *supra* note 30.

[39] *See* U.S. Gov't Accountability Office, *supra* note 31, at 21. As part of its marketing campaign, Purdue funded professional societies advocating for more aggressive pain management. *Id.* at 24.

[40] *See* Carrie Johnson, *OxyContin Makers Admit Deception*, Wash. Post (May 11, 2007), http://www.washingtonpost.com/wp-dyn/content/article/2007/05/10/AR2007051000892.html [https://perma.cc/N2YA-BC5N].

[41] *See* Harriet Ryan et al., *"You Want a Description of Hell?" OxyContin's 12-Hour Problem*, L.A. Times (May 5, 2016), http://www.latimes.com/projects/oxycontin-part1/ [https://perma.cc/N26C-GKVX].

### *C. Regulatory Issues Contributing to the Overuse of Extended-Release Oxycodone*

Purdue's success was attributable in part to low patenting standards that enabled the company to secure and extend market exclusivity for extended-release oxycodone, providing motivation for its aggressive marketing. A history of tepid enforcement against pharmaceutical companies engaging in illegal marketing further incentivized Purdue to make false claims about the safety and effectiveness of the drug. Both practices helped drive opioid overuse and misuse, with tragic public health consequences.

#### *1. Patenting Extended-Release Oxycodone*

Purdue was able to patent extended-release oxycodone in the United States despite the fact that its constituent elements—the active ingredient oxycodone and the controlled-release system Contin—had been developed decades earlier. German scientists Martin Freund and Edmund Speyer first synthesized oxycodone in 1916 in an effort to create a less addictive analgesic than either morphine or heroin,[42] which Bayer had been forced to pull from worldwide markets three years earlier.[43] Oxycodone was used in clinical practice in Germany as early as 1917,[44] and was first introduced in the United States in 1939.[45]

Use of oxycodone increased gradually during the twentieth century.[46] However, like all then-available opioids, oxycodone was generally considered contraindicated for treating chronic pain.[47] Emerging data from the drug's use in patients revealed that Freund and Speyer had vastly underestimated its strength and addictive potential.[48] In a 1957 bulletin on synthetic opioids, the World Health Organization concluded that oxycodone's "respiratory depressant effect and addiction liability" were "not materially different" from those of morphine."[49] Six years later, the California Attorney General estimated that up to one quarter of cases of addiction in the states were attributable to the combination product oxycodone/aspirin

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[42] Martin Freund & Edmund Speyer, *Uber die Umwandlung von Thebain in Oxycodeinon und Dessen Derivate*, 94 ADVANCED SYNTHESIS & CATALYSIS 135, 135 (1916).

[43] Richard Askwith, *How Aspirin Turned Hero*, SUN. TIMES (Sept. 13, 1998), http://www.opioids.com/heroin/heroinhistory.html [https://perma.cc/D5QZ-36ZE].

[44] Eija Kalso, *Oxycodone*, 29 J. PAIN & SYMPTOM MGMT. S47, S47 (2005).

[45] *See Oxycodone*, DRUGPEDIA, http://crdd.osdd.net/drugpedia/index.php/Oxycodone [https://perma.cc/KLW6-4YH5].

[46] *See* Robertson & Howlett, *supra* note 30.

[47] *See* Andrew Rosenblum et al., *Opioids and the Treatment of Chronic Pain: Controversies, Current Status, and Future Directions*, 16 EXPERIMENTAL & CLINICAL PSYCHOPHARMACOLOGY 405, 406 (2008).

[48] *See* Robertson & Howlett, *supra* note 30.

[49] Nathan B. Eddy et al., *Synthetic Substances with Morphine-Like Effect*, 17 BULL. WORLD HEALTH ORG. 569, 708 (1957).

(Percodan).[50] This news prompted the California Medical Association to recommend that oxycodone-containing drugs require a triplicate prescription.[51]

It was against this backdrop that Purdue entered the field of pain medicine. In 1972, the company developed Contin, a method to control the release of the active ingredient of a drug from a tablet.[52] Purdue subsequently applied Contin to morphine.[53] The resulting product—extended-release morphine (MS Contin)—quickly became the company's highest grossing drug,[54] generating annual sales of approximately $170 million in the early 1990s.[55]

As expiration of market exclusivity for extended-release morphine approached, Purdue grew increasingly concerned over sustaining its revenues.[56] An internal debate ensued, with the company's vice president for research advocating for the development of other controlled-release opioids:

> While we are "going laterally" with MS Contin to non-cancer pain indications, it would be unwise to "put all of our eggs into the MS Contin basket" in the face of the prospect of generic MS Contin competition that would "crush all of the analgesic eggs." It has also been said that [we] should market in controlled-release formulation every major opioid analgesic and combination analgesic.[57]

Purdue ultimately adopted the recommendation, combining Contin and oxycodone to form extended-release oxycodone. The United States Patent and Trademark Office (USPTO) granted Purdue a patent for the invention on November 30, 1993.[58]

Patents are government-issued rights that enable their holders to exclude others from making, using, or offering to sell the subject matter covered by the patents.[59] In the United States, utility patents last twenty years from their date of filing[60] and can protect "anything under the sun that is

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[50] *See* BARRY MEIER, PAIN KILLER: A "WONDER" DRUG'S TRAIL OF ADDICTION AND DEATH 82 (2003).

[51] *See id.* at 130. Under triplicate prescribing, three copies of a prescription must be generated: one for the patient to bring to the pharmacy, one for record-keeping by the prescribing physician, and one for the pharmacist to be submitted to a regulatory agency such as the state Attorney General's office.

[52] *See About MS Contin*, PURDUE PHARMA, http://www.purduepharma.com/healthcare-professionals/products/ms-contin/ [https://perma.cc/BR83-KWF6].

[53] *See id.*

[54] Barry Meier & Melody Petersen, *Sales of Painkiller Grew Rapidly, But Success Brought a High Cost*, N.Y. TIMES (Mar. 5, 2001), http://www.nytimes.com/2001/03/05/business/sales-of-painkiller-grew-rapidly-but-success-brought-a-high-cost.html [https://perma.cc/VL3M-HPQF].

[55] *See* Thomas H. Maugh II, *Mortimer Sackler Dies at 93; Arts Patron was Co-Owner of Purdue Pharma*, L.A. TIMES (Apr. 19, 2010), http://articles.latimes.com/2010/apr/19/local/la-me-mortimer-sackler19-2010apr19 [https://perma.cc/Z5NT-9C59].

[56] *See* Ryan et al., *supra* note 41.

[57] *Id.*

[58] *See* U.S. Patent No. 5,266,331 (filed Nov. 39 1993).

[59] *See* FTC v. Actavis, 133 S. Ct. 2223, 2231 (2013).

[60] *See* 35 U.S.C. § 154(a)(2) (2012).

made by man,"[61] provided it is novel,[62] useful,[63] and non-obvious.[64] The primary patent on a pharmaceutical product usually covers its active chemical ingredient. So-called secondary patents can also cover other aspects of a drug, such as its method of manufacturing or use in clinical care.[65]

Determinations as to whether inventions are obvious must be made from the perspective of a person possessing ordinary skill in the relevant field. In *Graham v. John Deere*, the Supreme Court provided an analytic framework for such determinations, stating that the "scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved."[66] The Court clarified this framework in the 2007 case *KSR International Co. v. Teleflex Inc.*,[67] rejecting a test in which obviousness could only be found if a teaching, suggestion, or motivation to combine could be identified in the prior art.[68] Instead, the Court adopted a less rigid standard,[69] noting, "[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill."[70]

In the case of extended-release oxycodone, the combination of Contin and oxycodone would have been obvious to any pharmaceutical chemist. One need only substitute "one device" with "morphine" and "similar devices" with "oxycodone" in the Court's opinion in *Teleflex*. Methods disclosed in the original patent for extended-release morphine additionally provided a reasonable guide on how to apply Contin to oxycodone.[71] In fact, the USPTO initially rejected Purdue's patent as obvious.[72] However, the company's response that a person of ordinary skill would not have sought to use a narrower dosage range for extended-release oxycodone than for other extended-release opioid analgesics prevailed.[73] Purdue's claim that extended-release oxycodone provided pain relief for ninety percent of patients within this narrower dosage range was false, and it would later emerge that Purdue was aware of this falsehood.[74] By failing to reject Purdue's patent application

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[61] *See* Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980).

[62] *See* 35 U.S.C. § 102 (2012). Utility patents cover the invention of a new and useful process, machine, manufacture, or composition of matter, or a new and useful improvement thereof. U.S. Patent and Trademark Office, Types of Patents (2016).

[63] *See* 35 U.S.C. § 101 (2012).

[64] *See* 35 U.S.C. § 103 (2012).

[65] *See* Tahir Amin & Aaron S. Kesselheim, *Secondary Patenting of Branded Pharmaceuticals: A Case Study of How Patents on Two HIV Drugs Could Be Extended for Decades*, 31 Health Aff. 2286, 2291 (2012).

[66] 383 U.S. 1, 17 (1966).

[67] 550 U.S. 398, 398–403.

[68] *See id.* at 418–19.

[69] *See id.* at 403.

[70] *Id.* at 401.

[71] U.S. Patent No. 3,634,584 (filed Feb. 13, 1969).

[72] Purdue Pharma L.P. v. Endo Pharm. Inc., 438 F.3d 1123, 1131 (Fed. Cir. 2006).

[73] *See id.*

[74] *See infra* Part I.C.3.

on obviousness grounds, the USPTO provided the company with a lengthy period of market exclusivity for extended-release oxycodone, incentivizing its aggressive marketing of the drug.

### *2. Extending Market Exclusivity for Extended-Release Oxycodone*

Non-rigorous patenting standards also enabled Purdue to extend its market exclusivity for extended-release oxycodone. As expiration of the primary patent for extended-release oxycodone approached, Purdue secured secondary patents on an abuse-deterrent formulation of the drug.[75] The FDA approved the formulation in 2010,[76] and Purdue ceased manufacturing the original formulation soon thereafter. This action forced patients who had been taking the original formulation onto the newer one—a so-called hard switch.[77] The company additionally filed a citizen petition asking the FDA to refuse to accept generic versions of the original extended-release oxycodone formulation on safety grounds.[78] To the surprise of some commentators,[79] the FDA acquiesced, effectively preventing the marketing of low-cost, therapeutically equivalent products that might undercut Purdue's incentive to continue to widely promote its new abuse-deterrent formulation.

Generic drug manufacturers challenged the secondary patents. A federal district court ruled that one was non-infringed and invalidated the other as obvious.[80] The latter patent was heavily based on previously patented "thermoforming" technology, which entailed heating and then pressurizing an object.[81] Purdue's patented method reversed these steps but was otherwise equivalent in "way, function, and result."[82] In declaring the patent invalid as both anticipated and obvious, the court noted that "the prior art included the

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[75] *See* U.S. Patent No. 7,776,314 (filed Dec. 9, 2004); U.S. Patent No. 8,114,383 (filed Nov. 20, 2003); U.S. FOOD & DRUG ADMIN., ABUSE-DETERRENT OPIOID—EVALUATION AND LABELING GUIDANCE FOR INDUSTRY 2 (2015) (defining abuse-deterrent drug formulations as those which reduce the ability of a user to obtain a high from the drug).

[76] *See* Jacob Sherkow, *Purdue Pharma & OxyContin: Regulatory Gamesmanship? A Debate*, LAW & BIOSCI. BLOG (May 5, 2013), https://law.stanford.edu/2013/05/05/lawandbiosciences-2013-05-05-purdue-pharma-oxycontin-regulatory-gamesmanship-a-debate [https://perma.cc/V7SH-GEKX].

[77] *See* Vincent C. Capati & Aaron S. Kesselheim, *Drug Product Life-Cycle Management as Anticompetitive Behavior: The Case of Memantine*, 22 J. MANAGED CARE & SPECIALTY PHARMACY 339, 339 (2016).

[78] Purdue Pharma L.P. Citizen Petition, No. FDA-2012-P-0760 (July 13, 2012). A citizen petition is an instrument through which an individual or group can request a federal agency to take, or refrain from taking, an administrative action.

[79] *See, e.g.*, Frommer Lawrence & Haug, *Generic OxyContin-Abuse Resistance Required Says FDA*, FDA LAWYERS BLOG (Apr. 22, 2013), http://www.fdalawyersblog.com/2013/04/generic-oxycontin-abuse-resis.html [https://perma.cc/R2QY-LJN4]; Nancy Shute & Audrey Carlsen, *FDA's Rejection of Generic OxyContin May Have Side Effects*, NPR (Apr. 18, 2013), http://www.npr.org/sections/health-shots/2013/04/17/177602393/why-fdas-rejection-generic-oxycontin-may-have-side-effects [https://perma.cc/3XV7-8AZ6].

[80] Purdue Pharma L.P. v. Teva Pharma., USA, Inc. (*In re* Oxycontin Antitrust Litig.), 994 F. Supp. 2d 367 (S.D.N.Y. 2014).

[81] *See id.* at 416.

[82] *Id.* at 420.

motivation and capability to create the [patent] with a reasonable expectation of success."[83] Upon appeal, the Federal Circuit affirmed the ruling.[84] Although the generic manufacturers were thus successful, generic versions of extended-release oxycodone remained off the market over the course of the litigation, providing Purdue with an extended window in which to promote the drug and reap windfall profits.

### *3. Enforcing Marketing Standards Against Purdue*

Ineffectual penalties for illegal marketing additionally incentivized Purdue to make misleading claims. In 1995, the year Purdue launched extended-release oxycodone Johnson & Johnson demonstrated the benefits of aggressive promotion. A federal court fined them $7.5 million that year for shredding thousands of documents pertaining to its involvement in marketing the acne medication tretinoin (Retin-A) as an anti-wrinkle agent.[85] This was a non-FDA-approved use of the product, which the agency prohibited manufacturers from directly promoting.[86] The fine, however, stood in stark contrast to revenue tied to the media campaign: a three-fold increase in tretinoin sales that generated one hundred million dollars in 1989 alone.[87]

In following suit with its aggressive marketing of extended-release oxycodone, Purdue made numerous problematic assertions. For example, the company heavily touted the convenience of its drug over other non-extended release opioids. As Purdue noted in its press release announcing FDA approval of extended-release oxycodone:

> Unlike short-acting pain medications, which must be taken every 3 to 6 hours—often on an "as needed" basis—OxyContin Tablets are taken every 12 hours, providing smooth and sustained pain control all day and all night. Dosing with OxyContin Tablets on a regular schedule spare patients from anxious "clock-watching" when pain must be controlled over long periods.[88]

Yet Purdue was aware of the inadequacy of the twelve-hour dosing regimen for many patients. Clinical trial data and follow-up reports from patients who received the drug indicated that the drug often wore off after six to eight hours.[89] Senior management at Purdue nevertheless instructed sales representatives to press prescribers not to prescribe extended-release ox-

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[83] *Id.* at 428.

[84] Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345, 1345 (Fed. Cir. 2016).

[85] *Ortho Fined $7.5 Million in Retin-A Case*, N.Y. Times (Apr. 11, 1995), http://www.nytimes.com/1995/04/11/business/ortho-fined-7.5-million-in-retin-a-case.html [https://perma.cc/X8PM-EREZ].

[86] *See id.*

[87] Richard Gorelick, *Retin-A Documents May Shed Light on Government Investigation*, Daily Pennsylvanian (Feb. 14, 1990), http://www.library.upenn.edu/docs/kislak/dp/1990/1990_02_14.pdf [https://perma.cc/4US2-QTST].

[88] Ryan et al., *supra* note 41.

[89] *See id.*

ycodone at shorter intervals, fearing that the drug would lose its competitive advantage over alternative opioid medications.[90] As one sales manager commented, shorter-interval prescribing needed to be "nipped in the bud. NOW!!"[91] Instead, prescribers were pressured to write prescriptions for stronger doses.[92]

Although civil claims and criminal charges were brought against Purdue and its executives, the resulting penalties paled in comparison to extended-release oxycodone profits. In May 2007, the company and its president, chief counsel, and former chief medical officer pled guilty to falsely marketing extended-release oxycodone as "less addictive, less subject to abuse and diversion, and less likely to cause tolerance and withdrawal than other pain medications."[93] As part of the plea bargain, Purdue agreed to pay the federal government $600 million and 27 states $20 million. The three executives agreed to $34.5 million in fines but avoided jail-time.[94] By contrast, Purdue has earned an estimated $31 billion in total revenues from extended-release oxycodone since its launch.[95] Rather than deterring fraudulent marketing, the penalties simply became a cost of doing business.

## II. Exacerbation of the Epidemic

A low patent bar and anticompetitive business practices also helped exacerbate the epidemic by affecting access to Reckitt Benckiser's partial opioid agonist buprenorphine/naloxone (Suboxone), an effective treatment for opioid use disorders. In response to growing opioid misuse and abuse, states focused on decreasing the supply of opioids on the market, leaving inadequately addressed the underlying demand for opioids among the U.S. population. The dearth of treatment services was compounded by Reckitt's successful extension of market exclusivity for buprenorphine/naloxone, keeping its price high. Unable to effectively access a possible treatment for their opioid use disorders, many Americans turned to illicit opioids.

### *A. Supply-Side Measures to Combat the Opioid Epidemic*

As the opioid epidemic intensified in the late 2000s, policy responses centered on reducing the supply of prescription opioids on the market. Several states passed laws targeting pill mills, pain management clinics that dis-

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[90] *See id.*
[91] *Id.*
[92] *See id.*
[93] *See* Barry Meier, *In Guilty Plea, OxyContin Maker to Pay $600 Million*, N.Y. Times (May 10, 2007), http://www.nytimes.com/2007/05/10/business/11drug-web.html [https://perma.cc/AQS4-LW32].
[94] *See* Barry Meier, *3 Executives Spared Prison in OxyContin Case*, N.Y. Times (July 21, 2007), http://www.nytimes.com/2007/07/21/business/21pharma.html [https://perma.cc/5QEL-D8RA].
[95] Ryan et al., *supra* note 41.

pensed large volumes of opioids, often for cash and with minimal medical oversight.[96] In 2010, for example, Florida enacted legislation mandating that pain management clinics register with the state, adopt minimum safety standards (e.g., use of counterfeit-proof prescription pads), and submit to annual inspections.[97] The same year, Texas required pain management clinics to be biennially certified and physician owned.[98] It further imposed an obligation on physician-owners to be on-site for at least one-third of operating hours and to review at least one-third of patient medical records.[99] A recent study found Texas's law to be associated with a twenty percent decrease in the number of opioids dispensed per month compared to the counterfactual—the number of opioids expected to have been dispensed had the law not been enacted—one year following implementation.[100]

Almost every state instituted prescription drug monitoring programs (PDMPs), registries of select controlled substance prescriptions that enable providers to identify which medications a patient previously received.[101] These programs vary with regard to the controlled substances they track, the speed with which information is updated, and whether use is required prior to issuing a prescription.[102] A study by Stephen Patrick and colleagues found that state adoption of a PDMP was associated with a reduction of approximately one prescription opioid-related overdose death per one hundred thousand people annually.[103] As expected, the more rigorous the requirements of the PDMP, the more impactful it was.[104]

### *B. Under-Treatment of Opioid Use Disorders*

Policymakers placed less focus on tackling the demand for opioids among the general population. Between 2009 and 2013, less than twenty-two percent of people with opioid use disorder received treatment.[105] Reasons for this gap included a shortage of treatment centers,[106] a lack of physi-

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[96] *See* Lainie Rutkow et al., *Effect of Florida's Prescription Drug Monitoring Program and Pill Mill Laws on Opioid Prescribing and Use*, 175 JAMA INTERNAL MED. 1642, 1643 (2015).

[97] FLA. STAT. § 458.3265 (West, Westlaw through the 2016 2d Reg. Sess. of the 24th Legis. (2016)).

[98] TEX. OCC. CODE ANN. §§ 168.102, 168.151 (West, Westlaw through the end of the 2015 Reg. Sess. of the 84th Legis. (2016)).

[99] *Id.*

[100] *See* Tatyana Lyapustina et al., *Effect of a "Pill Mill" Law on Opioid Prescribing and Utilization: The Case of Texas*, 159 DRUG ALCOHOL DEPENDENCE 190, 194 (2016).

[101] *See* Stephen W. Patrick et al., *Implementation of Prescription Drug Monitoring Programs Associated with Reductions in Opioid-Related Death Rates*, 35 HEALTH AFF. 1324, 1324 (2016).

[102] *See id.* at 1325.

[103] *See id.* at 1328.

[104] *See id.* at 1329.

[105] *See* DEMOCRATIC STAFF OF THE S. COMM. ON FIN., DYING WAITING FOR TREATMENT: THE OPIOID USE DISORDER TREATMENT GAP AND THE NEED FOR FUNDING 3 (2016).

[106] *See* Christine Vestal, *In Opioid Epidemic, Prejudice Persists Against Methadone*, PEW CHARITABLE TRUSTS (Nov. 11, 2016), http://www.pewtrusts.org/en/research-and-analysis/

cians trained in addiction medicine,[107] and stigma given that "the understanding of opioid use disorder as a medical illness is still overshadowed by its misconception as a moral weakness or a willful choice."[108]

Drug costs also played an important role. A 2003 survey of 814 nationally representative private health plans revealed that thirty-one percent did not cover buprenorphine/naloxone.[109] Of those that did, eighty percent placed it in tier three of their formulary, requiring the highest level of patient co-payment.[110] Several years later, most state Medicaid programs continued to restrict access to buprenorphine/naloxone by imposing duration limits or prior authorization requirements on its use.[111]

Such policies were implemented in large part because of the high price of the drug. In October 2012, the wholesale average cost of thirty eight-milligram buprenorphine/naloxone strips was $211.15.[112] Between 2009 and 2012, state Medicaid programs spent over $857 million on buprenorphine products.[113]

### *C. Regulatory Issues Contributing to Delayed Generic Buprenorphine/Naloxone Competition*

The price of buprenorphine/naloxone remained high a decade after its 2002 launch because of tactics that Reckitt used to delay generic competition. Patent protection for the original tablet formulation of buprenorphine/naloxone expired in 2009.[114] However, it was not until 2013 that the first generics entered the market.[115]

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blogs/stateline/2016/11/11/in-opioid-epidemic-prejudice-persists-against-methadone [https://perma.cc/K53M-8P3X].

[107] *See* Christine Vestal, *How Severe is the Shortage of Substance Abuse Specialists?*, Pew Charitable Trusts (Apr. 1, 2015), http://www.pewtrusts.org/en/research-and-analysis/blogs/stateline/2015/4/01/how-severe-is-the-shortage-of-substance-abuse-specialists [https://perma.cc/R73A-SCKL].

[108] Yngvild Olsen & Joshua M. Sharfstein, *Confronting the Stigma of Opioid Use Disorder—And Its Treatment*, 311 JAMA 1393, 1393 (2014).

[109] Constance M. Horgan et al., *Availability of Addiction Medications in Private Health Plans*, 34 J. Substance Abuse Treatment 147, 151 (2008).

[110] *See id.* at 153.

[111] Robin E. Clark, *The Evidence Doesn't Justify Steps by State Medicaid Program to Restrict Opioid Addiction Treatment with Buprenorphine*, 30 Health Aff. 1425, 1426 (2011).

[112] Ed Silverman, *Reckitt's Suboxone Strategy Is Really About Patients or Profits?*, Forbes (Oct. 12, 2012, 5:13 PM), http://www.forbes.com/sites/edsilverman/2012/10/12/reckitts-suboxone-strategy-is-really-about-patients-or-profits/ [https://perma.cc/CU38-CNV8].

[113] Deborah Sontag, *Addiction Treatment with a Dark Side*, N.Y. Times (Nov. 16, 2013), http://www.nytimes.com/2013/11/17/health/in-demand-in-clinics-and-on-the-street-bupe-can-be-savior-or-menace.html [https://perma.cc/F2H9-MQTM].

[114] Christopher Moraff, *Suboxone Creator's Shocking Scheme to Profit Off of Heroin Addicts*, The Daily Beast (Oct. 5, 2016, 1:03 AM), http://www.thedailybeast.com/articles/2016/10/05/suboxone-creator-said-its-pills-killed-kids-to-make-1-billion.html [https://perma.cc/9D3N-M7BB].

[115] Ed Silverman, *Senator Urges FTC to Step Up Investigation into Maker of Addiction Treatment*, STAT (Sept. 27, 2016), https://www.statnews.com/pharmalot/2016/09/27/ftc-antitrust-suboxone-markey/ [https://perma.cc/S7G5-BUFU].

Reckitt succeeded in forestalling generic entry by introducing a modified version of buprenorphine/naloxone. In 2010, the company received FDA approval of a film formulation of the drug,[116] having submitted a patent for both the film and its underlying delivery system in 2008.[117] Reckitt subsequently announced its intention to stop producing the tablet formulation of buprenorphine/naloxone and in September 2012 filed a citizen petition requesting that the FDA not approve any generic versions of it.[118] Reckitt argued that the tablets posed an unacceptably high safety risk, citing a study that found that accidental pediatric exposure to buprenorphine (the dangerous component) in one quarter of 2012 was more than eight times higher for tablets than for film.[119]

The FDA reviewed the petition carefully but was ultimately not swayed, issuing a denial five months later.[120] In its rejection letter, the agency responded that the study did not capture the degree of the exposures.[121] The FDA further noted that there was a decreasing rate of exposure over the study period.[122] The letter concluded by raising concern that Reckitt was engaging in a pattern of anticompetitive behavior and forwarded the matter to the Federal Trade Commission (FTC) for investigation.[123] On the same day it issued the letter, the FDA approved two generic versions of buprenorphine/naloxone, a decision that had been delayed pending resolution of the petition.[124]

Reckitt also capitalized on a relatively new feature of the prescription drug marketplace: a risk evaluation and mitigation strategy (REMS). In 2007, Congress gave the FDA authority to impose REMS on drugs with known or suspected safety concerns to make sure the benefits of use outweigh the risks.[125] Possible REMS components range from medication guides to more rigorous elements to assure safe use, which can include prescriber or pharmacy certification, dispensing limits, and follow-up testing.[126] Under federal law, brand-name and generic manufacturers of a drug must use a shared REMS unless the Secretary of the Department of Health and

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[116] Press Release, Reckitt Benckiser Pharma. Inc., Reckitt Benckiser Pharmaceuticals, Inc. Receives FDA Approval for Suboxone (Buprenorphine and Naloxone) Sublingual Film C-III (Sept. 7, 2010, 8:29 AM), http://www.fiercebiotech.com/biotech/reckitt-benckiser-pharmaceuticals-inc-receives-fda-approval-for-suboxone%C2%AE-buprenorphine-and [https://perma.cc/CE4X-LHSG].

[117] U.S. Patent No. 8,017,150 (filed Apr. 22, 2008).

[118] Reckitt Benckiser Pharma. Inc. Citizen Petition, No. FDA-2012-P-1028 (Sept. 25, 2012).

[119] *Id.* at 2.

[120] FDA Response to Reckitt Benckiser Pharma. Inc. Citizen Petition, FDA, No. FDA 2012-P-1028-0007 (Feb. 22, 2013).

[121] *Id.* at 14.

[122] *Id.* at 15.

[123] *Id.* at 15–16.

[124] *Id.* at 2.

[125] Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823, 926 (codified at 21 U.S.C. § 355-1(a)(1)(E) (2012)).

[126] 21 U.S.C. § 355-1(e)–(f) (2012).

Human Services determines that such an arrangement would be too burdensome or the REMS is patented.[127]

Given the risk of opioid abuse, the FDA subjected buprenorphine/naloxone to a REMS with elements to assure safe use.[128] When generic manufacturers prepared to enter the market, however, Reckitt refused to cooperate on a shared system.[129] As alleged in a complaint filed by thirty-seven states in 2016, Reckitt "[m]erely feigned cooperation with the shared REMS development process and used deceptive tactics for months to hide its true intent, which was to delay the generic industry from obtaining . . . approvals."[130]

The contrast between extended-release oxycodone and buprenorphine/naloxone was in this respect striking. The same regulatory issues that helped spur overutilization of the former drug resulted in reduced access to the latter.

### *D. A Shift from Prescription Opioids to Heroin and Fentanyl*

The resulting persistence of high opioid demand and reduced prescription opioid supply contributed to a burgeoning use of illicit opioids. Between 2010 and 2014, heroin-related overdose deaths increased 248%.[131] More recently, there has been a spike in the use of street-manufactured fentanyl, a potent synthetic opioid, facilitated by an influx of drug and drug manufacturing equipment from China.[132] In 2015 alone, fentanyl-related deaths spiked over 109% in Ohio, over 55% in Maryland, and over 77% in Florida.[133] The growing marketplace for illicit opioids has made systematically monitoring and combating the epidemic more difficult and compounded the risk of death or injury stemming from weak quality controls.

## III. Wider Problems

The regulatory factors that helped launch and exacerbate the opioid epidemic have also delayed generic entry and driven overuse of numerous other

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[127] 21 U.S.C. § 355-1(i)(1)(B) (2012).

[128] *See* Lindsay R. Hovestreydt, *The Impact of REMS on Pain Management*, U.S. Pharmacist (May 18, 2011), https://www.uspharmacist.com/article/the-impact-of-rems-on-pain-management [https://perma.cc/3MR4-UPYS].

[129] *See* FDA Response to Reckitt Benckiser Pharma. Inc. Citizen Petition, *supra* note 120, at 16.

[130] Complaint at 25, Wisconsin v. Indivior Inc., No. 2:16-CV-05073 (E.D.P.A. 2016).

[131] U.S. Drug Enforcement Admin., DEA-DCT-DIR-031-16, (U) National Heroin Threat Assessment Summary—Updated 2 (2016).

[132] *See* Richard G. Frank & Harold A. Pollack, *Addressing the Fentanyl Threat to Public Health*, 376 New Eng. J. Med. 605, 605 (2017); David Armstrong, *"Truly Terrifying": Chinese Suppliers Flood US and Canada with Deadly Fentanyl*, STAT (Apr. 5, 2016), https://www.statnews.com/2016/04/05/fentanyl-traced-to-china/ [https://perma.cc/RU4T-QDCK].

[133] Evan Horowitz, *The Heroin Epidemic Is Spreading*, Bos. Globe (Dec. 22, 2016), https://www.bostonglobe.com/metro/2016/12/22/the-heroin-epidemic-spreading/xA6vxWHhGMncXW6xfDCzFI/story.html [https://perma.cc/MD76-32Z3].

brand-name prescription drugs, resulting in high prescription drug prices and expenditures.

### *A. Non-Rigorous Patenting Standards*

Non-rigorous patenting standards have enabled pharmaceutical companies to obtain a steadily increasing number of patents on drugs,[134] extending the market exclusivity of these products. A 2012 investigation, for example, identified over one hundred secondary patents tied to the antiretroviral treatments ritonavir (Norvir) and lopinavir/ritonavir (Kaletra).[135]

Many such patents relate to subject matter that does not constitute a meaningful clinical advance. Novartis's transformative chronic myelogenous leukemia drug imatinib (Gleevec) offers a prime example. The primary patent for imatinib expired in 2015.[136] However, Novartis was able to extend its market exclusivity an additional year by patenting a modified crystal of the drug's active ingredient without evidence of improved safety or effectiveness.[137] Between 2001 and 2016, Novartis raised the list price of imatinib over fourfold, from $26,400 to over $120,000.[138]

Secondary patenting is most harmful in the context of hard switches. In such instances, patients have no recourse but to use the costly new product, which will not be eligible for substitution when generic versions of the original product emerge.[139] However, emerging case law suggests that hard switches could constitute an illegal restraint of trade. In *New York ex rel. Schneiderman v. Actavis, PLC*,[140] the Second Circuit affirmed a preliminary injunction requiring Actavis to continue selling the immediate-release formulation of the Alzheimer's drug memantine (Namenda) to circumvent the

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[134] *See generally* ADAM B. JAFFE & JOSH LERNER, INNOVATION AND ITS DISCONTENTS: HOW OUR BROKEN PATENT SYSTEM IS ENDANGERING INNOVATION AND PROGRESS, AND WHAT TO DO ABOUT IT (3d ed. 2007) (arguing in part that the lax application of patenting standards has led to a proliferation of patents).

[135] Amin & Kesselheim, *supra* note 65, at 2288.

[136] Rena M. Conti et al., *Changing the Cost of Care for Chronic Myeloid Leukemia: The Availability of Generic Imatinib in the USA and the EU*, 94 ANNALS HEMATOLOGY S249, S249 (2015).

[137] *See* U.S. Patent No. 6,894,051 (filed July 16, 1998); U.S. Patent No. 7,544,799 (filed Sept. 5, 2006); *see also* Gary Moss, *Has the Developed World Been TRIPSed Up?*, THE PATENT LAWYER, http://www.patentlawyermagazine.com/has-the-developed-world-been-tripsed-up/ [https://perma.cc/8NMS-RG3A]; Ameet Sarpatwari et al., *Factors Influencing Prescription Drug Costs in the United States—Reply*, 316 JAMA 2431, 2432 (2016) (noting that patenting determinations for crystalline structures, formulations, and single-isomer isolations of mixed enantiomer products "do[ ] not require an assessment of clinical superiority"); Novartis AG v. Union of India (2013) 13 S.C.R. 169 (India) (stating that Novartis made "no claim of superiority" for the modified crystal).

[138] Carolyn Y. Johnson, *This Drug Is Defying a Rare Form of Leukemia—and It Keeps Getting Pricier*, WASH. POST (Mar. 9, 2016), https://www.washingtonpost.com/business/this-drug-is-defying-a-rare-form-of-leukemia—and-it-keeps-getting-pricier/2016/03/09/4fff8102-c571-11e5-a4aa-f25866ba0dc6_story.html?utm_term=.ec0b5f147e46 [https://perma.cc/9V8X-BXQJ].

[139] Capati & Kesselheim, *supra* note 77, at 339.

[140] 787 F.3d 638 (2d Cir. 2015).

company's attempt to force patients onto the newer extended-release memantine (Namenda XR).[141]

Yet even without hard switches, secondary patenting can help maintain high drug prices. When drug manufacturers introduce a modified, patent-protected product onto the market, they generally promote it heavily and cease advertising of the original. Such promotion is usually successful in increasing sales of newer, non-substitutable products despite the existence of clinically comparable, less expensive alternatives.[142]

### *B. Eleventh-Hour Citizen Petitions*

Like Purdue and Reckitt, many pharmaceutical companies have used citizen petitions to delay generic entry. For example, in December 2015, just one day before the loss of its market exclusivity for the long-acting birth control device levonorgestrel intrauterine system (Mirena), Bayer filed a citizen petition requesting the FDA to refrain from approving any generic versions of the product that did not meet heightened safety requirements.[143] As of January 2017, the FDA had yet to rule on the petition.[144] Between 2011 and 2015, brand-name manufacturers filed 108 citizen petitions over generic drug applications, of which thirty-nine percent were filed within six months of loss of market exclusivity.[145] Only two percent were approved, but each consumed a substantial investment of FDA resources and time.[146]

### *C. REMS-Based Delays*

Likewise, several pharmaceutical companies have used REMS programs to obstruct generic drug applications to the FDA. Such obstruction has included the refusal to cooperate in a shared REMS, as seen with Reckitt. Delay has also been achieved through the creation of REMS-based restricted distribution networks, in which patients can only receive a drug through select pharmacies. Although these networks can facilitate safety monitoring and clinical support services, they have also been used to deny generic drug companies access to necessary samples of brand-name product for bioe-

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[141] *See id.* at 642–48. *But see* Mylan Pharm. v. Warner Chilcott Pub. Ltd. Co., Civ. No. 12-3824, 2015 WL 1736957 at *12 (E.D. Pa. Apr. 16, 2015) (denying relief under similar circumstances).

[142] *See* Jerry Avorn et al., *Scientific Versus Commercial Sources of Influence on the Prescribing Behavior of Physicians*, 73 JAMA 4, 7 (1982); *see also* Puneet Manchanda & Elisabeth Honka, *The Effects and Role of Direct-to-Physician Marketing in the Pharmaceutical Industry: An Integrative Review*, 5 YALE J. HEALTH POL'Y & ETHICS 785, 787–88 (2005); Ashley Wazana, *Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift?*, 283 JAMA 373, 378–79 (2000).

[143] *See* Michael A. Carrier & Carl Minniti, *Citizen Petitions: Long, Late-Filed, and At-Last Denied*, 66 AM. U. L. REV. 305, 346–47 (2016); Bayer Healthcare LLC Citizen Petition, No. FDA-2015-P-4600 (Dec. 3, 2015).

[144] Carrier & Minniti, *supra* note 143, at 347.

[145] *Id.* at 332, 338, 341.

[146] *Id.* at 341.

quivalent testing—a prerequisite for FDA approval.[147] In June 2016, Senator Patrick Leahy announced that the agency had received over one hundred reports from generic drug companies unable to access brand-name drug samples.[148] One report estimated that restricted distribution networks result in $5.4 billion in forgone savings from delayed generic drug entry annually.[149]

### *D. Fraudulent Marketing*

Finally, to boost profits, pharmaceutical companies have often engaged in false or misleading marketing. Over the past twenty-five years, the industry has paid $35.7 billion to settle claims of illegal marketing, including making false or misleading claims or failing to disclose known risks.[150] In 2012, for example, GlaxoSmithKline paid three billion dollars to settle civil claims and criminal charges that it downplayed the risk of the antidepressant paroxetine (Paxil) in adolescents, promoted the antidepressant bupropion (Wellbutrin) for unapproved uses, and hid data showing the increased risk of heart attacks from the diabetes drug rosiglitazone (Avandia).[151] Although the then-largest healthcare fraud settlement in U.S. history,[152] the total penalty was "only a portion of the drug maker's profits from the drugs involved."[153] Almost every major pharmaceutical company has been caught in similar marketing scandals.[154] However, the industry remains highly profitable,[155] supporting criticism that monetary penalties generally represent "a quite small percentage of . . . global revenue and often a manageable percentage of the revenue received from the product under scrutiny."[156]

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[147] *See* Ameet Sarpatwari et al., *Using a Drug-Safety Tool to Prevent Competition*, 370 New Eng. J. Med. 1476, 1476 (2014).

[148] *See The CREATES Act: Ending Regulatory Abuse, Protecting Consumers, and Ensuring Drug Price Competition: Hearing Before the Subcomm. on Antitrust, Competition Policy & Consumer Rights of the S. Judiciary Comm.*, 114th Cong. 1 (2016) (statement of Sen. Patrick Leahy), https://www.leahy.senate.gov/press/statement-of-senator-patrick-leahy-hearing-on-the-creates-act-ending-regulatory-abuse-protecting-consumers-and-ensuring-drug-price-competition [https://perma.cc/WP8S-MAFC].

[149] Alex Brill, Matrix Global Advisors, Lost Prescription Drug Savings from Use of REMS Programs to Delay Generic Market Entry 1 (2014).

[150] Sammy Almashat et al., Public citizen, Twenty-Five Years of Pharmaceutical Industry Criminal and Civil Penalties: 1991 Through 2015 7 (2016).

[151] Press Release, Dep't of Justice, GlaxoSmithKline to Plead Guilty and Pay $3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data. (July 2, 2012), https://www.justice.gov/opa/pr/glaxosmithkline-plead-guilty-and-pay-3-billion-resolve-fraud-allegations-and-failure-report [https://perma.cc/7AK8-QLN3].

[152] *Id.*

[153] Alexandra Sifferlin, *Breaking Down GlaxoSmithKline's Billion-Dollar Wrongdoing*, Time (July 5, 2012), http://healthland.time.com/2012/07/05/breaking-down-glaxosmithklines-billion-dollar-wrongdoing/ [https://perma.cc/6EMF-6TF7].

[154] *See* Almashat et al., *supra* note 150.

[155] Richard Anderson, *Pharmaceutical Industry Gets High on Fat Profits*, BBC News (Nov. 6, 2014), http://www.bbc.com/news/business-28212223 [https://perma.cc/BWH9-M5ST].

[156] Kevin Outterson, *Punishing Health Care Fraud—Is the GSK Settlement Sufficient?*, 367 New Eng. J. Med. 1082, 1083 (2012).

## IV. Possible Solutions

Several practical reforms can help address the legal and regulatory issues that have contributed to the opioid epidemic and the rise of prescription drug costs and spending. Most do not necessitate legislation.

### *A. Challenging Patents*

First, the federal government could challenge or sponsor non-profit organizations to challenge pharmaceutical patents. In 2012, Congress created a new administrative process called "inter partes review,"[157] through which any party can challenge the novelty or non-obviousness of a patent on the basis of prior patents and printed publications.[158] These challenges are heard by the Patent Trial and Appeal Board (PTAB),[159] an administrative body of experts familiar with complex scientific and patenting issues. Decisions must be reached within eighteen months of filing.[160] This timeline is generally much quicker than traditional litigation,[161] and can thus help ensure prompt entry of low-cost generic drugs into the market.

A recent successful PTAB challenge involving the multiple sclerosis drug glatiramer (Copaxone) offers one such example. Mylan argued that three drug-specific use patents held by Yeda Research and Development Company were obvious given the existence of a prior published study of the drug in patients with multiple sclerosis.[162] By ruling in Mylan's favor, the PTAB opened the door for immediate market entry of lower-cost generics.

In general, the success rate of PTAB challenges has been high. Of all 4288 petitions for inter partes review filed between September 2012 and March 2016, 790 (18%) had a final written decision.[163] Almost three fourths of these decisions (N=576) invalidated patents.[164] More aggressive use of inter partes review could in this respect speed the introduction of affordable generics for marginally modified drugs.[165]

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[157] Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 311, 125 Stat. 284 (2012).
[158] 35 U.S.C. § 311.
[159] 35 U.S.C. § 316.
[160] 37 C.F.R. § 42.100(c) (2016).
[161] Joanna Shepherd, *Disrupting the Balance: The Conflict Between Hatch-Waxman and Inter Partes Review*, 6 NYU J. Intell. Prop. & Ent. L. 14, 31 (2016).
[162] Steve Brachmann, *PTAB Invalidates Three Patents Covering Teva's Copaxone, Opens Door for Mylan's Generic Version*, IPWatchdog (Sept. 9, 2016), http://www.ipwatchdog.com/2016/09/09/ptab-invalidates-three-patents-teva-copaxone/id=72575/ [https://perma.cc/B47Z-U3JC].
[163] Monica Grewal et al., *Trends in Inter Partes Review of Life Sciences Patents,* 92 BNA Pat. Trademark & Copyright J. 1, 2–3 (2016).
[164] *Id.*
[165] Aaron S. Kesselheim et al., *The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform*, 316 JAMA 858, 865 (2016).

### *B. Imposing Time Restrictions on Citizen Petitions*

The FDA has already taken action to address the misuse of citizen petitions by brand-name drug manufacturers. Last year, the agency promulgated a final rule requiring petitioners to report when information in their citizen petitions first became known.[166] Armed with this knowledge, the FDA could in theory better exercise its existing authority to summarily deny citizen petitions filed "with the primary purpose of delaying the approval of an application" and which "does not on its face raise valid scientific or regulatory issues."[167]

In practice, however, it is unlikely the rule will bring about meaningful change. Most citizen petitions submitted with the primary aim of delay raise valid scientific or regulatory issues, which the FDA must investigate. In the case of buprenorphine/naloxone, for example, the agency would have been hard pressed to label the issue of accidental opioid exposure facially invalid. Policing whether companies truthfully report when information first became known will additionally prove challenging.

A more practical solution to combat "sham" citizen petitions would be for the FDA to impose time restrictions on filing. Brand-name manufacturers could be required to submit citizen petitions pertaining to generic drug applications nine months before the expiration of the primary patent on the brand-name drug.[168] As Avery et al. note, "Limiting opportunities to interfere with the ANDA approval process through such restrictions would stop dubious eleventh-hour citizen petitions and require petitioners to put forth their best arguments in a timely manner."[169]

### *C. Compelling Sample Sharing for Bioequivalence Studies*

Federal agencies have likewise taken initial steps to tackle the misuse of REMS. In March 2013, the FTC filed an amicus brief in *Actelion v. Apotex*,[170] in which several generic companies alleged that Actelion used the REMS for the pulmonary hypertension drug bosentan (Tracleer) to deny them access to samples for bioequivalence testing.[171] Although refraining from commenting directly on the case, the FTC argued that it was possible for such refusals to constitute antitrust violations.[172] In making this point, the commission commented that "the unique regulatory framework governing

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[166] 21 C.F.R. § 10 (2016).

[167] 21 U.S.C. § 355(q)(1)(E) (2012).

[168] Matthew Avery et al., *The Antitrust Implications of Filing "Sham" Citizen Petitions with the FDA,* 65 HASTINGS L.J. 113, 145 (2013).

[169] *Id.*

[170] Complaint at 8, Actelion Pharm. Ltd. v. Apotex, Inc., 2013 WL 5524078 (D.N.J. Sept. 6, 2013) (No. 12-5743).

[171] Brief for Fed. Trade Comm'n as Amicus Curiae Supporting Plaintiffs at 5, *Actelion*, 2013 WL 5524078 (No. 12-5743).

[172] *Id.* at *8.

the pharmaceutical industry may create conditions that increase the potential for anticompetitive conduct that prevents or delays generic competition."[173]

The following year, the FDA published draft guidance informing generic drug manufacturers of the ability to request safety certification of their bioequivalence testing protocols.[174] The guidance further assured brand-name drug manufacturers that sharing samples with the holders of such certificates would not constitute a REMS violation.[175]

In this case, legislative action may be necessary. Antitrust litigation is generally a timely, costly, and complicated affair. FDA safety certifications, moreover, will not be helpful when brand-name manufacturers use safety as a pretext for refusing to share samples. Congress should accordingly pass the Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act, which would enable generic drug manufacturers to secure injunctions compelling brand-name manufacturers to participate in court-supervised negotiations for developing shared REMS programs and to share product samples on "commercially reasonable terms" for bioequivalence testing.[176] Introduced in 2016, this legislation has made little headway to date.

### *D. Promoting Comparative Cost-Effectiveness Research and Dissemination*

To change the culture regarding fraudulent marketing in the pharmaceutical industry, some commentators have suggested that the FDA take a more concerted effort to rely less upon monetary settlements and instead pursue criminal convictions for corporate officers responsible for company misdeeds.[177] A framework for such a policy was outlined in the Department of Justice's September 2015 "Yates Memo," in which department lawyers were instructed not to "release culpable individuals from civil or criminal liability" or base decisions on a party's "ability to pay" when resolving a case.[178] Others have called on the federal government to more fully exercise its authority to exclude companies that do engage in fraudulent marketing from

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[173] *Id.*

[174] *How to Obtain a Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections Comparable to Applicable REMS for RLD: Guidance for Industry,* FOOD & DRUG ADMIN. (Feb. 4, 2016). http://www.policymed.com/2015/02/how-to-obtain-a-letter-from-fda-stating-that-bioequivalence-study-protocols-contain-safety-protectio.html [https://perma.cc/J2RE-T9V5] (demonstrating that "bioequivalence" requires generic drug manufacturers to undertake biochemical and pharmacokinetic studies in order to demonstrate that their generic drug is clinically indistinguishable from the brand name drug they seek to duplicate).

[175] *Id.*

[176] S. 3056, 114th Cong. (2016).

[177] *See generally* RENA STEINZOR, TOO BIG TO JAIL: INDUSTRIAL CATASTROPHES, CORPORATE MALFEASANCE, AND A GOVERNMENT MISSING IN ACTION (2014) (arguing for more accountability for and aggressive prosecution of corporate officers for industrial accidents).

[178] Memorandum from Sally Q. Yates, Deputy Att'y Gen., U.S. Dep't of Justice, on Individual Accountability for Corporate Wrongdoing to All U.S. Att'ys et al. (Sept. 9, 2015) https://www.justice.gov/archives/dag/file/769036/download [https://perma.cc/3WMM-S9KZ].

participating in federal healthcare programs, the so-called corporate death sentence.[179]

While these proposed policies are laudable, proactive measures are also needed. To address false or misleading marketing—and the one-sidedness of information in the commercial marketplace generally—Congress could authorize the FDA to impose user fees that would fund comparative cost-effectiveness research and dissemination. An increasing number of organizations, including the Institute for Clinical and Economic Review,[180] the Independent Drug Information Service,[181] and the American Society for Clinical Oncology,[182] are working on such research, but their resources are limited. Greater funding of such efforts would enable physicians and patients to make more informed, evidence-based treatment decisions.

## Conclusion

Weak patenting standards and ineffectual policing of both anticompetitive actions and fraudulent marketing have played a key role in driving the opioid epidemic and rising drug prices and spending. These regulatory shortcomings provide incentives and pathways for the overutilization of costly and often harmful branded prescription drugs while hindering access to low-cost generics. Several practical reforms—including more aggressive secondary patent challenges, filing deadlines for citizen petitions, legislation to compel sample sharing for bioequivalence testing, and marketing fees to promote evidence-based prescribing—can help provide Americans with relief and thus deserve greater attention.

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[179] Lise T. Spacapan & Jill M. Hutchison, *Prosecutions of Pharmaceutical Companies for Off-Label Marketing: Fueled by Government's Desire to Modify Corporate Conduct or Pursuit of a Lucrative Revenue Stream?*, 22 Annals Health L. 407, 407 (2013).

[180] Peter B. Bach & Steven D. Pearson, *Payer and Policy Maker Steps to Support Value-Based Pricing for Drugs*, 314 JAMA 2503, 2503 (2014).

[181] *Independent Drug Information Service*, Alosa Found., http://www.alosafoundation.org/independent-drug-information-service/ [https://perma.cc/SGT2-SCCK].

[182] Lowell E. Schnipper et al., *American Society of Clinical Oncology Statement: A Conceptual Framework to Assess the Value of Cancer Treatment Options*, 33 J. Clin. Oncology 2563, 2563 (2015).