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Robin Feldman
UC Hastings College of the Law, feldmanr@uchastings.edu

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Robin Feldman[*,1]

Hastings College of the Law, University of California, 200 McAllister St. San Francisco, CA 94102, USA
Corresponding author. E-mail: feldmanr@uchastings.edu

ABSTRACT

Presenting the first comprehensive study of evergreening, this article examines the extent to which evergreening behavior—which can be defined as artificially extending the protection cliff—may contribute to the problem. The author analyses all drugs on the market between 2005 and 2015, combing through 60,000 data points to examine every instance in which a company added a new patent or exclusivity. The results show a startling departure from the classic conceptualization of intellectual property protection for pharmaceuticals. Rather than creating new medicines, pharmaceutical companies are largely recycling and repurposing old ones. Specifically, 78% of the drugs associated with new patents were not new drugs, but

* Robin Feldman is the Arthur J. Goldberg Distinguished Professor of Law and Director of the Institute for Innovation Law at the University of California Hastings. Her most recent books in the life sciences are Drug Wars (Cambridge) and Rethinking Patent Law (Harvard). Professor Feldman also has published more than 50 articles in law journals including at Harvard, Yale, and Stanford, as well as in the American Economic Review and the New England Journal of Medicine. Professor Feldman's empirical work has been cited by the White House and numerous federal agencies. She has appeared frequently before committees of the US House and Senate, the Federal Trade Commission, the Department of Justice, the Patent & Trademark Office, and various committees of the California legislature. Professor Feldman recently participated in the GAO's preparation of a report to Congress on the future of Artificial Intelligence and in the Army Cyber Institute's threat casting exercise on weaponization of data.

1 In accordance with the protocols outlined in the *Harvard Journal of Law & Technology Open Letter on Ethical Norms*, upon final publication, all of the data will be publicly available for future use by other academics on the Inter-University Consortium for Political and Social Research (ICPSR), https://www.icpsr.umich.edu/icpsrweb/ (accessed Nov. 1, 2018); *see also* Robin Feldman et al., *Open Letter on Ethical Norms in Intellectual Property Scholarship*, 29 HARVARD J. L. & TECH. 339, 350–52 (2016) (signed by dozens of professors). In further accord with the *Open Letter*, donation information for the University of California Hastings Institute for Innovation Law, which Robin Feldman directs, is available at *Donors*, INST. FOR INNOVATION L.: UC HASTINGS COLLEGE OF L. (May 3, 2017), http://innovation.uchastings.edu/about/funding/funding-for-academic-year-2015-2016 [https://perma.cc/EK2K-XB72].

existing ones, and extending protection is particularly pronounced among blockbuster drugs. Once companies start down the road of extending protection, they show a tendency to return to the well, with the majority adding more than one extension and 50% becoming serial offenders. The problem is growing across time.

KEYWORDS: Drugs, Pricing, Patents, Evergreening, Pharmaceuticals

I. INTRODUCTION

The intellectual property system has a simple and intuitive design at its core. From the store of activities that should be free to all people, we remove some, for a limited time and a limited purpose, in the hopes that the pause will rebound to the benefit of all of society.[2] This conceptualization echoes basic Lockean theories on the formation of government, in which individuals emerge from perfect freedom in the state of nature, choosing to relinquish certain liberties (and only certain ones) for these individuals' mutual benefit.[3] One can wax poetic about the complicated pathways of the intellectual property system—the intricacies of state and federal powers,[4] the delicate dance

2 ROBIN FELDMAN & EVAN FRONDORF, DRUG WARS: HOW BIG PHARMA RAISES PRICES AND KEEPS GENERICS OFF THE MARKET 8 (2017); *see also* U.S. CONST. art. I, § 8, cl. 8 (the Intellectual Property Clause of the Constitution states that, 'The Congress shall have Power . . . To promote the Progress of Science and useful Arts, by securing for *limited times* to Authors and Inventors the exclusive Right to their respective Wrings and Discovers…' (emphasis added)); Pennock v. Dialogue, 27 U.S. 1, 16–17 (1829) ('[The Constitution] contemplates … that this exclusive right shall exist but for a limited period…'); Bonito Boats v. Thunder Craft Boats, 489 U.S. 141, 146 (1989) ('Congress may not create patent monopolies of unlimited duration . . .'); Letter from Thomas Jefferson to Oliver Vans (May 2, 1807), in THE WRITINGS OF THOMAS JEFFERSON 200–202 (Andrew A. Lipscomb ed., 1903) (Jefferson writing, 'Certainly an inventor ought to be allowed a right to the benefit of his invention for some certain time. It is equally certain it ought not be perpetual; for to embarrass society with monopolies for every utensil existing, & in all the details of life, would be more injurious to them than had the supposed inventors never existed'); WILLIAM C. ROBINSON, THE LAW OF PATENTS FOR USEFUL INVENTIONS 42–43 (1890) (arguing that '[t]he duty which the state owes to the people to obtain for them, at the earliest moment, the practical use of every valuable invention in the industrial arts is … a higher and more imperative duty than which it owes to the inventor'; *see generally* Edward C. Walterscheid, *Defining the Patent and Copyright Term: Term Limits and the Intellectual Property Clause*, 7 J. INTELL. PROP. L. 315 (1999–2000) (exploring term limits on rights granted in the Intellectual Property Clause).

3 See PETER LASLETT & JOHN LOCKE: TWO TREATISES OF GOVERNMENT: A CRITICAL EDITION 336–37, 341, 343, 351 (1967) (including a reprinting of the 1698 version of Locke's Two Treatises); *see also* Paul Brest, *State Action and Liberal Theory: A Casenote on Flagg Brothers v. Brooks*, 130 U. PA. L. REV. 1296, 1300 (1982) (noting that in the Lockean modality, courts embrace the natural rights view of a sphere of autonomous private conduct immune from state regulation); Robin Feldman, *Coming to the Community* in IMAGINING NEW LEGALITIES: PRIVACY AND ITS POSSIBILITIES IN THE 21st CENTURY 88 (Austin Sarat ed., 2012).

4 See Robin Feldman, *Federalism, First Amendment & Patents: The Fraud Fallacy*, 17 COLUM. SCI. & TECH. L. REV. 30, 32 (2015) (Discussing the overlap between federal and state laws with regard to intellectual property, and patent regulation in particular); *see also* Hoke v. United States, 227 U.S. 308, 322 (1913) (Noting that while 'state and Nation [have] different spheres of jurisdiction . . . it must be kept in mind that we are one people; and the powers reserved to the states and those conferred on the nations are adapted to be exercised, whether independently or concurrently, to promote the general welfare . . . .'). For a general discussion of federal preemption, see Jeanne C. Fromer, *The Intellectual Property Clause's Preemptive Effect*, in INTELLECTUAL PROPERTY AND THE COMMON LAW 265, 279 (Shayamkrishna Balganesh ed., 2014); Mark A. Lemley, *Beyond Preemption: The Law and Policy of Intellectual Property Licensing*, 87 CAL. L. REV. 111 (1999).

of biosimilars,[5] the vastness of open source and open science,[6] and the strange overlap of different protection regimes.[7] Nevertheless, the basic concept of the US intellectual property system is quite simple: give inventors the possibility of garnering a return from their innovations, and they will invest in creating those innovations and in sharing the fruits of their labors with society.[8]

At first glance, one might think the intellectual property system eschews competition. After all, the system is designed to grant benefits that block competitors, giving the rights holder free reign in the market, a result that is decidedly non-competitive.[9] That perspective, however, only skims the surface of the theoretical bases of intellectual property. The reality is far more nuanced and layered when one plunges the depths of the system's design.

At a fundamental level, the intellectual property system exudes a deep faith in the power of competition. Competition may be held in abeyance, but those who receive the benefit of a patent or exclusivity must pay for that privilege by disclosing sufficient information such that competitors will be able to step into the market. And as the protection clock winds down, other inventors can use that disclosure, making preparations to enter the competitive field or jump ahead to the next generation.[10]

Nowhere does this concept apply more fully than with pharmaceutical development. The processes of developing new drugs, conducting the clinical trials, obtaining FDA approval, and bringing the drugs to market are extraordinarily expensive.

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5 See FELDMAN & FRONDORF, *supra* note 2 at 142; *see generally* Jason Kanter & Robin Feldman, *Understanding and Incentivizing Biosimilars*, 64 HASTINGS L. J. 57 (2012) (analysing and identifying issues with the Biosimilars Act).

6 For background on the Open Science method, *see generally* Jennifer Molloy, *The Open Knowledge Foundation: Open Data Means Better Science*, PLOS BIOL. (Dec. 6, 2011), https://doi.org/10.1371/journal.pbio.1001195 (accessed Nov. 1, 2018); *see generally* Dasgupt Partha & Paul A. David, *Toward a New Economics of Science*, 23 RES. POL'Y 487 (1994); *see generally* Paul A. David, *Understanding the Emergence of 'Open Science' Institutions: Functional Economics in Historical Context*, 13 INDUS. & CORP. CHANGE 571 (2004); *see also* Robin Feldman, *The Open Source Biotechnology Movement: Is It Patent Misuse?*, 6 MINN. J. L. SCI. & TECH. 117, 122 (2004).

7 See *eg* Scott McBride, *Bioinformatics and Intellectual Property Protection*, 17 BERKELEY TECH. L. J. 1331, 1342–52 (2002) (discussing the applicability of patent law and copyright law to components of bioinformatics); see Scott D. Locke & David A. Kalow, *Preparing for Bioinformatics Litigation: How Will the Courts Confront the Next Generation of Biotechnology Patents?*, 1 BUFF. INTELL. PROP. L. J. 76, 78 n.8 (2001) (noting that patents and copyright database protections operate to protect bioinformatics); *see also* Peter Lee & Madhavi Sunder, *The Law of Look and Feel,* 90 S. CAL. L. REV. 529, 531(2017) (noting that the law of design is 'splintered among various doctrines in copyright, trademark, and patent law'). Design patent is 'confused and confusing' in the way it draws from copyright, patent, and trademark law.

8 Intellectual property in the international arena at times rests on the notion of a creator's moral rights, but the intellectual property system in the United States has been decidedly utilitarian since the Founding Fathers inked the patent and copyright clause into the Constitution. See ROBIN FELDMAN, RETHINKING PATENT LAW 178 (2012).

9 For sources discussing the contrast between antitrust and patent law, for example, see Robin C. Feldman, *The Insufficiency of Antitrust Analysis for Patent Misuse*, 55 HASTINGS L. J. 399, 403 (2003) (discussing the inadequacy of antitrust law to address potential economic harms that may flow from granting a patent, since antitrust law doesn't recognize harms unless a patented drug gets a large enough market share to constitute a monopoly); *see generally* Robin Feldman, *Patent and Antitrust Differing Shades of Meaning*, 13 VA. J. L. & TECH 5 (2008) ('In reductionist form, the two concepts pose a natural contradiction: One encourages monopoly, while the other restricts it').

10 See Robin Feldman, *Regulatory Property: The New IP,* 40 COLUM. J. L. & ARTS 53, 67–68 (2016).

Scholars and commentators disagree over the magnitude of the cost,[11] but no matter how one measures it, big is big. The prospect that a second-comer could simply copy the drug after all that effort would deter even the heartiest of souls, and thus the intellectual property system provides the opportunity to secure a return. In idealized form, a company invests in developing a drug: when the company succeeds, it obtains market exclusivity for a period of time, and when the exclusivity expires, generic companies step in to create a vigorous competitive environment.

In discussing the pharmaceutical industry, the broader term 'intellectual property' should be used, rather than the narrower term 'patent'. Although patent protection is a critical component of the incentive structure society provides for pharmaceutical development, it is not the only component.[12] The federal government offers more than 10 other forms of exclusivity that can be used to keep competitors at bay. Companies can earn exclusivity benefits for activities such as development of drugs for smaller populations[13] or for conducting pediatric studies.[14]

Whether society grants intellectual property in the form of a patent or a regulatory exclusivity, the systems are designed such that after a period of time, competitors may enter. Information revealed in the patent allows others to create a competing drug (rather than going through the research again, themselves).[15] Data used in clinical trials for the drug are available, after a period of exclusivity, so that follow-on generics need only prove their drug is the same, rather than repeating the original company's safety and efficacy trials.[16] Thus, when the benefit expires, competitors should step in and competition should drive prices down to competitive levels—at least in theory. The reality for pharmaceutical products, however, lies far from the system's theoretical design.

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11 A 2014 study from the Tufts Center for the Study of Drug Development found that developing a new drug costs approximately $2.5 billion dollars, which includes the costs of compound failures. See Tufts Center for the Study of Drug Development, Costs of Developing a New Drug (2014), https://csdd.tufts.edu/csddnews/2018/3/9/march-2016-tufts-csdd-rd-cost-study (accessed Nov. 1, 2018). This finding has been challenged on multiple fronts. See Steve Morgan et al., *The Cost of Drug Development: A Systematic Review*, 100 Health Pol'y 4 (2011), www.ncbi.nlm.nih.gov/pubmed/21256615 (accessed Nov. 1, 2018) (analysing 13 different studies to estimate that drug development costs range from $161 million to $1.8 billion); Aaron E. Carroll, *$2.6 Billion to Develop a Drug? New Estimate Makes Questionable Assumptions*, New York Times (Nov. 18, 2014), www.nytimes.com/2014/11/19/upshot/calculating-the-real-costs-of-developing-a-new-drug.html (suggesting that the disparity in the findings stem from methodological mistakes in the Tuft study, and noting that the Tufts Center is funded by pharmaceutical companies); Tufts Center for the Study of Drug Development, Financial Disclosure, https://csdd.tufts.edu/financial-disclosure/ (accessed Nov. 1, 2018).

12 See Feldman, *supra* note 10, at 75 (categorizing and analysing 13 forms of non-patent protection for pharmaceuticals, with a summary chart at Appendix A); *see also Michael* G. Daniel et al., *The Orphan Drug Act: Restoring the Mission to Rare Diseases*, 39 Am. J. Clin. Oncol. 210, 210 (2016).

13 See 21 U.S.C. §§ 360bb– 360cc (2012) (containing Orphan Drug Act definitions and benefits); see Feldman, *supra* note 10 at 54.

14 See 21 U.S.C. § 355a(b) (creating a market exclusivity for performing pediatric studies of a drug); *see also* Feldman, *supra* note 10, at 86; *see also infra* notes 51–52 and accompanying text (describing the 6-month exclusivity for generic first filers who make what are known as 'Paragraph IV' certifications under the Hatch-Waxman Act); *see also infra* notes 116–119, 121 and accompanying text (describing the Orphan Drug exclusivity and the exclusivity granted for pediatric studies).

15 See 35 U.S.C. §112 (Patent Act section mandating disclosure sufficient that a person skilled in the art can make and use the invention).

16 See Feldman, *supra* note 10, at 68 (describing how the Hatch-Waxman Act created a pathway for generics to use existing clinical trials data when they enter the market); *see also* 21 U.S.C. § 355(j) (2012).

It is no exaggeration to say that drug prices have skyrocketed. The cost of prescription medication is growing faster than any other form of health care spending, including hospitalization or nursing home care.[17] These price increases can be seen in specialty drugs—such as the antimalarial drug Daraprim,[18] which Martin Shkreli's company famously increased from $13.50 per tablet to $750 per tablet—and in more common drugs—such as the rheumatoid arthritis drug Humira, whose price has increased by 126%.[19]

Inspired by the rise, new medications are entering the market at astoundingly high prices. Gilead's new treatment for hepatitis C lists at a hefty $84,000 to treat a single patient,[20] Marathon's muscular dystrophy drug debuted in the United States this year at $89,000, for a drug that reportedly can be obtained in other countries at $1500.[21] Prices like this can be cost-prohibitive. For example, the cost for the Department of Defense to treat all infected patients in the VA with Gilead's hepatitis C drug, Sovaldi would amount to $12 billion—more than '20% of the department's $57 billion medical budget in fiscal year 2014'.[22] In California, just treating 3624 patients cost the state more than

17 See Altarum Institute Center for Sustainable Health Spending, *Health Sector Economic Indicators: Insights from National Monthly Price Indices through July 2015*, Altarum Institute (Sept. 11, 2015), http://altarum.org/sites/default/files/uploaded-related-files/CSHS-Price-Brief_September_2015.pdf; Murray Aitken, *Understanding the Dynamics of Drug Expenditure*, Quantiles IMS Institute 6 (2017), https://www.iqvia.com/institute/reports/understanding-the-dynamics-of-drug-expenditure-shares-levels-compositions-and-drivers (accessed Nov. 1, 2018) (noting that net drug expenditure in the USA increased from $377 per person in 1995 to $974 per person in 2015); *Id.* at 11 (showing that 'invoice price increases on protected drug brands' have been 'a significant driver of growth' in drug expenditures in the USA between 1996 and 2015); Aimee Picci, *Martin Shkreli-Style Drug Price Hikes are Everywhere*, Moneywatch (Feb. 2016) (citing Robert Langreth & Rebecca Spalding, *Shkreli Was Right; Everyone's Hiking Drug Prices*, Bloomberg (Feb. 2016), https://www.bloomberg.com/news/articles/2016-02-02/shkreli-not-alone-in-drug-price-spikes-as-skin-gel-soars-1-860 (accessed Nov. 1, 2018), https://www.cbsnews.com/news/martin-shkreli-style-drug-price-hikes-are-everywhere/ (accessed Nov. 1, 2018) (noting that '[a]bout 20 of the top prescription drugs have at least quadrupled' their prices from 2014 to 2016).

18 Andrew Pollack, *Drug Goes From $13.50 a Tablet to $750, Overnight*, New York Times (Sept. 20, 2015), https://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html (accessed Nov. 1, 2018) (noting that the price of Daraprim was as low as $1 in 2010 before a series of acquisitions).

19 CBS News, *Analysis Uncovers Huge Spike in Prescription Drug Prices*, CBS News (Apr. 5, 2016), http://www.cbsnews.com/news/prescription-drug-prices-spike/.

20 CBS News, *Lawmaker: Costly Hepatitis C Drug 'A Slap in the Face to Veterans'*, CBS News (Feb. 3, 2016), http://www.cbsnews.com/news/hepatitis-c-cure-veterans-affairs-congressional-hearing-cbs-news-investigation/.

21 See Joseph Walker, *Marathon Faces Scrutiny for Price of Muscular Dystrophy Drug*, Wall Street Journal (2017), https://www.wsj.com/articles/marathon-faces-scrutiny-for-price-of-muscular-dystrophy-drug-1488752704 (accessed Nov. 1, 2018); *see also* Dan Mangan & Meg Tirrell, *Marathon 'Pauses' Launch of $89,000 Muscular Dystrophy Drug in United States amidst Price Outrage*, CNBC (2017), http://www.cnbc.com/2017/02/13/marathon-pharmaceuticals-criticized-for-outrageous-pricing-of-drug.html (accessed Nov. 1, 2018).

22 See Patricia Kime, *VA, DoD Spend More Than $450M on Costly Hepatitis Drug*, USA Today (Jan. 8, 2015), http://www.usatoday.com/story/news/politics/2015/01/08/government-heptatitis-drug-costs/21462363/; *see also* Sean P. Keehan et al., *National Health Expenditure Projections, 2014-24: Spending Growth Faster Than Recent* Trends, 34 Health Aff. 1407, 1408 (2015) (describing a 'sharp rise in prescription drug spending growth from 2.5 percent in 2013 to 12.6 percent in 2014 . . . mainly due to innovative new specialty drug treatments for hepatitis C').

$387 million.[23] Put simply, states are forced to compromise, choosing between patient health and staying afloat.[24]

The cost of drugs designated for small patient groups is particularly high. These are known as orphan drugs, and drug companies are rushing into the field. In fact, orphan drugs account for 40% of the new drugs approved in the United States. As one commentator has noted, in today's pharmaceutical market, everyone seems to be an orphan.[25] A 2017 study found that the median price of a group of orphan drugs was $140,000 per patient, per year.[26] The price of ordinary drugs was nothing to sniff at, either. The median price for drugs outside the orphan category had climbed to almost $28,000 per patient, per year.[27]

Europe has also faced rising drug prices amidst a pharmaceutical framework that provides a host of protections and exclusivities beyond traditional patent terms.[28] The European Commission is currently conducting a review of the system, 'assessing whether the pendulum has swung too far in favor of the pharma industry while potentially penalizing the generics sector, governments, and other payers and patients'.[29]

In a competitive environment, other producers would enter the market, driving down these sky-high prices. Even in suboptimally competitive markets such as health care, one might expect to see some measure of competition, at least in certain circumstances. In particular, many drugs with high prices have been available far longer

[23] Pauline Bartolone, *California Pays Insurers Millions More for Hepatitis C Drugs* (Jan. 28, 2016), http://www.npr.org/sections/health-shots/2016/01/28/464708911/california-pays-insurers-millions-more-for-hepatitis-c-drugs.

[24] See *Id; see also* Daniela Altimari, *Pricey Hep C Drug Sparks Debate About Impact on State Budget,* HARTFORD COURANT (May 8, 2015), http://www.courant.com/politics/hc-hepatitis-c-drug-20150430-story.html (noting a shortfall of $108 million in the Connecticut Department of Social Services and observing that the prohibitive cost of Sovaldi is causing some states unwillingness to treat patients in need); *see also* Bob Ecker, *Hepatitis Drug Amongst the Most Costly for Medicaid,* NPR (Dec. 15, 2015) http://www.npr.org/sections/health-shots/2015/12/15/459873815/hepatitis-drug-among-the-most-costly-for-medicaid (nothing that Gilead's Sovaldi 'was one of the top pharmaceutical costs in most states' Medicaid budgets in 2014').

[25] See Matthew Herder, *When Everyone Is an Orphan: Against Adopting a U.S.-Styled Orphan Drug Policy in Canada,* 20 ACCOUNT. RES. 227, 227 (2013); *see also* Daniel et al., *supra* note 12 at 1; *see also* OFFICE OF GENERIC DRUGS, CTR. FOR DRUG EVALUATION & RESEARCH, 2015 OGD ANNUAL REPORT: ENSURING SAFE, EFFECTIVE, AND AFFORDABLE MEDICINES FOR THE AMERICAN PUBLIC 10 (2015), https://perma.cc/R7P9-4YYD; Feldman, *supra* note 10, at 73–80 (describing the manner in which some drug companies skirt the intent of the Orphan Drug Act by dividing patient populations into small slices or by encouraging off-label use of the drug and referencing a Gilbert & Sullivan dialogue in which everyone claims to be an orphan.)

[26] See EvaluatePharma, Orphan Drug Report, EVALUATE LTD. 9 (2017), http://info.evaluategroup.com/rs/607-YGS-364/images/EPOD17.pdf (accessed Nov. 1, 2018).

[27] See *Id.*

[28] Helen Collis, *Drug Lobby's Market Protections,* POLITICO (Oct. 5, 2017), https://www.politico.eu/article/future-of-pharma-incentives-fine-line-between-incentives-and-favoritism-drug-research/ (describing various protections that extend brand-name drug monopolies, including provisions for 'additional five-year protections awarded to approved medicines whose patents began before the date of approval for sale'; '6 months of market exclusivity' for 'testing medicines in children'; '2 years of market exclusivity' for 'approved orphan medicine[s] . . . studied in children'; and '10 years of market protection' for 'medicine[s] . . . developed specifically for children'.

[29] *Id.* (noting that Edith Schippers, the Dutch health minister, has called for a review and is leading the subsequent investigation); *see also* Alice Brown et al., *Pricing & Market Access Outlook,* QUINTILES IMS HEALTH (2017), https://www.iqvia.com/-/media/quintilesims/pdfs/pricing-and-market-access-outlook-magazine-web.pdf (accessed Nov. 1, 2018) (quoting a grim forecast: 'approximately 120 new orphan drugs will receive market authorization by 2025, with an estimated budget impact of €22 billion.').

than the 20-year term of a patent, and the modern drug approval system is designed to encourage generic versions of drugs after that time. So why is the system failing?

Anecdotal evidence has identified strategic behaviors various companies have deployed to great effect. One such practice is 'evergreening', which can be defined as artificially extending the life of a patent or other exclusivity by obtaining additional protections to extend the monopoly period.[30] Scholarly work, including our own, has documented these behaviors as examples have emerged in individual cases and in press reports.[31] What has been missing from the literature, however, is a comprehensive empirical view.[32] Just how pervasive are such behaviors? Is it simply a matter of certain bad actors, to whom everyone points repeatedly, or is the problem endemic to the industry? Only by answering this question can we contemplate the extent to which reforms are needed, as well as the extent to which strategic behavior to block generic competition may be contributing to rising drug prices. This study answers the questions.

Providing a robust empirical analysis was no easy task. Transparency is not in the industry's interests, and companies have been known to go to great lengths to camouflage strategic behavior.[33] After all, a pharmaceutical company would be loath to let regulators and legislators know what it is up to, let alone competitors who might mimic the clever strategies. To accomplish our study, we turned to government sources, analysing more than a decade of data published by the US Food and Drug Administration (FDA). This involved extracting and analysing detailed information on as many as 11 different aspects of roughly 1800 drugs.

The task would have been sufficiently challenging if the information were readily available. It was not. The project required teasing information painstakingly out of each monthly and annual publication, many of which are no longer available from the government in any form. Moreover, the complexities of pharmaceutical regulation and approval require intricate analysis of the information disclosed by the government, when that information is disclosed at all. In all, our work required assembling and analysing over 160,000 individual cells of data, all entered by hand.

The results, however, were striking, and they show a startling departure from the classic conceptualization of intellectual property protection for pharmaceuticals. The data demonstrate that throughout the industry, companies create serial barriers to hold off the type of competitive entry that is fundamental to our innovative system.

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30 See *eg* FELDMAN, *supra* note 8, at 170–79 (describing evergreening and providing case history examples); *see also infra* notes 56–61, 115–116 and accompanying text (explaining evergreening and identifying quantity within our dataset of those who apply repeatedly for patent and exclusivity extensions).

31 See *generally* FELDMAN & FRONDORF, *supra* note 2; Robin Feldman et al., *Empirical Evidence of Drug Pricing Games - A Citizen's Pathway Gone Astray* 20 STAN. TECH. L. REV. 39 (2017), Sept. 1, 2016; Michael A. Carrier, Nicole L. Levidow & Aaron S. Kesselheim, *Using Antitrust Law to Challenge Turing's Daraprim Price Increase*, 31 BERKELEY TECH. L. J. (2016), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2724604 (accessed Nov. 1, 2018); C. Scott Hemphill, *An Aggregate Approach to Antitrust: Using New Data and Rulemaking to Preserve Drug Competition*, 109 COLUM. L. REV. 629 (2009), https://ssrn.com/abstract=1356530 (accessed Nov. 1, 2018); Michael A. Carrier, *Eight Reasons 'No-Authorized-Generic' Promises Constitute Reverse Payment*, 67 RUTGERS U. L. REV. 697, 716 (2016); Stacey L. Dogan & Mark A. Lemley, *Antitrust Law and Regulatory Gaming*, 87 TEX. L. REV. 685 (2009).

32 One admirable empirical analysis exists of the period 1985–2005, which looks at secondary patents, rather than all forms of exclusivities. See Amy Kapczynski, Chan Park & Bhaven Sampat, *Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of 'Secondary' Pharmaceutical Patents*, 7 PLOS ONE 1,1 (2012).

33 See FELDMAN & FRONDORF, *supra* note 2, at 49–65 (describing elaborate deals and combinations of deals undertaken to cloak agreements in which brand-name companies pay generics to delay market entrance).

Key results from our 2005 to 2015 study include the following:

- Rather than creating new medicines, pharmaceutical companies are recycling and repurposing old ones. In fact, 78% of the drugs associated with new patents in the FDA's records were not new drugs coming on the market, but existing drugs.
- Adding new patents and exclusivities to extend the protection cliff is particularly pronounced among blockbuster drugs. Of the roughly 100 best-selling drugs, more than 70% had their protection extended at least once, with almost 50% having the protection cliff extended more than once.
- Looking at the full group, almost 40% of all drugs available on the market created additional market barriers by having patents or exclusivities added on to them.
- Once a company starts down this road, there is a tendency to keep returning to the well. Eighty per cent of those who added protections added more than one.
- Among those adding more than one barrier, some were serial offenders, with almost half adding 4 or more protections and some adding more than 20.
- The problem is growing across time. The number of drugs that had a patent added on to them almost doubled during the time period. The addition of certain other types of barriers increased at an even greater rate, with some tripling.[34]

These results may easily understate the landscape. In designing the methodology, we repeatedly adopted a conservative approach, following the path that would point away from suggesting a competitive barrier. In addition, the pharmaceutical industry has developed techniques for erecting competitive barriers that do not involve obtaining additional patents and exclusivities, techniques that would not be captured by our analysis.[35] Finally, we could only quantify those behaviors of which we are aware. Much behavior in the pharmaceutical industry remains obscured, and we cannot measure what we cannot see.[36]

Thus, for the first time in the literature, this study definitively shows that stifling competition is not limited to a few pharma bad apples. Rather, it is a common and pervasive

[34] See *infra* notes 119–136, 139–141.

[35] Feldman et al., *supra* note 31, at 71–85 (empirical work establishing the extent to which citizen petitions filed at the FDA are last ditch efforts by competitors to hold off generic entry); Hebert Hovenkamp et al., IP and Antitrust: An Analysis of Antitrust Principles Applied to Intellectual Property Law § 12.5 (1st ed. 2002)) (describing mechanisms 'whereby the brand-name drug company takes advantage of its market power to shift pharmacists, doctors, and consumers to "new" versions of drugs before a generic for the 'old' version is able to reach the market.'); Mark S. Levy, *Big Pharma Monopoly: Why Consumers Keep Landing on 'Park Place' and How the Game is* Rigged, 66 Am. U. L. Rev. 247, 276–79, 291–93 (2017) (describing product hopping techniques to thwart generic substitution); Feldman & Frondorf, *supra* note 2, at 86–87 (describing how Valeant's 'deep relationship' with special pharmacies allowed Valeant to ensure distribution of its brand-name drugs without affecting the reimbursement of the pharmacies).

[36] See Feldman & Frondorf, *supra* note 2, at 139–44; *see also* Michael Hiltzik, *How 'Price-Cutting' Middlemen are Making Crucial Drugs Vastly More Expensive,* Los Angeles Times (June 9, 2017), http://www.latimes.com/business/hiltzik/la-fi-hiltzik-pbm-drugs-20170611-story.html (accessed Nov. 1, 2018) ('The PBMs are sitting in the center of a big black box… They're the only ones who have knowledge of all the moving pieces.'); Ruth Johnson et al. v. OptumRx Inc. & Novo Nordisk Inc., No. 8:17-cv-00900 (D. Cent. Cal. filed May 23, 2017) (detailing a recent lawsuit filed against the pharmacy benefit manager OptumRx and drug company Novo Nordisk alleging the latter 'artificially inflated the price of Victoza—an

problem endemic to the pharmaceutical industry. Although the end of life for a patent or exclusivity may be a traumatic event in the life of a pharmaceutical enterprise, companies increasingly decline to 'go gentle into that good night'.[37]

In short, this is not an image of innovation and competitive entry. It is an image of a system that provides for repeated creation of competition-free zones, pushing a competitive market further and further out into the future. The problem is not only pervasive and persistent, but it is also growing across time. Against this backdrop, it is no wonder that drug prices are skyrocketing.

II. BACKGROUND

II.A. A brief tour of the modern drug approval process

The following section provides brief highlights of the modern drug approval process, with a focus on aspects relevant to our study.[38] The modern system for drug approval in the United States is a long and arduous process. Companies wishing to bring an entirely new drug to market must develop the drug, determine how to manufacture it on a mass scale and in a way that is consistently stable, and prove to the FDA that the drug is safe and effective through rigorous clinical trials. Survivors of this marathon—at least those whose innovation is significant enough to earn a patent—are rewarded with the right to exclude others from making, using, or selling the drug.[39]

The cost of obtaining a patent is miniscule compared to the hundreds of millions of dollars necessary to take a drug through clinical safety and efficacy trials.[40] Moreover, companies try to plant their patent stake in the ground as soon as possible, to mark off their territory and keep others out. Given both of these realities, companies obtain many patents that are never developed into viable products, including many patents that sit idly on the shelf.

With patenting occurring early in the drug development cycle, some of the patent term will have expired before the drug gets to market. Estimates suggest that the average

injectable prescription medicine use to treat Type 2 diabetes—to subsidize the payment of illegal kickbacks to OptumRx, a pharmacy benefit manager ("PBM") that negotiates drug prices on behalf of insurers, health plans, and their participants.').

37 The sentence is a reference to a work by Welsh poet Dylan Thomas, which concludes with the line, '[d]o not go gentle into that good night. Rage, rage, against the dying of the light!' See DYLAN THOMAS, THE COLLECTED POEMS OF DYLAN THOMAS: THE ORIGINAL EDITION 122 (Paul Muldoon ed., 2010).

38 For more in-depth descriptions of the drug approval process, *see Development & Approval Process (Drugs)*, FDA (Oct. 5, 2017), https://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm; *see also How Drugs are Developed and Approved*, FDA (Aug. 18, 2015), www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/default.htm; *see generally* BERNICE SCHACTER, THE NEW MEDICINES: HOW DRUGS ARE CREATED, APPROVED, MARKETED, AND SOLD (2005); *see generally* Kimiya Sarayloo, *A Poor Man's Tale of Patented Medicine: The 1962 Amendments, Hatch-Waxman, and the Lost Admonition to Promote Progress*, 18 QUINNIPIAC HEALTH L. J. 1 (2015); *see generally* Martin S. Lipsky & Lisa K. Sharp, *From Idea to Market: The Drug Approval Process*, 14 J. AM. BOARD FAM. PRACT. 362 (2001).

39 35 U.S.C. § 154(a)(2) (providing for 20 years of protection from the date of the patent application).

40 Aylin Sertkaya et al., *Key Cost Drivers of Pharmaceutical Clinical Trials in the United States*, NCBI PUBMED.GOV (Feb. 8, 2016), https://www.ncbi.nlm.nih.gov/pubmed/26908540 (noting that costs for clinical trials can range from $1.4 million to $52.9 million, depending on the therapeutic area of the drug and the phase of the trial); *see generally* Rebecca S. Eisenberg & W. Nicholson Price, *Promoting Healthcare Innovation on the Demand Side*, 4 J. L. & BIOSCI. 3 (2017) (article outlining the various incentives surrounding the high cost of clinical trials).

remaining patent period for a new drug is 12 years. Although far less than a term of 20 years from the time of a patent application, 12 years of exclusivity is a considerable reward, particularly for a blockbuster drug that will garner many billions of dollars a year in revenue.

One should note that even with patents outside the pharmaceutical space, companies will not necessarily enjoy a full 20 years of exclusivity on the market. It takes time to develop and market any product, as well as time to get through the patent office's approval process. In addition, many products contain numerous patents, along with trade secrets and other knowhow, such that a single patent will not lead immediately to a marketable product.[41] The lag time for drug development, however, is likely to exceed the lag time for many other products, even if the difference is not a full 8 years.

All good things must come to an end, however,[42] and when the patent expires, the system is designed so that generic companies can immediately step into a pharmaceutical market and compete. The Hatch-Waxman system, along with the accompanying regulatory and judicial structure, provides the vehicle for rapid entry of generic drugs.[43] Under Hatch-Waxman, generic hopefuls can clear the legal and regulatory hurdles ahead of time in order to hit the ground running.

A generic company would not have the potential for monopoly returns from excluding others from the market, given that the generic will have nothing new to patent. Thus, generic companies would lack the financial incentive to engage in lengthy and costly clinical trials. Nor would repeating those trials necessarily represent a good use of societal resources, considering that the brand-name company has already established the safety and efficacy of the chemical formula.[44] In light of these constraints, Hatch-Waxman allows generic companies to reference the safety and efficacy data from the brand-name company's original drug application, which is known as a 'New Drug Application' or 'NDA' for short.[45] The generic company need only demonstrate bioequivalence.[46] In other words, the generic company does not need to show that the formula is safe and effective, only that its product is the same as the brand.

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41 FELDMAN, *supra* note 8, at 54. The one exception to this rule is patents procured by non-practicing entities, colloquially called 'patent trolls'. Given that these entities do not make any products but simply assert patents against companies who make products, patent trolls are able to put their newly minted patents into use the minute they are granted. See *eg* Joe Mullin, *Famous Patent 'Troll's' Lawsuit Against Google Booted out of East Texas*, ARS TECHNICA (Feb. 2017), https://arstechnica.com/tech-policy/2017/02/famous-patent-trolls-lawsuit-against-google-booted-out-of-east-texas/ (accessed Nov. 1, 2018) (describing various patent infringement lawsuits by an ambitious non-practicing entity, Eolas Technologies, against Microsoft, Google, Amazon, JC Penney, and Wal-Mart).

42 FELDMAN & FRONDORF, *supra* note 2, at 9.

43 FELDMAN & FRONDORF, *supra* note 2, at 21–33 (describing in detail the history, design, and implementation of the complex Hatch-Waxman system).

44 The Hatch-Waxman system covers small molecule drugs, not biologics. Biologics are large, complex cell-derived drugs, and replicating a biologic is much more challenging. The generic equivalent of a biologic drug is known as a biosimilar or an interchangeable. Such drugs are governed by the Biologics Price Competition and Innovation Act, rather than the Hatch-Waxman Act. Greater safety and efficacy testing is required for biosimilars than for generics. Biologics Price Competition and Innovation Act of 2009, PUB. L. NO. 111–148, Title VII, Subtitle A, 124 Stat. 119 (2010).

45 FELDMAN & FRONDORF, *supra* note 2, at 21–33.

46 See *Id.*

As part of keeping prices low, generic companies generally do not engage in extensive advertising, either to providers or directly to consumers. Rather, they depend on drug substitution laws that allow pharmacists to substitute a cheaper, generic version when a physician prescribes a medication.

In creating the Hatch-Waxman system, Congress recognized that the US Patent and Trademark Office (USPTO) unfortunately grants many patents of dubious quality. The problem is not surprising, given that on average, the patent office spends only 18 hours across a 2-year period examining a patent application.[47] This is painfully little time for patents, particularly pharmaceutical patents that may contain hundreds of claims. Although the number of patent examiners has doubled since 2005,[48] the number of patents approved each year has doubled as well, rising to over 300,000 new patents in the fiscal year ending August 2017.

Patents of questionable validity can improperly block competitors out of the market. In addition, a different problem occurs when a perfectly valid patent is applied inappropriately to a drug. For example, the FDA requires companies to submit any patents that relate to a drug within 30 days of the drug's approval. Under the Hatch-Waxman system for approval of generics, there are repercussions for brand-name companies that do not file within the proper time limits.[49] The FDA does not scrutinize the company's representations, however, but merely records whatever the company submits in what is known as the 'Orange Book'. Thereafter, a competitor seeking approval of a generic version of the drug must battle every patent listed in the Orange Book in relation to the drug.[50] Thus, simply listing a patent in the Orange Book can operate to block or delay competition, even if that patent does not cover the drug.

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47 Robin Feldman, *Intellectual Property Wrongs*, 18 STAN. J. L. BUS. FINANCE 250, 264 (2013) (citing Mark A. Lemley, *Rational Ignorance at the Patent Office*, 95 NW. U. L. REV. 1495, 1500 (2001)). Other scholars cite a slightly higher figure of thirty hours, see Lauren Cohen et al., *'Troll' Check? A Proposal for Administrative Review of Patent Litigation*, 97 B. U. L. REV. 1775, 1786–87 (2017) (noting 'an estimate of thirty hours for an individual examiner to review each of the roughly six hundred thousand new applications filed per year.'). Cohen et al. eventually agree the estimate is closer to twenty hours spent on reviewing a patent application. See *Id.* at fn. 75 (mentioning that 'More realistic estimates of examiner time per application put the average time available for these activities at about twenty hours per application, rather than thirty.').

48 There were 8195 patent examiners in FY 2016, compared to 4177 in FY 2005. *Compare* U.S. PATENT & TRADE OFF. 2016 ANN. REP., https://www.uspto.gov/sites/default/files/documents/USPTOFY16PAR.pdf (accessed Nov. 1, 2018) *with* U.S. PATENT & TRADE OFF. PERFORMANCE & ACCOUNTABILITY REP. FOR FISCAL YEAR 2005, https://www.uspto.gov/sites/default/files/about/stratplan/ar/USPTOFY2005PAR.pdf (accessed Nov. 1, 2018). During the same period, the number of issued patents rose from roughly 150,000 to over 300,000. See Dennis Crouch, *FY2017: PTO On Course for Record Number of Issued Patents*, Patently-O (Aug. 12, 2017), https://patentlyo.com/patent/2017/08/fy2017-course-patents.html (accessed Nov. 1, 2018).

49 Generic drug makers are not required to certify to patents that are not timely filed if the generic application is submitted before the patent. See *Patents and Exclusivity*, U.S. FOOD & DRUG ADMIN. 1 (2015), https://www.fda.gov/downloads/drugs/developmentapprovalprocess/sm allbusinessassistance/ucm447307.pdf (accessed Nov. 1, 2018); 21 C.F.R. 314.53 (2018); *see also* Kurt Karst, *One Sponsor's Failure is Another Sponsor's Fortune: The Importance of Timely Listing (and Challenging) Orange Book Patents,* FDA LAW BLOG (Nov. 25, 2013), http://www.fdalawblog.net/2013/11/one-sponsors-failure-is-another-sponsors-fortune-the-importance-of-timely-listing-and-challenging-or/ (accessed Nov. 1, 2018).

50 Specifically, a company seeking approval of a generic version of the drug must provide a certification, regarding every patent listed in the Orange Book in relation to the drug, that the patent either has expired or will expire before the generic brings the drug to market or stating that patent information has not been filed. Alternatively, the generic can challenge the validity of the patent or its application to a particular drug through the Paragraph

To address the problem of invalid patents or patents invalidly applied, Hatch-Waxman provides an incentive for generics to engage in such battles with an established brand-name company. Specifically, the first generic to successfully challenge a drug patent or the application of that patent to its generic application will be the only generic allowed on the market for 6 months.[51] During this 6-month period, a duopoly market will exist, in which the only players are the brand-name company and the first generic.[52]

The introduction of generics is a shock to the system for a pharmaceutical company. Prices can drop as much as 20% when the first generic enters the market; with multiple generics, the prices may eventually drop by 80–85%.[53] As a result, drug companies have a powerful incentive to delay competitive entry for as long as possible. Even small delays can have a big impact on a company's bottom line. A few months of delay can be worth hundreds of millions of dollars for blockbuster drugs, whose revenues reach billions of dollars a year.[54]

It should come as no surprise that drug makers do all they can to soften the blow of losing market monopoly. Some strategies to mitigate the effect of falling off the protection cliff are relatively straightforward, such as raising prices on those drugs that are still protected. Other strategies involve what is known as 'evergreening'.[55] Although commentators use the term in slightly different contexts,[56] we will use its broadest connotation of trying to refresh one's monopoly protection on a drug.

Simple techniques can involve obtaining new protections on existing drugs by filing for additional patents, sometimes on methods of producing or manufacturing the

IV process, which triggers litigation between the parties to resolve the matter. Paragraph IV litigation is a lengthy and expensive process. 21 U.S.C. § 355(j)(2)(A)(vii) (detailing the requirements for certification when filing an ANDA); Annie Gowen, Comment: *Saving Federal Settlement Privilege after Actavis*, 83 U. CHI. L. REV. 1505, 1510 (2016) (noting that 'Paragraph IV litigation can be extremely expensive'). Thus, brand-name companies have an incentive to liberally list patents in the Orange Book, placing the burden on generics to engage in litigation for the purpose of knocking the patents out.

51 The brand-name company, which already has approval to market, can continue the brand product or sell a lower-priced version to compete with the new generic. The brand's version is known as an 'authorized generic'. Feldman et al., *supra* note 31, at 50 n.35.

52 This process continues to be the subject of extensive manipulation and anticompetitive behaviors. FELDMAN & FRONDORF, *supra* note 2, at 34–65 (describing pay-for-delay deals in which the generic company settles its Hatch-Waxman suit by agreeing to stay off the market for a period of time in exchange for cash payments of other complex side deals).

53 FELDMAN & FRONDORF, *supra* note 2, at 20 (citing Ernst R. Berndt & Murray Aitken, *Brand Loyalty, Generic Entry and Price Competition in Pharmaceuticals in the Quarter Century after the 1984 Waxman-Hatch Legislation* 10 (National Bureau of Economic Research, Working Paper No. 16431, 2010), www.nber.org/papers/w16431.pdf; *Facts about Generic Drugs*, U.S. FOOD & DRUG ADMIN., www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm (last updated June 28, 2016).

54 *Id.* at 67–69 (noting that branded drugs making large yearly sales, such as the $1.3 billion annual sales of the drug Flonase, have the potential to gain hundreds of millions of dollars in just months of delay).

55 *Supra* note 30 and accompanying text.

56 *Compare* Dorothy Du, *Novartis AG v. Union of India: 'Evergreening,' Trips, and 'Enhanced Efficacy' Under Section 3(d)*, 21 J. INTELL. PROP. L. 223, 228 (2014) (describing evergreening as 'the acquisition of secondary patents on reformulations or minor modifications of pharmaceutical products in order to unfairly extend the monopoly over the drug beyond the life of the initial patent.') *with* Janice M. Mueller & Donald S. Chisum, *Enabling Patent Law's Inherent Anticipation Doctrine,* 45 HOUS. L. REV. 1101, 1106 (describing evergreening as 'obtaining related patents on modified forms of the same drug, new delivery systems for the drug, new uses of the drug, and the like'.).

drugs or on other aspects. For example, in an empirical study of secondary pharmaceutical patents between 1985 and 2005, Kapczynski, Park & Sampat found that secondary patents—covering ancillary elements of a drug such as formulation or method of use, as opposed to the primary chemical compound—were highly common.[57] These supplementary formulation patents added an average of 6.5 years of patent life, and supplementary method of use patents added an average of 7.4 years of patent life.[58] Other work has determined that secondary patents are likely to be overturned by generic challengers, if the case is litigated to completion.[59]

More complex evergreening strategies involve developing new formulations, dosage schedules, or combinations that can be used to obtain new patents. These can be combined with attempts to move the market to the slightly altered product, by advertising extensively, pressuring doctors to write prescriptions with terms such as 'Dispense as Written' or 'Brand Medically Necessary', or even withdrawing the old product from the market entirely. Using these techniques, brand-name companies try to prevent pharmacists from being able to fill a prescription with a generic.[60] At the very least, the brand-name company might be able to bifurcate the market, with some patients moving to the new version for which no generic is available.

Many of these evergreening strategies involve applying for new patents. Even if the patents are of questionable validity, the process of challenging them through Hatch-Waxman litigation is expensive and lengthy for a generic, again allowing years of additional profits for the brand-name company.[61]

If companies are able to develop new formulations, dosage schedules, combinations, and the like, in a way that justifies obtaining new patents or exclusivity protections, these companies not only minimize damage from tumbling off the cliff but may also be able to delay going over the edge in the first place. Our data suggest that this is occurring in a widespread manner throughout the industry.

Consider the dementia medication Namenda, a blockbuster drug that was scheduled to lose patent protection in 2015.[62] The company launched a longer-acting version of the original drug product and began encouraging patients and doctors to switch to the patent-protected, longer-acting version in order to undermine generic competition.[63] In our dataset we recorded one version of Namenda, approved in October 2003, for which the protection cliff was extended once in 2009. There was another version of Namenda approved in April 2005, for which the protection cliff was extended twice:

57 See Kapczynski et al., *supra* note 32, at Table 1.

58 *Id.* at 5.

59 See C. Scott Hemphill & Bhaven Sampat, *Drug Patents at the Supreme Court,* 339 SCIENCE 1386, 138 (Mar. 22, 2013) (finding that 89% of patents in pay-for-delay settlements are secondary patents; when the lawsuits are pursued to completion, rather than settled, brand companies are less likely to win with secondary patents than with the active-ingredient patents, with comparative win rates of 32% and 92%, respectively).

60 For a detailed description of these and other evergreening techniques, see FELDMAN & FRONDORF, *supra* note 2, at 69–79.

61 See Robin Feldman, *Drug Wars: A New Generation of Generic Pharmaceutical Delay*, 53 HARV. J. LEGIS. 499, 529–30 (2016) (citing U.S. Pharmaceutical Sales-2013, DRUGS.COM, http://www.drugs.com/stats/top100/2013/sales (last updated Feb. 2014)) (describing this technique in detail and explaining how AstraZeneca effectively shifted the market from Prilosec to Nexium by switching the former to an over-the-counter prescription drug, a move that helped establish Nexium as the second best-selling drug with almost $6 billion in sales).

62 See Ashish Kumar Kakkar, *Patent Cliff Mitigation Strategies: Giving New Life to Blockbusters*, 25 EXPERT OPIN. THER. PAT. 1353, 1357 (2015).

63 *Id.*

once in 2007 until 2014 and once in 2009 until 2015. Finally, Namenda XR was approved in 2010, for which the protection cliff was extended once in 2011 until 2029. Throughout this series of maneuvers, Namenda was able to extend its protection at least 24 years.

These are not the only strategies companies use to extend protection. As described above, the FDA takes the company's word for whether a patent should be listed as applying to a particular drug. The same is true for the company's description of what uses of the drug are covered by the patent's claims. Specifically, the FDA requires that the drug company submit a short statement describing the approved use (or uses) claimed by the patent, which the FDA then assigns a number and lists in the Orange Book as a use code.[64] Scholars have demonstrated that brand-name companies often submit use codes that are overbroad or inaccurate in describing the actual content of the patent.[65]

Given that the FDA does not read or construe patent claims, generics have little recourse for correcting incorrect use codes.[66] In 2012, the Supreme Court ruled in *Caraco* that generic companies can file statutory counterclaims to seek correction of inaccurate use codes,[67] but the approach requires entering into the extensive legal dance of submitting a Paragraph IV certification, attracting a lawsuit from the brand-name company claiming you have infringed, and then successfully defending against that infringement suit.[68]

In response to continued concerns about use codes, new FDA regulations, that became effective at the end of 2016, have established the 'Orange Book Patent Listing Dispute List'.[69] To dispute the accuracy of a use code under this newly implemented system, one may submit a 'statement of dispute' to the FDA, which the FDA will then send to the company whose use code is in dispute. That company must confirm the correctness of the use code, or otherwise withdraw or amend the patent information, and must also include a description explaining how the existing or amended use code is accurate. The process, however, has no teeth. The FDA will simply post information on these use code disputes online under the 'Orange Book Patent Listing Dispute List'.

In addition, although there is some penalty for failing to list a patent in the Orange Book in a timely manner,[70] the same is not true for use codes. Once a patent has been submitted, the company can determine at any point in the life of the patent that the patent covers a new use.[71]

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64 See Terry G. Mahn, *The Patent Use Code Conundrum – or Why FDA Can't Read (Patents)*, Pharmaceutical Compliance Monitor (Oct. 17, 2014), http://www.pharmacompliancemonitor.com/patent-use-code-conundrum-fda-cant-read-patents/7715/.

65 See Arti Rai, *Use Patents, Carve-Outs and Incentives in the Drug-Patent Wars*, 367 New Eng. J. Med. 491, 491 (2012) (noting that brand-name drug manufacturers have attempted to defeat certain generic company strategies by listing use codes that substantially exceed the scope of the use patent).

66 See Mahn, *supra* note 64.

67 See Caraco v. Novo Nordisk, 132 S. Ct. 1670 (2012).

68 See Rai, *supra* note 65.

69 See Kurt Karst, *Adieu, 'Orange Book FR Safety or Effectiveness Determinations List'; Hello, 'Orange Book Patent Listing Dispute List'*, FDA Law Blog (June 6, 2017), http://www.fdalawblog.net/2017/06/adieu-orange-book-fr-safety-or-effectiveness-determinations-list-hello-orange-book-patent-listing-di/.

70 See *infra* note 112 and accompanying text (describing requirements for a listing to be considered 'timely filed').

71 *Caraco*, 132 S. Ct. at 1675 (noting that although the FDA requires brand manufacturers to submit descriptions of the scope of their patents, known as use codes, the FDA does not attempt to determine

Obtaining new patents from the Patent Office and adding use codes to the Orange Book are not the only ways to extend one's protection on a drug. There are more than 10 different exclusivities one can obtain from the FDA, all of which can create competition-free zones for a drug company for a specified period of time. Sometimes called regulatory exclusivities or regulatory property,[72] these programs were approved by Congress during periods in which Congress passed legislation opposed by the pharmaceutical industry.[73] Drug companies can apply for the benefits for a variety of reasons, including performing pediatric testing, performing other new clinical studies, developing so-called 'Orphan Drugs', and developing drugs for tropical diseases.[74] These benefits can operate to extend protection by adding to the length of the patent term, creating a time period in which other companies are not permitted to receive approval to market the drug or to use existing safety and efficacy data, adding to the length of already existing non-patent exclusivities, or providing for combinations of these benefits.[75] Additional details on these exclusivities can be found in the Methodology section and in the Results section.

Of course, attempts to block out competitors may not always be successful. Competitors may be able to overturn or avoid weak patents, challenging them as either invalid or not infringed. Other behaviors can be used to avoid the patent deluge in limited circumstances, such as producing a drug with a label designating a narrow use while knowing that physicians are likely to suggest off-label use of the drug.[76] Even where such approaches are successful, however, the cost and waste of rent-seeking behavior, and behavior to counter such rent seeking, does not provide a model of an effectively functioning market.

In short, despite the quaint theory that competitors will enter after a pharmaceutical patent expires, the reality is quite different. Numerous strategies and opportunities exist that allow companies to extend their protection and prolong the period of market monopoly for their drugs. Such game-playing involving patents and exclusivities has been explored primarily from a theoretical standpoint and through case studies, with no comprehensive, quantitative examination of such strategies across the industry. Our study fills the gap.

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if that information is accurate, but simply assumes the information is an accurate description of the breadth of their patent scope.) For an unusual counterexample, consider the case of Johnson and Johnson's drug, Depomed. The company filed with the FDA that it 'became aware' that the patent claim was broader than what was reflected in the use code on file. *Cf.* Kurt Karst, *A New Orange Book First: FDA Unilaterally Changes a Patent Use Code*, FDA Law Blog (Nov. 20, 2016), http://www.fdalawblog.net/2016/11/a-new-orange-book-first-fda-unilaterally-changes-a-patent-use-code/. Consistent with its ministerial role, the Agency acquiesced and added a use code. *Id.* In this case, however, the FDA pushed back against the company and withdrew the use code as uninterpretable, an action which one source described as extremely unusual. *Id.*

72 See *generally* Feldman, *supra* note 10.

73 See *Id.* at 66.

74 See *Id*; *see also* text accompanying notes 119–120 (briefly describing the Orphan Drug Act and subsequent manipulations).

75 See Feldman, *supra* note 10, at 69, 72–73, 83–92, 103 (describing 13 regulatory exclusivities with a chart of all of them at Appendix A).

76 See *eg* Feldman & Frondorf, *supra* note 2, at 102–04 (discussing so-called skinny labels).

III. METHODOLOGY[77]

III.A. Overview

We sought to compile a large volume of FDA data that would allow us to examine the prevalence and specific contours of patent and exclusivity game-playing in an empirically rigorous manner. We hypothesized that the behavior of repeatedly adding patents and exclusivities would be detectable in a widespread manner across drug products, and that such behavior is increasing across time.

We used data published in the FDA's 'Orange Book' to test our hypotheses.[78] Locating FDA data and converting it into a format conducive to analysis was a formidable task. Although each monthly supplement and annual edition across time contains a wealth of information, only the most recent edition is available from the FDA.[79] We were able to locate archived copies of the monthly and annual editions from another researcher to obtain our source data. From that data, we extracted all the patent and exclusivity information from the 11 years of Orange Books included in our study, examining each to determine detailed information on the nature of the addition or change, as detailed in Section III. B.ii. Enormous effort was required to gather the dataset and render it usable for empirical analysis. Consistent with our prior practices,[80] as well as our commitment to transparency and high ethical standards in data-driven academics,[81] this dataset is publicly available. As pharmaceutical pricing gains focus in public policy debates, we hope the dataset will assist other researchers, regulators, and the general public in future investigations into the pharmaceutical industry.

III.B. Methodology details

III.B.i. Just what are the cumulative and annual editions of the Orange Book?

At the beginning of each year, the FDA publishes an 'Annual Edition' of the Orange Book, with information current up to the last day of the previous year. The Annual Edition lists all approved drugs, whether they are on the market as of that moment, had never been marketed, or have been discontinued from marketing. The patent and exclusivity section of the Annual Edition contains information on the active patents and exclusivities attached to approved drugs.

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77 An expanded version of the methodology with additional details is available along with the data on the Inter-University Consortium for Political and Social Research (ICPSR), https://www.icpsr.umich.edu/icpsrweb/.

78 *Orange Book Data Files*, U.S. FOOD & DRUG ADMIN. [hereinafter *Orange Book Data Files*], https://www.fda.gov/drugs/informationondrugs/ucm129689.htm (last updated Feb. 24, 2017).

79 On its Orange Book Frequently Asked Questions page, the FDA states that, 'Over time, there will be an archive for the annuals and each year's December Cumulative Supplement.' Thus, it appears that the FDA plans to make prior editions of the Orange Book available at some point in the future, but those prior editions are not easily accessible online at the present. Moreover, the FDA plans only to make the Cumulative Supplements from December available, excluding the Cumulative Supplements from the other months of the year. Using the December supplement, one would be able to see all the new patents and exclusivities added that year, but one would not be able to parse out in which month the patents and exclusivities had been added prior to December. For more details on the difference between 'Annual Editions' and 'Cumulative Supplements', and the information contained in each, *see infra* text accompanying notes 81–84.

80 See Robin Feldman et al., *Database from Empirical Evidence of Drug Pricing Games – A Citizen's Pathway Gone Astray* (Mar. 7, 2017), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2924673 (the publicly available dataset from our prior paper on drug pricing games involving citizen petitions, Feldman et al., *Empirical Evidence*, *supra* note 31).

81 See *supra* note 2 and accompanying text.

The FDA also publishes a 'Cumulative Supplement' every month of the year, containing new information received and processed since the publication of that year's annual edition. The FDA explains in the Orange Book that the Agency aims to update the cumulative supplement 'by the end of the following month's second work week (e.g., November's supplement will be updated by the end of the second full work week in December)' and that patent and exclusivity information is 'current to the date of publication'.[82] This lag in the publication of the Orange Book leads to some minor imprecision in terms of the date on which the information was submitted and the date in which it is published.

Each cumulative supplement lists both the new patents and exclusivities that were added in that specific month, as well as the patents and exclusivities added in earlier cumulative supplements from that year. Certain lines in the patent and exclusivity section in each cumulative supplement are marked with a symbol indicating that the listing was added to the Orange Book that month and had not appeared in previous cumulative supplements of the Orange Book from that year.[83]

III.B.ii. Compiling the patent and exclusivity data

The process of compiling data on patents and exclusivities added to drugs between 2005 and 2015 consisted of three general stages: (1) transferring all patent and exclusivity additions from the cumulative supplement for each month between January 2005 and December 2015 to a central dataset; (2) transferring all patent and exclusivity information from the 2005 annual edition of the Orange Book to the dataset, so that this information serves as a reference for analysing the additions after the 2005 annual edition; and (3) double checking all of the entries in our dataset to minimize the likelihood of human error.

III.B.iii. Transferring patent and exclusivity data from the cumulative supplements

The first step in our data-gathering process was to transfer all patents and exclusivities marked as new additions from each month between January 2005 and December 2015 to a comprehensive dataset that included a wide range of information. For each patent or exclusivity, we recorded the active ingredient name, the product name, the New Drug Application (NDA) number, the month and year of the addition, whether the addition was a patent or exclusivity, the patent number (if applicable), the code(s) attached to the patent or the exclusivity code, the expiration date, the strength(s) of the drug to which the Orange Book addition applied, and whether a 'delist request' flag was

[82] See *eg Cumulative Supplement 1: January 2015: Approved Drug Products with Therapeutic Equivalence Evaluations, 35th Edition*, Dept. of Health and Human Services, U.S. Food & Drug Admin. ii (2015).

[83] There may be a few new additions to the patent and exclusivity section of the Orange Book that are added between the publication of the December cumulative supplement from one year and the annual edition from the next year (published at the very beginning of that next year). These new patents and exclusivities that happen to be added during this narrow window appear in the annual edition, but are not accounted for in the December or January cumulative supplements, and thus, are never marked as new additions. Theoretically, there should be no gap between the December cumulative supplement of one year and the January cumulative supplement of the next year, although we know that these unmarked new additions have occurred from individual examples we have identified. We suspect that this situation of new patents and exclusivities falling through the cracks between years is extremely rare. Also reassuring is that the effect of any failure to identify these hidden patent and exclusivity additions would be to understate our results, creating the impression that there are fewer patents and exclusivities than in actuality.

attached to the patent.[84] After transferring the above information available in the Orange Book, we used the Drugs@FDA database—an online repository of basic data on most drug products approved since 1939—to obtain the approval date for each New Drug Application in our dataset.[85] In all, the patent and exclusivity information from every month between January 2005 and December 2015 amounted to 3834 pages of data that we sifted through by hand.

Drug strengths, in particular, posed data entry challenges. In the Orange Book, each strength of a drug is listed separately. Thus, if a certain patent or exclusivity applies to multiple strengths of a drug, the patent or exclusivity will be listed multiple times. In most cases, we found that if a patent or exclusivity was applied to one strength of a drug, it was eventually applied to all strengths of the drug. Thus, listing a patent or exclusivity multiple times in our dataset, for each corresponding strength, could amount to a form of double-counting and create an inaccurate picture of the level of patent and exclusivity activity. To choose the most conservative approach possible, we listed each patent and exclusivity that applied to a drug only once. This required extremely careful parsing of the Orange Book. In most cases, a list of added patents would be identical across all strengths of a drug, but occasionally, there were minute distinctions that could easily be missed, such as an extra patent added onto just one out of eight different strengths of the same drug.

More generally, when considering an analysis of how many drugs are involved in a particular behavior—in our case, how many drugs had patents or exclusivities added to them between 2005 and 2015—one must choose the level at which to conduct the analysis. The term 'drug' can have several different meanings, depending on the chosen definition and context. For example, one can choose to define a drug on the level of the active ingredient, the branded product name, the specific new drug application number, or the specific strength or formulation.

Consider the opioid addiction treatment drug, Suboxone. The active ingredients in Suboxone are buprenorphine hydrochloride and naloxone hydrochloride. There are, however, brand-name drug products other than Suboxone that are identified with the exact same two active ingredients, including Bunavail and Zubsolv. Moreover, within the brand-name Suboxone itself, there are two different new drug application numbers: drug application 20733, approved in October 2002, and drug application 22410, approved in August 2010. Within Suboxone drug application 22410 alone, there are four different strengths of the drug, corresponding to the same drug application number.

For our analysis, we chose to define 'drug' at the level of the new drug application number, given that many anecdotal reports indicate pharmaceutical game-playing at that level of granularity.[86] For example, if one version of a drug (at the new drug

[84] A delist request flag indicates that the drug company has requested that the patent be removed from the Orange Book reference for their drug, but that the patent has remained listed because a first generic applicant may retain eligibility for 180-day exclusivity based on based on successfully asserting that the patent is invalid or should not be applied to the drug. *Orange Book Data Files*, *supra* note 78 (providing descriptions of all data fields available in the Orange Book files, including the 'patent delist request flag' data field).

[85] See *Drugs@FDA: FDA Approved Drug Products*, U.S. FOOD & DRUG ADMIN. [hereinafter Drugs@FDA], https://www.accessdata.fda.gov/scripts/cder/daf/ (accessed Nov. 1, 2018).

[86] See *generally* FELDMAN & FRONDORF, *supra* note 2, at 26–27 (2017) (explaining how Abbreviated New Drug Applications, the generic counterpart to the New Drug Application, are the 'battleground for many of the games that are played between brand-name companies and generics'); Michael A. Carrier, *A Real-World*

application level) is on the verge of losing patent protection, the pharmaceutical company might switch from a capsule to a tablet and submit a new drug application for the drug in tablet form, with new protections stemming from the revised formulation.[87] We did not go as far down as the level of strength, however, because we felt it could be misleading to define a 10-mg strength and a 20-mg strength of one drug as two separate drugs—resulting in counting two occurrences of strategic behavior—given the commonplace understanding of what 'drug' means. Moreover, as noted above, a patent or exclusivity applied to one strength was usually applied to all strengths of the drug.

There may, indeed, be game-playing involving different strengths of the same drug. For example, for a generic drug to receive approval, it must match the brand-name product in dosage strength.[88] If a new formulation does not have the same dosage or strength, pharmacists are not allowed to substitute the generic under most state drug substitution laws; such substitution is the major pathway for generic drug companies.[89] Thus, although we do not count the same patent applied to different dosages as more than one occurrence, our dataset does track instances in which a patent or exclusivity that had already been applied to one strength of a drug is applied to a new strength of that drug, so that future research can identify and analyse the behavior.

The definition of 'drug' could include drugs listed in Abbreviated New Drug Applications (ANDAs). ANDAs are the applications filed by companies seeking approval for a generic version of a drug.[90] Generic applications are likely to be listed in the patents and exclusivities section of the Orange Book; however, only in relation to what the

Analysis of Pharmaceutical Settlements: The Missing Dimension of Product Hopping, 62 FLA. L. REV. 1009, 1022–24 (2010) (noting how the drug company Cephalon introduced a new drug product, Nuvigil, with a different New Drug Application number, when it began to face generic competition on its sleep-disorder medication Provigil); Steve D. Shadowen, Keith B. Leffler & Joseph T. Lukens, *Anticompetitive Product Changes in the Pharmaceutical Industry*, 41 RUTGERS L. J. 1, 21–26 (2009) (analysing New Drug Application approval reports to examine anti-competitive product changes in the industry); *see also* C. Scott Hemphill & Bhaven N. Sampat, *Evergreening, Patent Challenges, and Effective Market Life*, 31 J. HEALTH ECON. 327, 329 (2012) (similarly choosing to measure at the new drug application level of granularity when examining generic litigation challenges and suggesting that the relevant activity level occurs with all dosage strengths swept together).

87 See *eg* Jessie Cheng, *An Antitrust Analysis of Product Hopping in the Pharmaceutical Industry*, 108 COLUM. L. REV. 1471, 1491–92 (2008) (explaining how Abbott and Fournier, the drug companies that manufactured the cholesterol drug TriCor, began selling a tablet formulation shortly after Teva filed an application to sell a generic version of TriCor in its original capsule form); FELDMAN & FRONDORF, *supra* note 2, at 541 (describing how Reckitt Benckiser developed a new film version of its opioid addiction drug Suboxone around the time the exclusivity was expiring on its tablet version); Robin Feldman & Connie Wang, *A Citizen's Pathway Gone Astray—Delaying Competition from Generic Drugs*, 376 NEW ENG. J. MED. 1499, 1500 (2017) (describing how, on the eve of generic competition, Warner Chilcott began marketing a new version of its acne medication Doryx with two score lines as opposed to one).

88 Orange Book Preface: Approved Drug Products with Therapeutic Equivalence Evaluations, CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN. (36th ed. last updated June 10, 2016), http://www.fda.gov/drugs/developmentapprovalprocess/ucm079068.htm.

89 See Tobin Klusty, *A Legal Test for the Pharmaceutical Company Practice of 'Product Hopping'*, 17 AM. MED. ASSOC. J. ETHICS 760, 760 (2015).

90 Though the terms 'NDA' and 'ANDA' are commonplace in life science parlance, we use the terms 'new drug application' and 'generic drug application' in most places, to prevent confusion stemming from a paper littered with insider acronyms. As one of the authors has noted previously, writing in clear, straightforward language presses those in the legal field to be faithful to supportable logic, rather than subject to the whims of prejudice masked in obscurity. See ROBIN FELDMAN, THE ROLE OF SCIENCE IN LAW 180 (2009) (excerpted in Feldman, *Plain Language Patents*, 17 TEX. INTELL. PROP. L.J. 289 (2009) and discussing the dangers that arise when legal actors cloak themselves in scientific jargon); *see also Id.* at 5–7, 174–95 (exploring the issue further).

Orange Book calls, the 'PC' or 'patent challenge' exclusivity, a 180-day period of exclusivity awarded to the first generic drug to successfully challenge a brand-name patent under Paragraph IV of the Hatch-Waxman Act. Our research, however, examines the use of exclusivities to obstruct generic entry. The 180-day exclusivity represents the exact opposite—the successful entry of a generic competitor—and thus, does not fall within the scope of our study. As such, we excluded all patent challenge exclusivities from our dataset and did not include generic drugs in our figures for the overall number of drug products.

There was also the question of which actions taken by the pharmaceutical companies should be considered part of the same game occurrence. If a drug has one patent added to it in March 2012 and one patent in April 2012, but both patents expire in April 2020, should we consider them to be part of the same game? It is certainly true that a larger number of patents have the potential to create greater barriers. Competitors wishing to challenge the validity of the protections built around a product in theory could be forced to overturn each and every one, although branded companies do not always choose to assert all of them. As a result, each addition does add to the arsenal of protection, increasing the difficulty of competitive entry.

Such multiple patents can be used for other strategic behaviors as well, even if they expire on the same date. Specifically, companies frequently separate their patent applications into different parts, which are then processed at the USPTO as what are known as continuations. Although they will all have the same final expiration date, they move through the patent office at different rates of speed and will be granted at different times. Having some pieces move more slowly allows companies to keep an eye on their competitors in the market, subtly adding language during the process that will better cover what a competitor has developed, although this may apply more appropriately in areas other than pharmaceuticals, which could have fewer direct competitors.[91] The Federal Circuit has expressed its approval of this behavior.[92] Nevertheless, a patent may be separated into different parts for perfectly legitimate reasons, and it is difficult at the level of data analysis we are applying to discern the difference with confidence. Thus, in the interest of fairness and careful conservatism, we did not count those as separate instances.

As a further exercise, however, we calculated our metrics in both scenarios—that is, counting patents that expire on the same day as separate and additions and not counting patents that expire on the same day as separate additions—to see the effect on our qualitative takeaways. We saw little qualitative difference between the two sets of calculations.

Finally, for the purposes of this paper, we included only small molecule drugs, rather than biologics, in our dataset. Small molecule drugs are simple, stable, single-molecule entities that are produced through chemical synthesis and are easy to replicate.[93] Commonplace drugs, such as aspirin, that are familiar to most people are small molecule

[91] Mark A. Lemley & Kimberly A. Moore, *Ending Abuse of Patent Continuations*, 84 B.U. L. Rev. 63, 83 (2004) (noting that 'the existence of continuation applications facilitates evergreening'). For an in-depth description of continuations and divisionals, *see generally Id.*

[92] See Feldman, *supra* note 8, at 52.

[93] See *Small Molecule versus Biological Drugs*, Generics and Biosimilars Initiative (June 29, 2012), http://www.gabionline.net/Biosimilars/Research/Small-molecule-versus-biological-drugs; *What Are 'Biologics' Questions and Answers*, U.S. Food & Drug Admin. (last updated Feb. 6, 2018), https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cber/ucm133077.htm. Also, the New Drug

drugs. In contrast, biologic drugs are large, complex products produced in living cell cultures for which it is currently impossible to create identical copies.[94] Examples of biologics include vaccines, blood products, and advanced gene therapies.[95] The FDA does not include biological products—or their generic counterparts termed 'biosimilars' or 'interchangeables'—in the Orange Book but has established a separate publication, colorfully known as the 'Purple Book'.[96]

Unfortunately, the Purple Book is much less comprehensive than the Orange Book and does not include a patent and exclusivity section. As a result, our analysis could not extend to biologics. If data on the patents and exclusivities attached to biological products can be obtained in the future, whether through the FDA deciding to make such data public in the Purple Book or through a FOIA request, conducting an analogous inquiry into activity in the biologics sphere would be a worthwhile endeavor. Biologics and their generic counterparts are also a younger phenomenon. Congress created a system for expedited approval of copies of biologic drugs in 2010,[97] and the first biosimilar was approved only in 2015.[98] Thus, the skirmishes over generic versions of biologics are in their infancy. Over time, however, greater FDA reporting and transparency will be critical for tracking and evaluating behavior in this increasingly important sector of the industry.

III.B.iv. Transferring patent and exclusivity data from the 2005 annual Orange Book

The next step in assembling our dataset involved transferring over all patent and exclusivity information listed in the *annual* edition of the Orange Book from the year 2005 (as opposed to the cumulative supplements from 2005, which at this point, had already been entered into the dataset) in order to provide baseline information. Specifically, when a patent or exclusivity is marked as a new addition in a cumulative supplement, the Orange Book does not identify which component of the listing warranted the new addition flag. It could be that the entire listing—patent number, expiration date, patent codes, and all—is new, but it could also be that just one element is new. Thus, it was necessary to create baseline information to know which patents and exclusivities were already on the books at the start of our time period so that we could tease out which part of the listings flagged as new in any of the 2005 cumulative supplements constituted the addition. The annual edition for 2005 is published at the beginning of 2005, and it contains information that is current up to the last day of the previous year. Thus,

Application (NDA) format is distinct to small molecule drugs. Biologics have a separate type of application called a Biologics License Application (BLA). *Biologics License Applications (BLA) Process (CBER)*, U.S. Food & Drug Admin., https://www.fda.gov/biologicsbloodvaccines/developmentapprovalprocess/biologicslicenseapplicationsblaprocess/default.htm (accessed Nov. 1, 2018).

94 See *Small Molecule versus Biological Drugs, supra* note 93.

95 See *What Are 'Biologics' Questions and Answers, supra* note 93.

96 *Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations*, U.S. Food & Drug Admin. (last updated Oct. 31, 2018), https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm.

97 Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, 124 Stat. 804, 807 (2009).

98 Biosimilar Product Information, U.S. Food & Drug Admin. (last updated Nov. 1, 2018), https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm580432.htm.

entering the 2005 annual supplement provided the necessary baseline information for the initial year of our dataset.[99]

III.B.v. Verifying the accuracy of the patent and exclusivity data

Ultimately, this process of collecting patent and exclusivity data for the 11 years from 2005 to 2015—both the monthly supplements and the 2005 annual edition—yielded 16,141 individual rows of data, with 9 to 11 data field columns per row. This amounts to over 160,000 individual cells of data, all entered by hand.

Any process of manually compiling over 160,000 individual data points, many of which were random strings of numbers, is subject to human error. Thus, after completing the dataset, we looked through the data second time and double-checked every entry from the monthly supplements and the 2005 annual edition for accuracy. A small number of errors were found and corrected.

We are optimistic that by double-checking every Orange Book listing in our dataset, we were able to catch the overwhelming majority of errors. Though it is certainly possible some errors remain, given the massive volume of data, we are confident that the overall conclusions would remain unchanged, even in the presence of a small number of data entry errors. Moreover, the coding process, which is described in the section below, effectively required us to go through the data line by line a third time, further reducing the possibility of significant inaccuracies in our dataset.

III.B.v.1.Coding the patent and exclusivity data. As noted above,[100] Orange Book entries do not explicitly identify whether the entire listing is new or whether just one element of the listing is new, and if so, which component of the patent or exclusivity is new. In addition, the information that does exist requires careful interpretation. For example, in some cases, a patent listing appears identical to another previous listing. The only change is that while the patent was applied previously to strengths 1 and 2, for example, it is now being applied to strengths 3 and 4, as well. Although this might initially appear to be a new patent, to categorize it as such would be misleading, given that the substance of the change involves adding an existing patent to new strengths. These and many other circumstances necessitate individualized interpretation and analysis. Thus, we individually examined each line in our dataset, reading every entry in the context of the patents and exclusivities that came before.

The changes we tracked that we considered to be significant for our analysis of pharmaceutical game-playing included:

- Patents added for the first time, regardless of whether the addition included any drug substance, drug product, and/or use codes[101];

[99] All listings from this annual edition are clearly marked as being from 'pre-2005' in our dataset, to avoid confusion with patents and exclusivities that had been added from January 2005 onward. Patents and exclusivities from the 2005 Annual Orange Book were used only as a reference from which to interpret patents and exclusivities added between 2005 and 2015; they were not included in our count of how many patents and exclusivities were added to the Orange Book in our study timeframe.

[100] See *supra* note 99 and accompanying text.

[101] A drug substance code indicates that the company believes the patent covers the active ingredient. A drug product code indicates that the company believes the patent covers the formulation and composition. A use code indicates the company believes the method-of-use patent covers a particular indication or use of the

- The addition of drug substance, drug product, and/or use codes to existing patents;
- Exclusivity additions (a full list of the exclusivities tracked can be found in Appendix A);
- Patents marked with a 'delist request' flag;[102]
- Cases in which existing patents or exclusivities were added to a new strength of the same drug.
- There were other changes that we tracked but excluded from our analysis because it was unclear whether these changes were relevant to strategic pharmaceutical game-playing. These changes include cases in which:
- The patent term increased or decreased[103];
- A drug substance, drug product, and/or use code was removed;
- A change to a patent was applied to another use code listing of the same patent;[104]
- A listing was determined to be an error in the Orange Book, whether made on the part of the company or the Orange Book staff—a category we call 'errors'[105];

drug product—use codes can apply across multiple applications, multiple products, and multiple patents. See *Orange Book Data Files, supra* note 78; 21 C.F.R. 314.53(b).

102 See *supra* note 84 (explaining delist request flags).

103 There are several plausible explanations for a patent term increase or decrease, suggesting that these patent terms should not be included in our dataset of manipulations. A patent term *extension* is governed by 35 U.S.C. §156 and is meant to compensate for delays in the regulatory approval process for pharmaceuticals and other products subject to pre-market approval. A patent term *adjustment* is governed by 35 U.S.C. § 154(b) and applies to *all* patents—not just those attached to products such as drugs that are subject to pre-market approval. The patent term adjustment is meant to compensate for delays at the Patent Office in examining and issuing patents, as opposed to FDA delays in approving drug products. Approximately 80% of patents receive patent term adjustments due to Patent Office delay, and of that group, the average adjustment is about 600 days. See Dennis Crouch, *Patent Term Adjustment (PTA) Statistics,* PATENTLYO (July 27, 2011), http://patentlyo.com/patent/2011/07/pta.html.

104 As noted earlier, *see supra* notes 64–71, when a single patent has more than one use code attached to it, the patent is listed separately for each use code. For instance, Imbruvica (drug number 205552) was approved on Feb. 12, 2014. That month, Imbruvica added patent number 8476284 to the Orange Book. In the supplement for that month, the patent was listed once with use code 1456 attached. Immediately after that listing, the patent was listed again with use code 1491 attached. Rather than the patent being listed once, with both use code 1456 and use code 1491 listed under the patent codes column, the patent was listed two separate times—once for each use code. Thus, some tracked listings do not represent a new change to the patent, but rather, a change already made to the patent with one use code, being applied to the same patent with a different use code.

105 We categorized a listing as an error when we found an original entry line that might appear to be a separate addition of new patent or exclusivity information, but in reality, was entered in error by the company or the Orange Book staff. Whether something is an error is, unsurprisingly, not indicated explicitly in the Orange Book. We were able to surmise which entries were most likely errors by observing patterns in the Orange Book data. Consider the June 2008 supplement for Vytorin (drug number 21687). There are four strengths of the drug listed. Strengths 1, 2, and 4 show the addition of miscellaneous exclusivity number 54 with expiration date June 5, 2011 and a pediatric exclusivity added onto that exclusivity with expiration date December 5, 2011. For strength 3, miscellaneous exclusivity number 54 is also listed with the same expiration date of June 5, 2011, but the pediatric exclusivity is listed as changing that expiration date to December 5, 2008—years shorter than the December 5, 2011 expiration date listed with the pediatric exclusivity for the other strengths. If that were accurate, it would suggest that the pediatric exclusivity for that one strength had the effect of actually shortening the expiration date of the patent from June 2011 to December 2008. That, however, cannot be accurate. Application of a pediatric exclusivity adds 6 months; it does not decrease the expiration date by

- A listing was determined to be a correction of a previous error on the part of the company or the Orange Book staff—a category we call 'corrections'[106]; and
- The Orange Book listing was ambiguous.[107]

Some of the changes in the second list—changes we tracked but excluded from our analysis—could conceivably be related to pharmaceutical game-playing in one way or another. For example, there are cases in which a single drug product can receive multiple patent term extensions by strategically having two new drug applications approved on the same day and then extending a different patent for each.[108] Despite this possibility, our overarching philosophy in making methodological decisions was to err on the side of caution and make the conservative choice, with the result that, if anything, we are understating as opposed to overstating the results.

After completing the coding process, our data consisted of a complete set of every patent and exclusivity added to the Orange Book between January 2005 and December 2015, with each line categorized into a specific type of Orange Book addition or change. With this dataset in hand, we moved on to establishing a set of metrics for drawing conclusions from the large volume of data we had compiled and organized.

III.B.v.2. Establishing key metrics. As described above, our goal in assembling the dataset was to quantitatively evaluate the use of patents and exclusivities as a

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$2^1/_2$ years. Thus, we could be confident this was an error in the Orange Book. Our classification of this entry as an error is confirmed by the supplement in the following month of July 2008. That supplement once again lists four strengths for Vytorin, but this time, the pediatric exclusivity expiration date for all of them is December 5, 2011, including for strength 3. We classified listings as errors only in obvious cases such as these, categorizing less obvious cases as ambiguous.

106 As noted above, we categorized a listing as an error when we found an original entry line that might appear to be a separate addition of patent or exclusivity information, but in reality, was merely a separate line entered in error by the company or the Orange Book staff. The mirror image of these are new listings added to the Orange Book that do nothing but correct previous Orange Book errors. The difference between the two categories is essentially that with errors, two entries appear that would only be one, if they had been entered correctly. The proper information can be seen in later additions of the Orange Book, but in a way that the information is not flagged as a new addition. With corrections, a new entry appears flagged as an addition, but the new entry is simply a correction of a previous Orange Book error. Either way, our goal was to avoid double counting those things that were merely the result of errors by the company or the Orange Book staff, whenever we could identify them.

107 There were several listings for which we could not definitively determine the nature of the Orange Book addition or change. In the interest of erring on the conservative side, we simply classified these listings as 'ambiguous' and excluded them from our analysis. For example, in June 2014, patent number 8746242 was added to the drug Incruse Ellipta (drug number 205382). The next month, the same patent number 8746242 was listed under the same drug number 205382 once again, with the expiration date increased by one day to October 11, 2030. The marginal change to the expiration date, as well as how soon after the initial listing the new expiration date was published, cast doubt on whether this was truly a patent term extension or adjustment or if it was simply a correction of an Orange Book error. Thus, we classified the re-listing of the patent with the revised expiration date as ambiguous, and excluded it from our analysis.

108 See Kurt Karst, *Looking a Gift Horse in the Mouth – Why Would a Company Refuse a Patent Term Extension?* FDA Law Blog (May 1, 2008), http://www.fdalawblog.net/2008/05/looking-a-gift/. Examples of products that have used this multiple patent term extension strategy to their advantage include Omnicef, Lyrica, Mycamine, and Vimpat. See Kurt Karst, *False Friends: FDA's 'Gift' on NESINA – Present or Poison? It May Depend on Which Hatch-Waxman Language is Spoken,* FDA Law Blog (May 3, 2013), http://www.fdalawblog.net/2013/05/false-friends-fdas-gift-on-nesina-present-or-poison-it-may-depend-on-which-hatch-waxman-language-is/.

lifecycle management strategy for pharmaceutical products. To accomplish this task, we created metrics including the following:

- The number of drugs that had patents or exclusivities added to them in the Orange Book between 2005 and 2015, compared to the total number of drugs available between 2005 and 2015;
- The number of drugs that had patents or exclusivities added to them in the Orange Book, broken down by year for each year between 2005 and 2015;
- The number of drugs that had an exclusivity added to them, broken down by type of exclusivity;
- Exclusivities examined on this more granular level include orphan drug exclusivity, new patient population exclusivity, new product exclusivity, pediatric exclusivity, and indication exclusivity.[109]
- The total quantities of patents and exclusivities added between 2005 and 2015;
- The number of drugs that had a high quantity of patents add to them in a single year between 2005 and 2015;
- The number of separate times that each drug had something added to it in the Orange Book (a measure of 'serial offenders');
- The number of drugs newly approved in a year compared to the number of drugs that had something added to them in the Orange Book in that year; and
- Percentage of the approximately 100 top-selling, non-biologic drugs between 2005 and 2015 that extended the initial 'protection cliff'.

The Results section describes the metrics and their application, but the methodology of some metrics is best described here. Specifically, the first metric provides the total number of drugs that had a patent or exclusivity added to them, or had any other relevant change made in the Orange Book relative to the overall number of drugs in existence and listed in the Orange Book in the 11 years between 2005 and 2015.

The denominator in this metric—the overall number of drugs—required an immense amount of sleuthing through online data repositories and internet archiving sites to calculate with any level of precision. As with many other crucial pieces of FDA data, figures for the total number of drugs (at the level of new drug applications) listed in the Orange Book each year are not readily available.[110] The FDA does make a copy of the

[109] For most exclusivities, there is a one-to-one relationship between the number of exclusivities that a drug receives and the number of times that exclusivity appears in the Orange Book. Pediatric exclusivity, however, is not a one-and-done situation. It appends 6 months of market protection to the end of *all* patents and exclusivities listed in the Orange Book that contain the same active moiety on which the pediatric studies were conducted. See *Patents and Exclusivity*, *supra* note 49. Thus, in our analysis, we counted the number of times a particular pediatric exclusivity was applied to a patent and the number of times that pediatric exclusivity was applied to an exclusivity, rather than the overall number of pediatric exclusivities that were granted by the FDA.

[110] Each supplemental version of the Orange Book contains a section entitled, 'Report of Counts for the Prescription Drug Product List Counts Cumulative by Quarter' which contains a number for 'drugs products listed'. The FDA defines 'drug products' for this report, however, at the level of strengths. Moreover, the number reported in the Orange Book is not separated by whether the drug product is a new drug or a generic application. One way to obtain these figures would be to go through each PDF annual edition of the Orange Book and hand count the relevant number of drugs. One would have to not only count the number of drugs, but also keep track of the specific new drug application numbers in each edition, to compare the new drug application

Orange Book available in ASCII text, tilde-delimited format, which would be more easily imported to obtain an overall figure for the number of drugs with significantly less effort than hand-counting would require, but only for the most recent month.

Although the FDA currently updates the ASCII text file version of the Orange Book every month, this has not been the case across time. Internet archived versions show month-long periods that go by without a single change occurring in the ASCII text file versions of the Orange Book, while we know from the hard copy versions that dozens, or even hundreds, of changes occur each month.

On the flip side, the number of dates on which the archival system captured the FDA's webpage and the distribution of those dates across any given year appear to be somewhat random. For example, for the year 2014, the webpage was captured once in February, once in April, twice in September, and three times in December. Meanwhile, in 2011, the webpage was captured every month of the year, at least two times each month. In September 2011, the number of days the webpage was captured reached a high of seven times, and there were a few occasions in 2011 that the webpage was captured more than one time in a single day. Thus, we compared each Internet-archived version of the Orange Book ASCII text files with the versions immediately before and after to cull out those archived versions that were mere duplicates.

Finally, we note that the comprehensiveness of our collection of Orange Book text files was at the mercy of whatever was available through Internet-archiving sources. It is possible that there was a gap between two of our archived webpages during which a certain drug was added and then removed. We would have no record of this drug's existence in the Orange Book and consequently, it would not have been included in our count of unique drugs listed in the Orange Book between 2005 and 2015. This possibility is unlikely, however, given that there was rarely much of a temporal gap between the various versions we obtained. Moreover, most drugs would remain listed in the Orange Book for longer than the 1-week or 2-week periods for which we occasionally did not have any archived versions of the Orange Book.

With the archived versions in hand, we were able to obtain a figure for the total number of drugs (at the new drug application level) available in each year. We then combined the yearly information, sorting for unique new drug numbers among that aggregate list of new drug numbers, resulting in a figure for the total number of drugs available in our entire 2005–2015 timeframe. We compared the number of drugs that had patents, exclusivities, or other changes added on to them, between 2005 and 2015, to the total number of drugs available in those 11 years, to get a sense of how prevalent the behavior is in the overall universe of pharmaceutical products. The outcomes of this analysis will be detailed in the Results section.

Our final metric involves extension of what is commonly referred to as the 'patent cliff'.[111] We examined the latest expiration date in the original set of protections and then determined if a new protection was subsequently added with a later expiration

numbers from year to year and eliminate duplicates. Given that the list of drug products in each Orange Book is hundreds of pages long—with generic drug applications interspersed among new drug applications, and each strength listed separately—this would have required an extraordinary amount of additional time and resources.

[111] See *eg* Mike May, *Pharma Positions to Survive the Impending Patent Cliff*, 15 NAT. MED. 1243 (2009); Eric Sagonowsky, *Big Pharma Faces $26.5B in Losses this Year as Next Big Patent Cliff Looms, Analyst Says*, FIERCEPHARMA (Apr. 21, 2017, 8:04 AM), https://www.fiercepharma.com/pharma/big-pharma-faces-26-5b-patent-loss-threats-year-analyst-says; Jessica Hodgson, *Big Pharma Tries to*

date.[112] We refer to this benchmark as the 'protection cliff' rather than the 'patent cliff,' given that many of the relevant 'cliffs' apparent in our dataset stemmed from exclusivities, not patents.

Our analysis focused on the best-selling drugs from the time period between 2005 and 2015, and, as with the entire study, we focused on non-biologic drugs. The high profit margins for blockbuster drugs provide a strong incentive for drug companies to invest in finding ways to extend protection. Thus, we chose the subset of our data for which we believed the protection cliff analysis would be most relevant.

To assemble a list of best-selling drugs from our study timeframe, we consulted the lists available through Drugs.com and Medscape.com. These websites obtain information from Verispan's Vector One National (VONA) database and from the IMS Health database.[113] From those lists, we selected the top 50, non-biologic brand drugs from

Look Past 'Patent Cliff', WALL STREET JOURNAL (Oct. 24, 2012, 4:36 PM), https://www.wsj.com/articles/SB10001424052970203897404578076173187345806.

112 In defining the 'original' set of protections, we chose to examine those patents and exclusivities that were added within the 2 months following the month of drug approval. Our logic was the following: patents that are attached to a drug prior to approval must be submitted to the Orange Book within 30 days (1 month) of approval to be considered 'timely filed', which has relevance for staving off generic competition, *supra* note 49. The FDA requires that drug companies submit patent information for publication in the Orange Book on FDA Form 3542. The form must be submitted within 30 days of the approval of the drug for the patent information to be considered 'timely filed'. Generic drug makers are not required to certify to patents that are not timely filed if the generic application is submitted before the patent. See *Patents and Exclusivity*, *supra* note 49; 21 C.F.R. 314.53; *see also* Kurt Karst, *One Sponsor's Failure is Another Sponsor's Fortune: The Importance of Timely Listing (and Challenging) Orange Book Patents*, FDA LAW BLOG (Nov. 25, 2013), http://www.fdalawblog.net/2013/11/one-sponsors-failure-is-another-sponsors-fortune-the-importance-of-timely-listing-and-challenging-or/. We added an additional month on top of the 'timely filed' month as a buffer to account for possible Orange Book staff delays in publishing a patent or exclusivity once it has been submitted by the drug sponsor. The Orange Book explicitly states at the end of the patent and exclusivity section that, 'Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 C.F.R. 314.53(d)(5).' See *eg Cumulative Supplement 1: January 2015*, *supra* note 82 at A-6. Thus, if a drug was approved in January 2015, we would define anything added in January, February, or March 2015 as part of the 'original' set of protections. We added the extra 2 months to err on the side of overincluding patents and exclusivities within our definition of 'original', thereby avoiding the possibility of inflating the amount of strategic behavior. For many drugs that were approved prior to 2005, the first patents and exclusivities we have in our dataset are simply drawn from the 2005 Annual Edition of the Orange Book. As such, we do not have specific month and year information for when those patents and exclusivities were added. Rather, the best we can say is that they were added prior to 2005. In those cases, we considered all of the 'pre-2005' patents and exclusivities to be the original set. Once again, we erred on the side of conservatism, given that there could easily have been protection cliff extensions prior to 2005 that we are not counting. For those drugs that were approved between 2005 and 2015, but for which no patent or exclusivity was added within the first 2 months after the approval month, we used the first month that any patent or exclusivity was added to define the original set, even if that month was past our general 2-month marker. This conceivably could represent an extension of exclusivity in some cases. For example, a drug whose formulation is not sufficiently novel to receive a patent—perhaps because a patent on something too similar was granted to another party in the past and has expired—could receive FDA approval. Thus, new patents or exclusivities added arguably could be described as an extension of the old patent protection. Nevertheless, we considered such possibilities either too remote or impossible to determine, and thus chose to benchmark the first month of any patent or exclusivity as the approval month, in those cases.

113 *Pharmaceutical Sales 2005*, DRUGS.COM, https://www.drugs.com/top200_2005.html (accessed Nov. 1, 2018) (Drugs.com is the largest independent medicine information website. It makes available lists of the top 100 or 200 best-selling drugs from each year between 2003 and 2012. It sources its data from either Verispan's Vector One National (VONA) Database, which pulls data on prescription activity from national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefit managers, etc., and

each year.[114] We then eliminated any duplicate drugs that overlapped in the top 50 from one year to the next. Our final grouping included a total of 106 best-selling drugs from the 10 years of 2005 to 2014, for which we analysed the frequency of protection cliff extension behavior.

We also chose to leave out the best-selling drugs from 2015. Our study only extends through 2015, and examining extension of a patent cliff requires a sufficiently long period of the drug's lifecycle so that one can analyse movement across time. For drugs that did not have a first set of patents or exclusivities added to them until 2015, it would be impossible to analyse any future extension of the protection cliff.

One could argue that, on the whole, the later years in our dataset would be less fruitful for the same reason, thereby understating the results. This, of course, may be true and is consistent with our overall study design, which is intended to err on the side of understating results. In addition, with the later years in our dataset, there would at least be some possibility of relevant activity to analyse for those years, as opposed to 2016 for which there would be no possibility of examining any future extension of the protection cliff. Finally, the possibility that strategic behavior may be increasing over time makes the latest years important to consider.

IV. RESULTS

IV.A. Overview

The study results demonstrate definitively that the pharmaceutical industry has strayed far from the patent system's intended design. The patent system is not functioning as a time-limited opportunity to garner a return, followed by open competition. Rather, companies throughout the industry seek and obtain repeated extensions of their competition-free zones. Moreover, the incidence of such behavior has steadily increased between 2005 and 2015, especially on the patent front and for certain highly valuable exclusivities. Most troubling, the data suggest that the current state of affairs is harming innovation in tangible ways. Rather than creating new medicines—sallying forth into new frontiers for the benefit of society—drug companies are focusing their time and effort extending the patent life of old products. This, of course, is not the innovation one would hope for. The greatest creativity at pharmaceutical companies should be in the lab, not in the legal department.[115] The following sections describe the results obtained through our analysis in detail, but below are the key takeaways from the study:

- Rather than creating new medicines, pharmaceutical companies are recycling and repurposing old ones. In fact, 78% of the drugs associated with new patents

has been used by the FDA itself in its reports, see *FDA Drug Safety Communication: Serious allergic reactions reported with the use of Saphris (asenapine maleate)*, U.S. FOOD & DRUG ADMIN. (last updated Aug. 4, 2017), https://www.fda.gov/Drugs/DrugSafety/ucm270243.htm. The other source of data used by Verispan is IMS Health, which provides information and technology services to the healthcare industry); Megan Brooks, *Top 100 Most Prescribed, Top-Selling Drugs*, MEDSCAPE (Aug. 1, 2014), http://www.medscape.com/viewarticle/829246 (data also sourced from IMS Health).

[114] As explained earlier, biologics are outside the scope of our study, though they have come to represent an increasingly large percentage of the best-selling drugs in recent years and would be an interesting avenue for future research, *supra* note 93–98 and accompanying text.

[115] Dr. Donald Kennedy, Comm'r, U.S. Food & Drug Admin., Keynote Address at the UC Hastings Conference: Faces of Forensics (Mar. 2008).

in the FDA's records were not new drugs coming on the market, but existing drugs. In some years, the percentage reached as high as 80%.

- Adding new patents and exclusivities to extend the protection cliff is particularly pronounced among blockbuster drugs. Of the roughly 100 best-selling drugs, more than 70% extended their protection at least once, with more than 50% extending the protection cliff more than once.
- Looking at the full group, almost 40% of all drugs available on the market created additional market barriers by having patents or exclusivities added to them.
- Many of the drugs adding to the Orange Book are 'serial offenders'—returning to the well repeatedly for new patents and exclusivities. Of the drugs that had an addition to the Orange Book, 80% of those had an addition to the Orange Book on more than one occasion, and almost half of these drugs had additions to the Orange Book on *four or more occasions.*
- The number of drugs with a high quantity of added patents in a single year has substantially increased. For example, the number of drugs with three or more patents added to them in one year has doubled. Similarly, the number of drugs with five or more added patents has also doubled.
- Overall, the quantity of patents added to the Orange Book has more than doubled, increasing from 349 patents added in the year 2005 to 723 in 2015.
- The number of drugs that had a patent added to them in the Orange Book almost doubled.
- There were striking increases in certain exclusivities, such as orphan drug exclusivity, new patient population exclusivity, and new product exclusivity. In particular, the number of drugs with an added orphan drug exclusivity tripled. In addition, the number of times a use code was added to a patent more than tripled, suggesting that this has become a new favored game.

To provide a broad sense of the types of metrics we are using, some could be characterized as 'intensity' measures, which capture the breadth and depth of patent and exclusivity activity in the industry. Another set of our metrics can be characterized as 'temporal' measures, which evaluate whether there are any trends in the behavior under examination across time during our 11-year timeframe from 2005 to 2015.

IV.B. Number of drugs that had patents and/or exclusivities added to them in the Orange Book, compared to the total number of drugs available

As an initial inquiry, we wanted to determine the extent to which companies are adding patents and exclusivities to drugs. Is this a limited activity, confined to well-worn anecdotes that everyone repeats, or does it occur throughout the industry? Our results demonstrate that adding patents and exclusivities is a common behavior, endemic to pharmaceuticals. In fact, between 2005 and 2015, almost 40% of all drugs available on the market had patents, exclusivities, or other changes added to them.

Table 1 shows the total number of FDA-approved drugs available on the market in each year of our study. Table 2 shows the number of drugs that had a patent or exclusivity added to them as a percentage of the total number of drugs. The figure is broken down in terms of the number of drugs with an added patent, the number of drugs with

Table 1. Total Number of Unique, Small Molecule Drugs Listed in the Orange Book, 2005–2015.

Year	*Total no of Drugs Listed (at the New Drug Application Level)*
2005	2402
2006	2354
2007	2354
2008	2353
2009	2362
2010	2397
2011	2425
2012	2436
2013	2470
2014	2533
2015	2547
2005–2015 (number of unique drugs throughout the period)	3372

Table 2. Number of drugs with Added Patents and/or Exclusivities Out of All Drugs, 2005–2015.

Category	*Number of Drugs*	*Percentage Out of All Drugs*
Drugs with an patent	1059	31.4%(1059/3372)
Drugs with an added exclusivity	978	29.0%(978/3372)
Drugs with any relevant change/addition	1322	39.2%(1322/3372)
All drugs available	**3372**	**100%(3372/3372)**

an added exclusivity, and the number of drugs that had any relevant change made to it (which includes not only adding a patent and/or exclusivity, but also other significant changes such as adding a use code.)

IV.C. Increase in number of drugs with changes, broken down by year

To assess whether patent and exclusivity activity has undergone change over time or remained relatively stagnant, we broke down our data by year, looking first at the number

Table 3. Number of Drugs with an Added Patent by Year, 2005–2015.

Year	*Number of Drugs with an Added Patent*	*Total Number of Drugs Available*	*Percentage of Drugs with an Added Patent out of Total*
2005	166	2402	6.91% (166/2402)
2006	213	2354	9.04% (213/2354)
2007	191	2354	8.11% (191/2354)
2008	263	2353	11.17% (263/2353)
2009	201	2362	8.50% (201/2362)
2010	205	2397	8.55% (205/2397)
2011	201	2425	8.28% (201/2425)
2012	239	2436	9.81% (239/2436)
2013	267	2470	10.8% (267/2470)
2014	288	2533	11.36% (288/2533)
2015	300	2547	11.77% (300/2547)

of drugs with an added patent, then at the number of drugs with an added exclusivity, and then at the number of drugs with any relevant change made at all.

IV.C.i. Number of drugs that had a patent added to them, by year

As shown in Table 3, the number of drugs that had a patent steadily increased between 2005 and 2015, almost double from 166 drugs in 2005 to 300 drugs in 2015. This increase is also reflected in the percentage of drugs that with an added patent out of the total universe of drugs available in each year. While 6.91% of all drugs listed in 2005 added an added patent in 2005, 11.77% of all drugs listed in 2015 had a patent to them in 2015.

The upwards trend is even more apparent in visual form, as shown in Figure 1.[116]

IV.C.ii. Number of drugs that with an added exclusivity, by year

We also broke down the exclusivity data by year. This figure involved 19 different exclusivities, including well-known and highly significant ones, such as the orphan drug exclusivity and the pediatric exclusivity, but also lesser-known exclusivities, such as the GAIN (Generating Antibiotic Incentives Now) exclusivity.[117]

Unlike the patent data, the exclusivity data contained no discernable trend over time, as the numbers in Table 4 demonstrate. Given the number of exclusivities lumped together, however, any trends could be obscured by underlying trends—and perhaps opposing trends—within individual exclusivities. The graphic above contains a visual

[116] The only clear exception to the trend is the number of drugs that had patents added to them in 2008, which is much higher than the immediately preceding and following years.

[117] See *Appendix A* (full list of exclusivities examined).

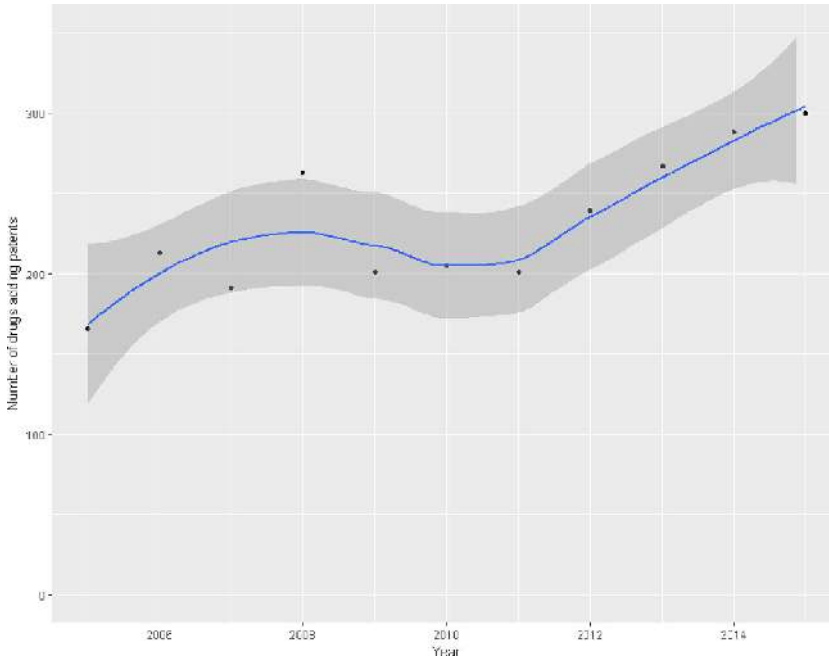

Figure 1. Number of drugs with an added patent by year, 2005–2015.

Table 4. Number of Drugs with an Added Exclusivity by Year, 2005–2015.

Year	*Number of Drugs with an Added Exclusivity*	*Total Number of Drugs Available*	*Percentage of Drugs with an Added Exclusivity out of Total*
2005	138	2402	5.74% (138/2402)
2006	141	2354	5.98% (141/2354)
2007	141	2354	5.98% (141/2354)
2008	129	2353	5.48% (129/2353)
2009	135	2362	5.71% (135/2362)
2010	115	2397	4.79% (115/2397)
2011	97	2425	4.00% (97/2425)
2012	133	2436	5.45% (133/2436)
2013	119	2470	4.81% (119/2470)
2014	136	2533	5.36% (136/2533)
2015	131	2547	5.14% (131/2547)

Table 5. Number of Drugs with any Relevant Orange Book Change or Addition by Year, 2005–2015.

Year	*Number of Drugs with an Orange Book Change or Addition*	*Total Number of Drugs Available*	*Percentage of Drugs that with an Orange Book Change or Addition out of Total*
2005	304	2402	12.65% (304/2402)
2006	354	2354	15.03% (354/2354)
2007	332	2354	14.10% (332/2354)
2008	392	2353	16.65% (392/2353)
2009	336	2362	14.22% (336/2362)
2010	320	2397	13.35% (320/2397)
2011	298	2425	12.28% (298/2425)
2012	372	2436	15.27% (372/2436)
2013	368	2470	14.89% (368/2470)
2014	424	2533	16.73% (424/2533)
2015	431	2547	16.92% (431/2547)

some readers may not be accustomed to. The gray shaded area around the blue prediction line is called a 'prediction band.' It represents the range of values we have 95% confidence will capture predictions and thereby provides a degree of reassurance in the validity of the results. Section IV D presents a more granular picture of individual exclusivities, identifying increases and decreases within the group, as different approaches gain and lose popularity.

IV.C.iii. Number of drugs with any relevant Orange Book change or addition, by year

In Table 5, we present figures for the number of drugs that made any relevant Orange Book change or addition, broken down by year for each year between 2005 and 2015. Such changes include not only adding a patent and/or exclusivity, but also other significant changes such as adding a use code.

As illustrated in Figure 2, there is a slight upward trend in the number of drugs with any relevant Orange Book change or addition, especially in the five most recent years between 2011 and 2015. It is unsurprising that the trend is subtle, given that this metric is largely a combination of the patent data, for which there was a well-defined upward trend, and the exclusivity data, for which there was no discernable trend.[118]

[118] As with the patent data, 2008 stands out as an exception from the overall trend. Possible explanations for the 2008 exception were explored above, *supra* note 116.

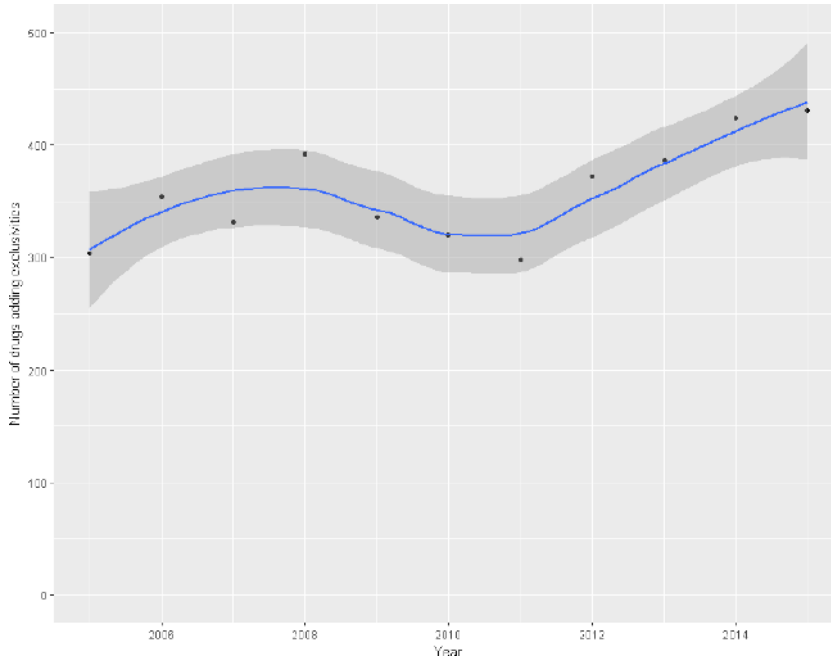

Figure 2. Number of drugs with any relevant Orange Book change or addition by year, 2005–2015.

IV.D. Number of drugs with an added exclusivity, broken down by type of exclusivity

The lack of a trend line in the number of drugs with an added exclusivity over time could be due to the lack of trends in any of the individual exclusivities, but it could also be attributable to the cancelling out of opposing trends in individual exclusivities. To answer this question, we analysed the exclusivity data on a more granular level. By examining each of the 19 exclusivities included in our dataset individually, we found that there were several that exhibited increases in frequency between 2005 and 2015 and several others that exhibited decreases in frequency.

The exclusivities for which there was an upward trend include orphan drug exclusivity, new patient population exclusivity, new product exclusivity, and new use. The exclusivities for which there was a downward trend include pediatric exclusivity (both as applied to patents and to other exclusivities), and indication exclusivity. Below, we will focus on the two exclusivities that exhibited particularly strong increasing trends: The Orphan Drug exclusivity and adding a new use designation to an existing patent.

IV.D.i. Increase in orphan drug exclusivity

Orphan drug exclusivity is a 7-year exclusivity granted to drugs that are approved and designated specifically to treat diseases and conditions affecting populations of 200,000 individuals or fewer.[119] The exclusivity was established through the Orphan Drug Act,

[119] See *Patents and Exclusivity, supra* note 49.

originally passed in 1983 and amended through the Hatch-Waxman Act in 1984.[120] The orphan drug program was initially intended to spur investment in neglected fields of medical research and development—drugs to treat rare diseases that affect only a small number of people in the USA.[121] Policy makers feared that there were insufficient financial incentives to develop treatments for small patient populations, and that as a result, these populations would languish untreated.[122] Today, however, it seems that 'everyone is an orphan', with orphan drugs accounting for more than 40% of drugs approved by the FDA.[123]

Part of the reason for the rapid expansion of the orphan drug program is the enormous value of the 7-year exclusivity. Most regulatory exclusivities awarded by the FDA extend a drug's protected lifetime by a few months, or perhaps a few years at most. For instance, pediatric exclusivity extends exclusive marketing and data rights for a drug by 6 months, and the exclusivity awarded for new clinical studies lasts for 3 years.[124] At 7 years, orphan drug exclusivity is by far the longest lasting of the forms of regulatory property granted by the FDA. With such strong exclusivity protections, manufacturers of orphan drugs are able to raise prices to shockingly high levels. The median cost for a patient to use an orphan drug for a single year is nearly $100,000 dollars, compared to roughly $5000 for non-orphan drugs.[125] Given that just a few months of additional market protection can be worth hundreds of thousands of dollars for a drug company, winning an additional 7 years is akin to winning the lottery.

More important, drug companies have figured out how to raise prices under orphan drug protections, and then spread those high prices across patient populations much broader than the small groups envisioned at the passage of the Orphan Drug Act. This technique is referred to as 'spillover pricing'.[126] The most common way that drug companies are able to accomplish spillover pricing is through off-label use, which occurs when doctors prescribe a medication for a use other than the one for which it was originally approved by the FDA.[127] Consider the drug Epogen, which was approved to treat a small population afflicted with anemia related to end-stage renal disease, and as such,

[120] See Orphan Drug Act, Pub. L. No. 97-414, 97 H.R. 5238, 97th Cong. (1983); Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (hereinafter, 'Hatch-Waxman Act'), *supra* note 44.

[121] See Feldman, *supra* note 10, at 73–80 (exploring the history and implementation of the Orphan Drug Act, as well its consequences for pharmaceutical competition, in detail).

[122] *Id.* at 74.

[123] The quoted phrase is drawn from the title of an article by Matthew Herder. See Matthew Herder, *When Everyone Is an Orphan: Against Adopting a U.S.-Styled Orphan Drug Policy in Canada*, 20 Account. Res. 227, 227 (2013); Michael G. Daniel et al., *The Orphan Drug Act: Restoring the Mission to Rare Diseases,* 39 Am. J. Clin. Oncol. 210, 210 (2016); Office of Generic Drugs, Ctr. for Drug Evaluation & Research, 2015 Annual OGD Annual Report: Ensuring Safe, Effective, and Affordable Medicines for the American Public 10 (2015). In 2015, approximately 47% of novel approved drugs were orphan drugs.

[124] See Feldman, *supra* note 10, at Appendix A (providing a detailed chart of the key exclusivities awarded by the FDA).

[125] See Daniel et al, *supra* note 12, at 2 (citing Andreas Hadjivasilou, EvaluatePharma, Orphan Drug Report 2014, 8 (Oct. 2014), http://info.evaluategroup.com/rs/evaluatepharmaltd/images/2014OD.pdf).

[126] See Feldman, *supra* note 10, at 77.

[127] Most commonly, 'off-label use' refers to the prescription of a currently available medication for an indication (disease or symptom) that has not received FDA approval. It can, however, also refer to the use of a medication in a patient population, dosage, or dosage form that has not received FDA approval. See Christopher M. Wittich et al., *Ten Common Questions (and Their Answers) About Off-Label Drug Use*, 87 Mayo Clin. Proc. 982 (2012). The practice of off-label use is common, with rates of up to 40% in adults and up to 90% in some

received orphan drug designation.[128] After receiving this designation, however, Epogen was prescribed off-label to treat a wide variety of types of anemia, expanding the patient population paying the high price of Epogen dramatically.[129]

Another approach for gaming the orphan drug exclusivity system is through 'salami slicing'.[130] This strategy involves dividing up the patient population into separate slices—perhaps separating those with an early stage of the disease from those with an end stage, or those who developed a genetic disease from one mutation from those who developed it through another mutation—and obtaining a different orphan drug exclusivity for each slice. Through 'salami slicing', if the original and intended population for a drug is greater than 200,000, and thus too large to qualify for orphan drug designation, the drug company can simply divide that original group up into subpopulations that are small enough to qualify.

A drug does not actually have to be newly developed to qualify for orphan drug exclusivity. As such, long-existing drugs can be revived and repurposed for an orphan drug indication. In fact, a troubling investigation by one media organization concluded that one-third of orphan drugs approved since the program began in 1983 were either repurposed mass market drugs or drugs that received multiple orphan approvals.[131]

Consider the drug, 3,4-diaminopyridine (3,4-DAP), which was used by patients with a rare neuromuscular disease and had been shown to be safe and effective as early as 1983.[132] Though the drug had never been officially approved, it had been provided to patients at no cost for many years thanks to a generous company and the FDA's 'compassionate use' Investigational New Drug ('IND') program.[133] In 2015, however, a different company submitted an application for a slightly modified version of the drug that does not require refrigeration, obtaining orphan drug designation in the process.[134] As a result, the company projected that it would be able to charge between $37,500 and

hospitalized pediatric populations. See Madlen Gazarian et al., *Off-Label Use of Medicines: Consensus Recommendations for Evaluating Appropriateness*, 185 MED. J. AUST. 544 (2006). Off-label prescriptions are legal, and can allow for life-saving innovation in clinical practice. See Randall S. Stafford, *Regulating Off-Label Drug Use – Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008).

128 See Shannon Gibson & Barbara von Tigerstrom, *Orphan Drug Incentives in the Pharmacogenomic Context: Policy Responses to the US and Canada*, 2 J. L. & BIOSCI. 263, 263–91 (2015).

129 *Id.*

130 *Id.*

131 See Sarah Jane Tribble & Sydney Lupkin, Drugmakers *Manipulate Orphan Drug Rules to Create Prized Monopolies*, KAISER HEALTH NEWS (Jan. 17, 2017), https://khn.org/news/drugmakers-manipulate-orphan-drug-rules-to-create-prized-monopolies/ (Kaiser Health News is not associated with the Kaiser Permanente health maintenance organization).

132 See Ted M. Burns et al., *Editorial by Concerned Physicians: Unintended Effect of the Orphan Drug Act on the Potential Cost of 3,4-Diaminopyridine*, 53 MUSCLE NERVE 165, 166–67 (2016).

133 *Id.* Through the 'compassionate use' program, patients with serious or life-threatening diseases are able to gain access to drugs that are still undergoing clinical trials, if there are no comparable or satisfactory therapeutic alternatives available. See Alexander Gaffney, *Regulatory Explainer: FDA's Expanded Access (Compassionate Use) Program*, REG. AFF. PROF. SOC'Y (Feb. 4, 2015), https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2014/2/regulatory-explainer-fda-s-expanded-access-(compassionate-use)-program.

134 See Sabrina Tavernise, *Patients Fear Spike in Price of Old Drugs*, NEW YORK TIMES (Dec. 22, 2015), http://www.nytimes.com/2015/12/23/health/patients-fear-spike-in-price-of-old-drugs.html.

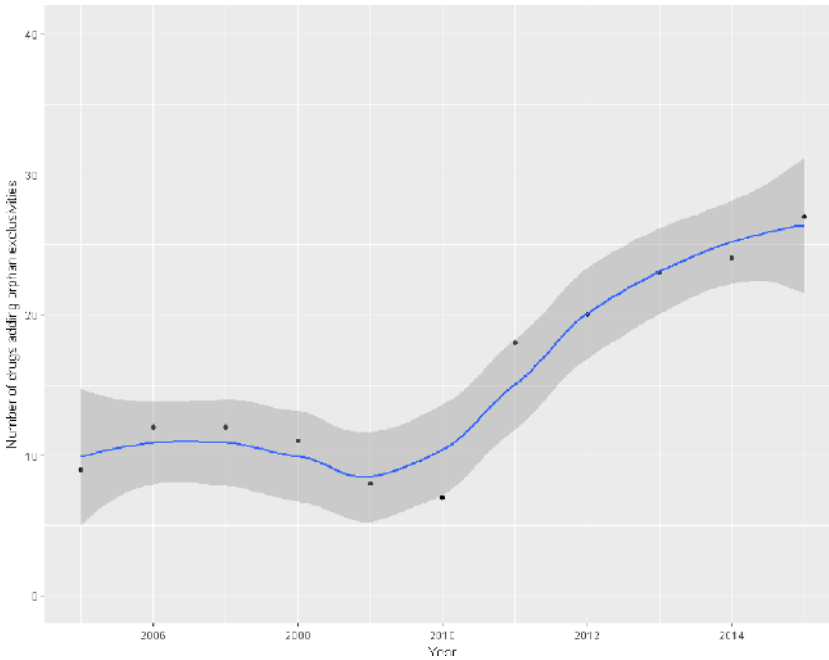

Figure 3. Number of drugs with an added orphan drug exclusivity, 2005–2015.

$100,000 per patient per year—for a drug that those same patients used to receive for free.[135]

In our study, we found that the number of drugs with added orphan drug exclusivities to the Orange Book underwent a notable increase between 2005 and 2015, with a large jump between 2010 and 2011, and a steady climb upwards from 2011 through 2015 (see Figure 3).

Between 2005 and 2015, the number of drugs with an added orphan drug exclusivity tripled from 9 drugs in 2005 to 27 drugs in 2015. Between 2010 and 2015, the number of drugs with an added orphan drug exclusivity nearly quadrupled from 7 drugs in 2010 to 27 drugs in 2015.[136]

IV.D.ii. Increase in new patient population exclusivity

The new patient population exclusivity is a subcategory within the 'new clinical investigation' exclusivity defined in 21 CFR 314.108. In categorizing exclusivities for the

[135] See Alison Kodjak, *FDA Approval Could Turn a Free Drug for a Rare Disease Pricey*, NPR (Dec. 23, 2015), http://www.npr.org/sections/health-shots/2015/12/23/460719043/fda-approval-could-turn-a-free-drug-for-a-rare-disease-pricey.

[136] Our results most likely understate the explosion of orphan drug products on the market, as many orphan drugs are approved and regulated as biologics, which fall outside the scope of our study, *supra* note 114. In 2001, 5 of the 10 best-selling biologic drugs were originally approved as orphan drugs and 3 others were approved for orphan indications in addition to the original indication. See Daniel et al., *supra* note 12, at 211. It is no surprise that so many orphan drugs fall within the biologics category, given that modern biologics are usually targeted at small, particularized patient populations of the type that would qualify a drug for orphan designation. See Feldman, *supra* note 10, at 76. As the biologics field grows into its own, and more comprehensive patent and exclusivity data on biologics trickles out, orphan drug biologics will certainly be an area of interest.

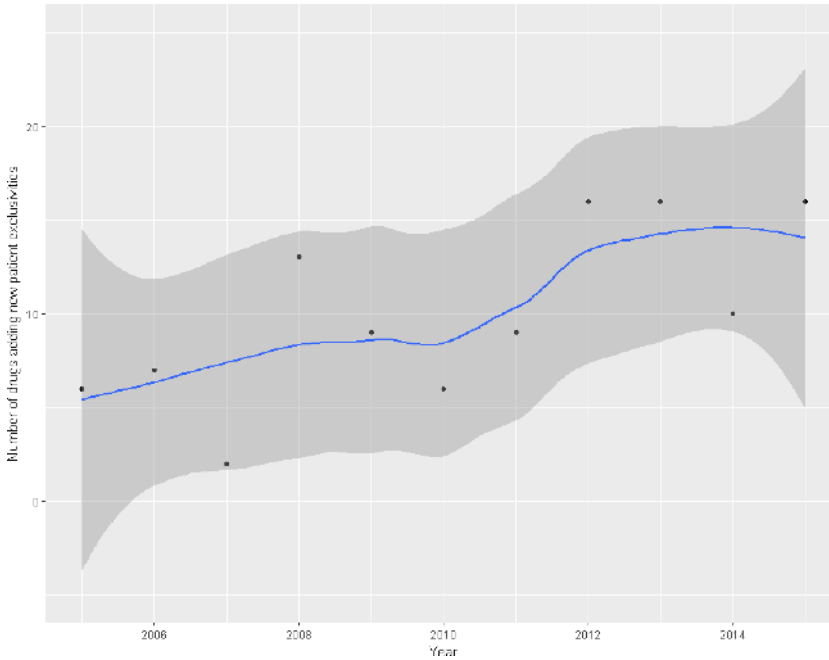

Figure 4. Number of drugs with an added new patient population exclusivity, 2005–2015.

patent and exclusivity section of the Orange Book, the FDA has chosen to break down the new clinical investigation, more commonly known as new clinical studies, exclusivity into its constituent elements. Thus, the Orange Book does not contain a new clinical investigation exclusivity code, but it does contain codes for new patient population exclusivity, new product exclusivity, dosage schedule exclusivity, indication exclusivity, prescription to over-the-counter switch exclusivity, and a variety of other exclusivities that could stem from a new clinical study. Here we examine the new patient population exclusivity, which is a 3-year exclusivity granted to a drug that has been approved for use in a new patient population based on a new clinical investigation. For instance, the drug Seroquel (drug number 20639) received two periods of new patient population exclusivity: one for the treatment of schizophrenia in adolescents 13 to 17 years of age and one for the treatment of bipolar mania in children and adolescents 10 to 17 years of age.[137]

Figure 4 shows the number of drugs with an added new patient population exclusivity for each year between 2005 and 2015.

For the new patient population exclusivity, there was a generally upward trend across time, though not as dramatic as that seen with orphan drug exclusivity. The number of drugs with an added new patient population exclusivity nearly tripled from 6 drugs in 2005 to 16 drugs in 2015. It is not altogether surprising that the trend in frequency of new patient population exclusivity mirrors that of orphan drug exclusivity, as the two

[137] See Kurt Karst, *A Flurry of Generic Drug Labeling Carve-Out Citizen Petitions; Scorecard Updated*, FDA Law Blog (Oct. 3, 2011), http://www.fdalawblog.net/2011/10/a-flurry-of-generic-drug-labeling-carve-out-citizen-petitions-scorecard-updated/.

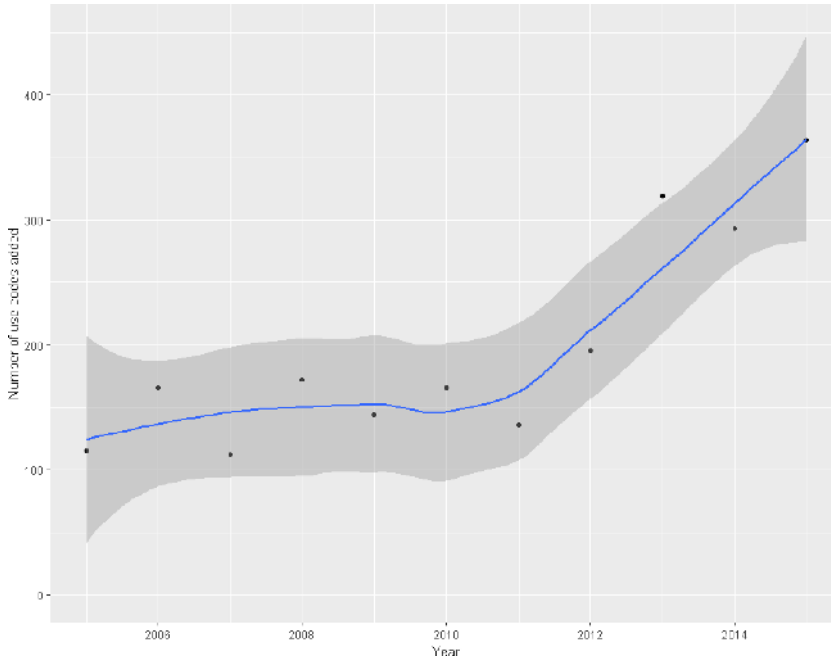

Figure 5. Number of times a use code was added to a patent, 2005–2015.

exclusivities are intimately related. Orphan drug exclusivity is granted to drugs that are developed to treat small patient populations of fewer than 200,000 individuals. As discussed earlier,[138] drug companies often use 'salami slicing' to divide up a broader patient population into smaller, particularized populations that would qualify the drug for orphan drug exclusivity. Given that this technique often involves defining new patient populations, it makes sense that many drugs that qualify for orphan drug exclusivity might also qualify for new patient population exclusivity, and that an increase in orphan drug activity would correspond with a rise in grants of new patient population exclusivity.

IV.D.iii. Increase in new use codes

Our findings for the number of times a use code was added to a patent each year between 2005 and 2015 is shown in Figure 5,[139] and the number of drugs that had at least one use code added to them in each of those years is shown in Figure 6.[140]

There was a notable increase in the number of use codes added to the Orange Book in our 11-year timeframe, rising from 115 use codes in 2005 to 364 in 2015. These results are corroborated by a study of use codes conducted by Kurt Karst, in which he

[138] See *supra* note 130 and accompanying text.

[139] It should be noted that our measurement was of the number of instances in which a use code was added to a patent. This would include instances in which a patent and its associated use code were added at the same time, as well as instances in which a use code was added to a previously listed patent. Often times, one use code number is added to multiple different patents under the same drug, or multiple patents listed under two different drugs—thus, this is not a measurement of unique use codes.

[140] Those numbers are: 115 166 112 172 144 166 136 195 319 293 364, respectively.

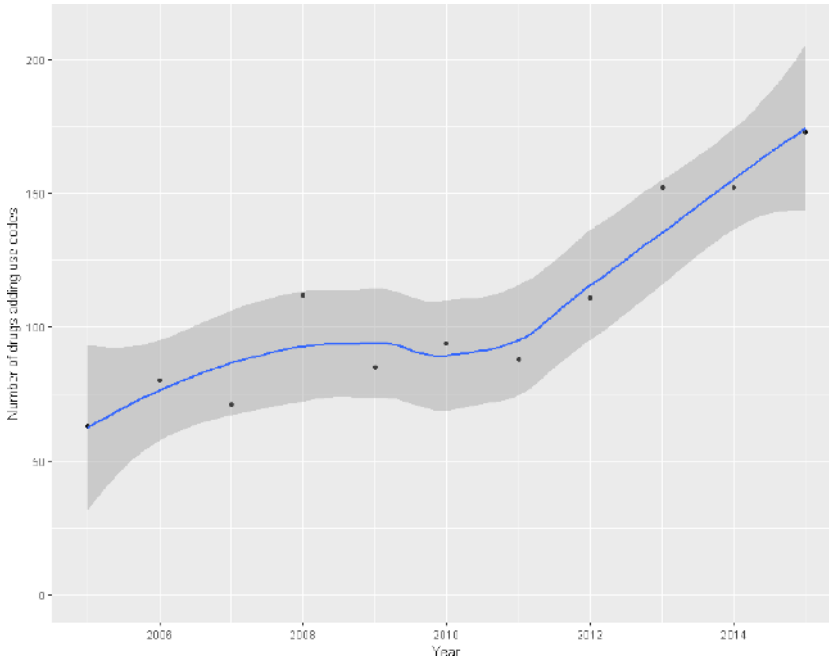

Figure 6. Number of drugs that added at least one use code, 2005–2015.

found that the total number of use codes listed in the Orange Book nearly tripled between 2003 and 2013.[141]

The number of drugs with at least one added use code also exhibited an upward trend between 2005 and 2015, more than doubling from 63 drugs in 2005 to 173 drugs in 2015. One might attribute the rise in the number of drugs with at least one added use code to a general rise in the number of drugs with anything added to them to the Orange Book between 2005 and 2015. Even accounting for the rise in drugs with additions in the Orange Book, however, there is still a rise in the frequency of drugs with added use codes. In 2005, 63 out of the 233 drugs with any relevant addition or change to the Orange Book (27%) had at least one added use code. In 2015, 173 out of the 353 drugs that had any relevant addition or change made to them in the Orange Book (49%) had at least one added use code. Thus, the fraction of drugs with added use codes in the Orange Book rose from less than a third to just about one half during that 11-year period.

141 See Kurt Karst, *Updated Analysis Shows Patent Use Codes Have Nearly Tripled Since August 2003*, FDA Law Blog (July 8, 2013), http://www.fdalawblog.net/2013/07/updated-analysis-shows-patent-use-codes-have-nearly-tripled-since-august-2003/. The metric used in Karst's analysis differs from ours in that he measured the cumulative, total number of use codes listed in the Orange Book each year, while we measured the number of distinct times that a use code was added to a patent, non-cumulatively by year. Thus, our figures for each year cannot be compared directly to Karst's. For instance, Karst counted 627 total use codes listed in the Orange Book as of 2005. This would include use codes added to patents in 2005, as well as use codes that were added in previous years. Meanwhile, we counted 162 instances in 2005 in which a use code was added to a patent.

Table 6. Quantity of Patents and Exclusivities Added, 2005–2015.

Year	*Quantity of Patents Added*	*Quantity of Exclusivities Added*
2005	349	195
2006	499	206
2007	363	207
2008	503	199
2009	458	196
2010	380	148
2011	419	147
2012	522	204
2013	539	163
2014	614	185
2015	723	169

IV.E. Quantity of patents and exclusivities added between 2005 and 2015

An important distinction exists between the number of drugs that had a patent or exclusivity added to it and the total *quantity* of patents and exclusivities added. An individual drug could have just one added patent or one added exclusivity, but it also could have dozens of different added patents and exclusivities. Looking at total quantities of patents and exclusivities across the time period provides a picture of the amount of Orange Book activity at the level of sheer numbers of patents and exclusivities added, rather than at the level of the specific drugs tied to those patents and exclusivities. Similar to the previous metrics, we provide an aggregate figure for the entire time frame and then break down the numbers by year between 2005 and 2015. The results from this inquiry are shown in Table 6.

While there was no clear trend over time in the number of exclusivities added, there was a reliable increase across the 11 years in the number of patents added, especially in the last 5 years between 2011 and 2015. The quantity of patents added double from 349 patents in 2005 to 723 patents in 2015.

The increase over time for the quantity of patents added reflects the upward trend in the number of drugs with patent added to them each year between 2005 and 2015. Likewise, the lack of a trend in the quantity of exclusivities added in that time period corresponds with the absence of any pattern in the number of drugs that added an exclusivity across time.

The question is whether the increase in the quantity of patents is a sign of misbehavior on the part of the drug companies. For example, if more drugs were entering the market, we would see increase in the number of patents. This increase would likely be innocuous. On the other hand, if the number of patents per drug was increasing,

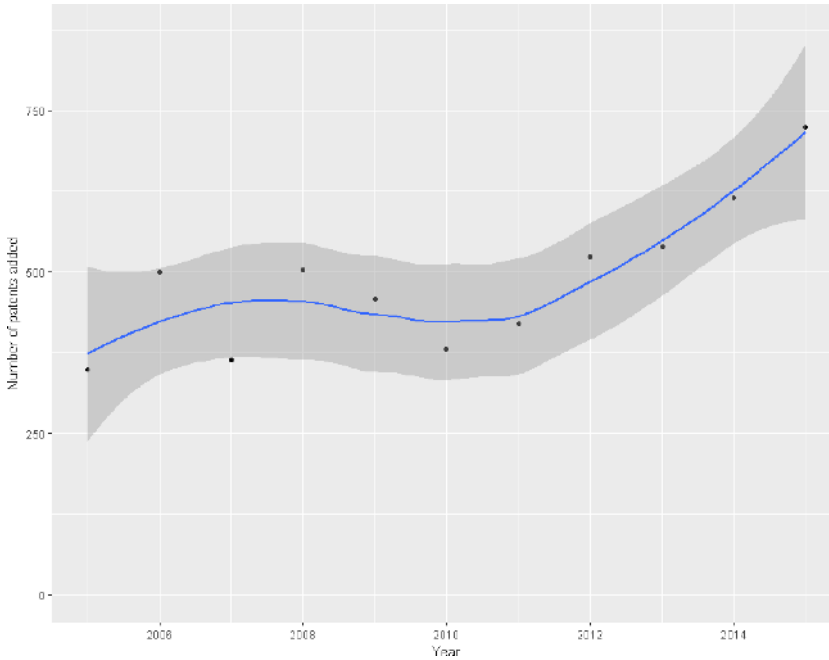

Figure 7. Quantity of patents added, 2005–2015.

there would be evidence of misbehavior as drug companies constructed broader and broader protections around existing drugs.

However, there is one scenario in which a static average number of patents could be a sign of an unhealthy patent system. If the average number of patents is high, the fact it is unchanging does not give it a clean bill of health. This, in fact, is a sign of entrenched habits of misbehavior. In that circumstance, we would not be seeing increasing misbehavior because misbehavior is the norm.

To determine which scenario the patent system is in, we analysed the average number of patents added per drug for each year between 2005 and 2015, shown in Figure 7.

Here we can see the system is in a combination of scenarios. The average number of patents added per year increased from an average of 1.7 patents in 2005 to an average of 2.25 patents in 2015. This increase is slight but non-negligible, and future researchers may wish to keep an eye on whether this continues.[142] Moreover, the average number of patents added is high across all years.

These average figures are dragged down by the drugs that did not add any patents in a particular year, but the increase across our timeframe is still clearly evident. This indicates that the growth in the quantity of patents added between 2005 and 2015 is attributable to two factors working in concert: (1) the growth in the number of drugs

[142] One should note that 2006 appears to be somewhat of an outlier. It is the one point in the range—albeit a range with limited points—that lies outside the 95% confidence band, and it is only slightly below the 2015 figure.

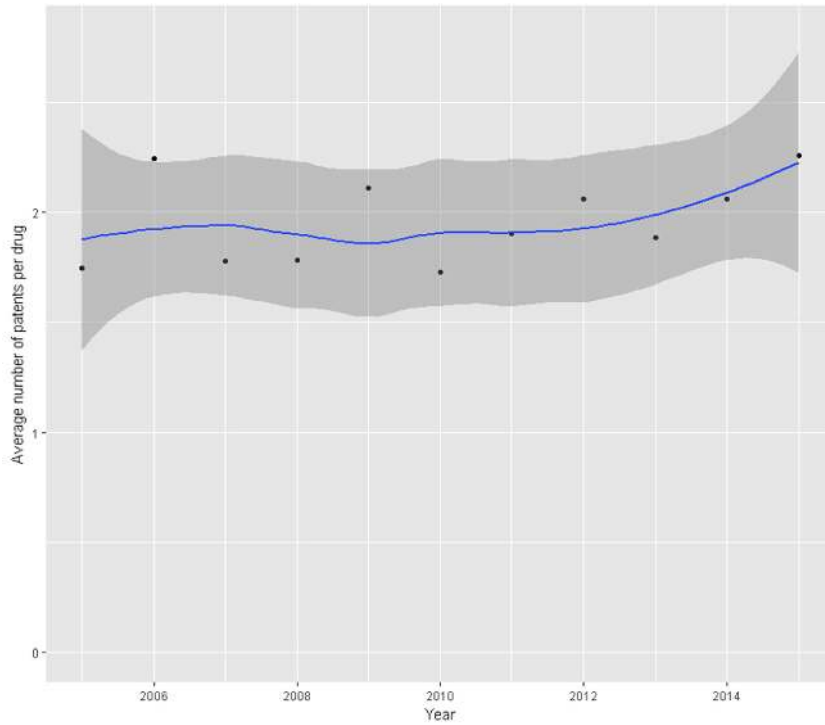

Figure 8. Average number of patents added per drug, 2005–2015.

adding patents and (2) the growth in the average number of patents added per each one of those drugs.

IV.F. Number of drugs that added a high quantity of patents in a single year

Our next metric examined the number of drugs that added a *high quantity* of patents in a single year. The growth in the average number of drugs per year could be due to many drugs adding a slightly higher number of patents or it could be due to a smaller subset of drugs adding a high quantity of patents. In Figures 8 and 9, we show the number of drugs that added a high quantity of patents in a single year, with a 'high quantity' defined as three or more patents in Figure 9 and five or more patents in Figure 10.

There was a clear increase in the number of drugs with three or more added patents in a single year between 2005 and 2015. The figure more than doubles from 37 drugs in 2005 to 76 drugs in 2015. When the definition of a 'high quantity' of patents was changed from three to five, the results were similar. The number of drugs with five or more added patents in a single year also doubled between 2005 and 2015, from 14 drugs in 2005 to 34 drugs in 2015.

The upward trend in the number of drugs with a high quantity of added patents in a single year seems to indicate that drug companies are increasingly applying for as many patents as possible and seeing what they get. Unfortunately, it is likely that as more patents are added to a drug, the quality of the patents declines. Typically, the subsequent patents are more likely to be 'secondary patents', which, instead of covering the

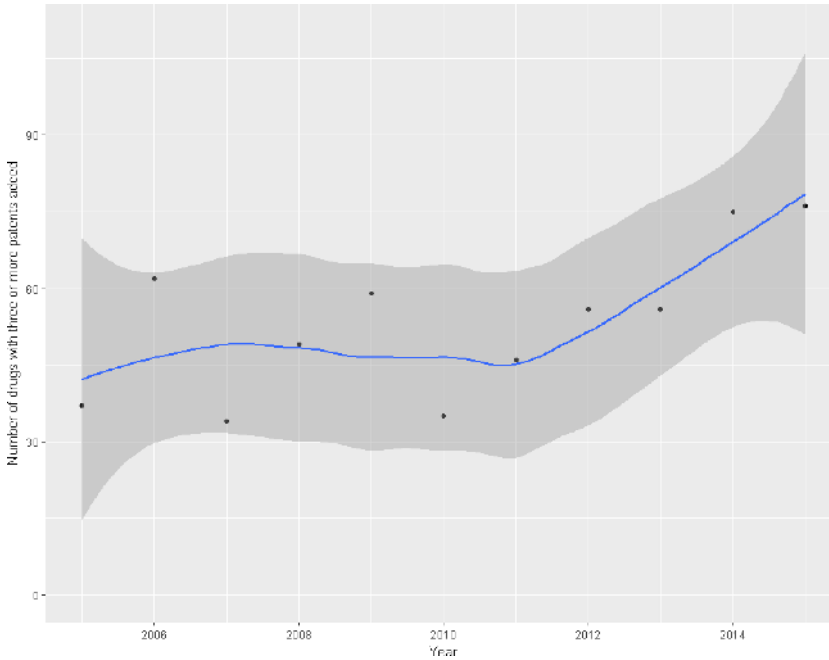

Figure 9. Number of drugs with three or more added patents in a year, 2005–2015.

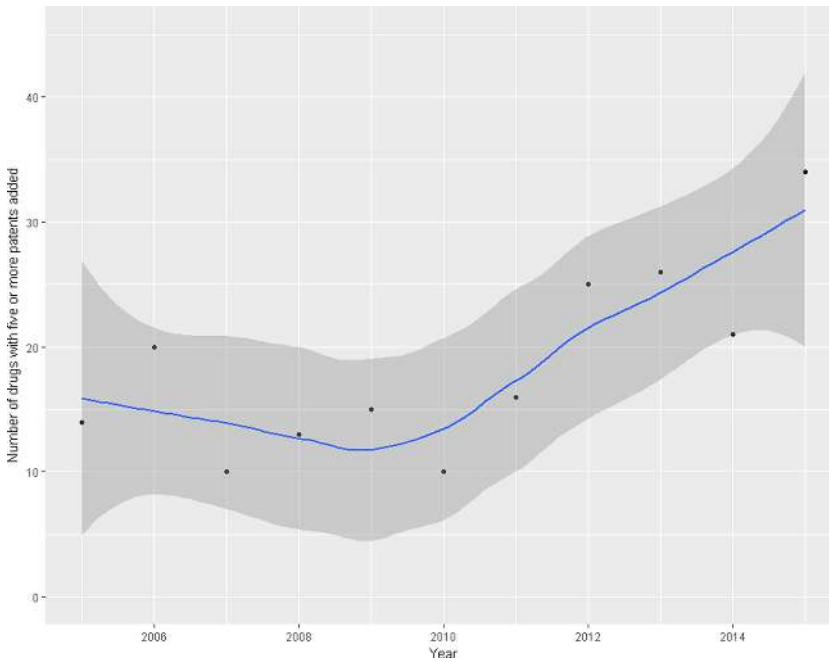

Figure 10. Number of drugs with five or more added patents in a year, 2005–2015.

active ingredient or base compound, cover modified forms of the active ingredient, associated uses of existing chemical compounds, new combinations of old chemical compounds, dosage regimens, and specific formulations (ie tablet vs. capsule).[143] For instance, while the first patent added to a drug might cover the core active ingredient of the drug, the fifth patent might be covering a therapeutically negligible change to the formulation or composition of the drug. As such, the increase in the number of drugs with a high quantity of added patents in a year might be an indication that the pharmaceutical game-playing strategy of evergreening is becoming increasingly common.[144]

IV.G. Number of 'serial offender' drugs

Some drugs in our dataset had patent or exclusivities added to them in to the Orange Book only once during our 11-year timeframe. Other drugs, however, repeatedly returned to the well, having one set of patents and exclusivities added to them, then having another set added a few months later, coming back with another round a few years after that, and so on. To capture this behavior, we measured the number of months during which a drug had a patent or exclusivity added to it in the Orange Book. This means that regardless of whether the drug 1 patent or 10 patents added to it that month, we considered that month as one instance of patent activity. We did this to remain as conservative as possible in our calculations.

Table 7 shows that a surprisingly large percentage of drugs returned to the well repeatedly. Out of the drugs that had at least one Orange Book addition, 80% had additions on *more than one occasion*. Moreover, 49% received additions on *four or more occasions,* and 20% received additions on *seven or more occasions*. As these results demonstrate, drugs that repeatedly bolster their patent and exclusivity protections are not the rarity they might once have been.

IV.H. Number of drugs newly approved compared to number of drugs with to the orange book additions in a year

The next metric examined the number of drugs that were newly approved each year[145] compared to the number of drugs that had patents and exclusivities added to them in the Orange Book in each year. In other words, within all the drugs on the market that had patents and exclusivities added to them each year, which ones were drugs that were newly approved that year, and which ones were drugs that had been approved in the past.

This metric is significant in that it provides an indication of how much patent and exclusivity activity is due to innovation in the pharmaceutical industry and how much of it is attributable to the recycling or repurposing of old drugs. If the number of drugs with added patents and exclusivities to the Orange Book each year far exceeds the number of new drugs approved each year, the result suggests that many drugs are receiving patents and exclusivities—not for innovation represented by a newly approved drug—but rather for changes made to old drugs that were approved previously.

143 See Kapczynski et al., *supra* note 32, at 1.

144 See *supra* note 30 and accompanying text.

145 Newly approved drugs can be determined by scrolling down to the 'Drug Approval Reports by Month' section of the following FDA website. See *Drugs@FDA*, *supra* note 85.

Table 7. Number of Times Each Drug had an Orange Book Addition.

Number of Patents AND/OR *Exclusivities Added*	*Number of Drugs (Total: 1349)*	*Cumulative Number and % (ie at least 18+, AT least 17, at least 16, etc.)*
18+	29	29/1349 (2.15%)
17	3	32/1349 (2.37%)
16	10	42/1349 (3.11%)
15	10	52/1349 (3.85%)
14	10	62/1349 (4.60%)
13	12	74/1349 (5.49%)
12	13	87/1349 (6.45%)
11	23	110/1349 (8.15%)
10	25	135/1349 (10.01%)
9	33	168/1349 (12.45%)
8	55	223/1349 (16.53%)
7	60	283/1349 (20.98%)
6	81	364/1349 (26.98%)
5	125	489/1349 (36.25%)
4	173	662/1349 (49.07%)
3	208	870/1349 (64.49%)
2	212	1082/1349 (80.21%)
1	267	1349/1349 (100%)

Of course, a company *could* bring a novel drug to market and not apply for any type of patent or exclusivity. It would be unlikely, however, for them to do so, given the associated market benefits of patents and exclusivities. A company could also gain approval for a new drug late in the year, and, in doing so, have those patents appear in the following year's Orange Book. We could not eliminate that possibility from our dataset, which represents a limitation of our analysis. In addition, we would expect that the number of drugs falling into any year end would be small.

Finally, we should note that our analysis is likely to significantly understate the amount of repurposing and recycling of old drugs. We examined drugs at the New Drug Application level. Anecdotal evidence suggests that with some product-hopping and evergreening behavior, companies change the name and make insubstantial formulation changes to the drug, submitting the new product under a different 'new drug

Table 8. Number of Drugs Newly Approved Compared to Number of Drugs with Orange Book Additions in a Year.

Year	*Number of Drugs with Orange Book Additions*	*Number of Drugs with Orange Book Additions that Were Approved that Year*	*Percentage of Drugs with Orange Book Additions that Were Not Newly Approved That Year*
2005	263	63	76.05%
2006	281	71	74.73%
2007	267	53	80.15%
2008	335	61	81.79%
2009	273	70	74.36%
2010	264	65	75.38%
2011	258	50	80.62%
2012	309	71	77.02%
2013	326	70	78.53%
2014	348	75	78.45%
2015	355	85	76.06%
Total	**3279**	**734**	**77.62%**

application' than the original one.[146] Our dataset did not connect different new drug applications to each other, and we could not capture that behavior. Thus, the dramatic results below are still only part of the dismal picture.

As is evident from Table 8, the number of drugs with additions to the Orange Book dwarfs the number of newly approved drugs in every single year between 2005 and 2015. On average, 77.62% of drugs with Orange Book additions in a particular year were not new approvals from that year. This suggests a large degree of repurposing and recycling of existing drugs in the pharmaceutical industry, and concomitantly, less innovation and invention than the patent process is intended to create.

When looking at just patent additions, the narrative is the same. As seen in Table 9, 77.55% of drugs with a patent added to them between 2005 and 2015 were existing drugs. Strikingly, this problem grew over the timeframe of our study, with the number of existing drugs with added patents almost doubling from 2005 to 2015.

The concern with repurposing and recycling of old drugs is the following: while many of the changes made to those old drugs may earn new patents and exclusivities, they may not be significant from a patient benefit or therapeutic point of view.

[146] For example, the maker of the colitis drug Asacol, which already had a protective coating, wrapped the drug in an extra ineffective cellulose capsule, naming the new drug, Delzicol as part of a product hop. Feldman & Frondorf, *supra* note 61, at 530. Although the FDA found the new drug bioequivalent, Delzicol is listed as a separate new drug application from Asacol in the Orange Book. *Cf., Id.* at 530.

Table 9. Number of Drugs Newly Approved with an Added Patent Compared to Number of Drugs with an Added Patent in a Year.

Year	*Number of Drugs with an Added Patent*	*Number of Drugs with an Added Patent that Were Approved that Year*	*Number of Drugs with an Added Patent that Were not Approved that Year*	*Percentage of Drugs with Orange Book Additions that Were Not Newly Approved That Year*
2005	166	45	121	72.89%
2006	213	53	160	75.12%
2007	191	37	154	80.63%
2008	263	42	221	84.03%
2009	201	53	148	73.63%
2010	205	51	154	75.12%
2011	201	38	163	81.09%
2012	239	50	189	79.08%
2013	267	63	204	76.40%
2014	288	61	227	78.82%
2015	300	76	224	74.67%
Total	**2534**	**569**	**1965**	**77.55%**

As such, society may be lavishing expensive rewards on suboptimal behavior.[147] The concern is even greater if one considers that many of these secondary patents may be of questionable validity. This is not to suggest that the changes would never have any value, to any patient, under any circumstances. Rather, minor changes to dosage or delivery systems, for example, may have some amount of value to some patients. Similarly, applying an old drug to a different disease brings the advantage of years of experience in the field, which can provide important information on safety. These advantages may not, however, justify the magnitude of the patent reward that is conferred. From society's standpoint, one might be better off with incentives that drive scientists back to the bench to look for advances of greater significance.[148]

[147] As an example, see the FDA's Center for Drug Evaluation Research Exclusivity Board's memorandum on granting both orphan drug exclusivity and new chemical entity exclusivity to Teva's drug Deutetrabenazine and noting that 'it is appropriate to grant orphan drug designation to [the drug] without a plausible theory of superiority'. Kurt R. Karst, *FDA Determines that Deuterated Compounds are NCEs and Different Orphan Drugs Versus Non-deuterated Versions*, FDA Law Blog (2017), http://www.fdalawblog.net/2017/07/fda-determines-that-deuterated-compounds-are-nces-and-different-orphan-drugs-versus-non-deuterated-v/ (citing CDER Exclusivity Board, Determination of Whether SD-809 (Dutetrabenazine) and Tetrabenazine are Different Active Moieties (2015).

[148] Some scholars have suggested tailoring the patent award to provide different strengths of protection based on different invention characteristics, such as time-to-market. See *eg* Benjamin Roin, *The Case for Tailoring*

Table 10. Percentage of Top 106 Best-Selling Drugs that had their 'Protection Cliff' Extended.

Year the Drug Entered Top 50 Best-Selling Drugs	*Number of New Top 50 Drugs By Year*[a]	*Number of Drugs that had their Cliff Extended at Least Once*	*Number of Drugs that had their Cliff Extended More than Once*
2005	50	39/50 (78%)	33/50 (66%)
2006	5	2/5 (40%)	2/5 (40%)
2007	5	4/5 (80%)	1/5 (20%)
2008	6	5/6 (83%)	3/6 (50%)
2009	6	4/6 (67%)	3/6 (50%)
2010	5	3/5 (60%)	2/5 (40%)
2011	9	7/9 (78%)	3/9 (33%)
2012	5	4/5 (80%)	3/5 (60%)
2013	10	5/10 (50%)	3/10 (30%)
2014	5	3/5 (60%)	1/5 (20%)
All	**106**	**76/106 (72%)**	**54/106 (51%)**

[a]As explained in the Methodology section, *supra* note 114 and accompanying text, we first compiled the top 50, best-selling, non-biologic drugs from each year between 2005 and 2014. There is, however, a great deal of overlap between the best-selling drugs from one year to the next. We eliminated duplicates from year to year, which is why the number of drugs from each year between 2005 and 2014 is far less than 50.

IV.I. Percentage of top 105 best-selling drugs from 2005 to 2015 that had the 'protection cliff' extended

Our final metric is the percentage of the 106 best-selling drugs between 2005 and 2014 that had the 'protection cliff' extended. Blockbuster drugs are the ones for which the pharmaceutical companies have the most to lose if their exclusivity period ends, and the most to gain by extending the lifetime of the drug, even by just a few months. Thus, if competition blocking behavior is to be found anywhere, it would be found here. The results from this metric—broken down between drugs that had their protection cliff extended at least once and drugs that had their protection cliff extended more than once—are shown in Table 10. The results are striking.

Out of the 106 top-selling drugs from between 2005 and 2014, more than 70% had their protection cliff extended at least once and more than 50% had their protection cliff extended more than once. The magnitude of the behavior highlights the extent to which stifling competition has become the norm in the pharmaceutical industry. When

Patent Awards Based on Time-to-Market, 61 UCLA L. Rev. 672 (2014). This approach, however, would add significant complexity to the system and provide endless opportunities for game-playing. As noted below in the section discussing the need for ruthless simplification, complexity breeds opportunity. Drug companies have proven quite adept at exploiting those opportunities in ways that run counter to society's interests. See *infra* text accompanying notes 164–167.

more than 70% of best-selling drugs had their protection extended, it is clearly the go-to approach for profitability.[149]

One can easily anticipate such maneuvering to continue going forward, particularly given the top-selling drugs going off patent. Between 2014 and 2020, an estimated $253 billion in worldwide drug sales is at risk due to expiration of patents on blockbuster drugs.[150] Without societal action, the future is likely to look like more of the same.

V. SOLUTIONS

As described in the opening of this article, the intellectual property system in general and the patent system in particular are designed to provide an opportunity for innovators to garner a return. Competition may be held in abeyance for a limited time, but those who receive the benefit must pay for the privilege by disclosing sufficient information that competitors will be able to step in. This design reflects the deeply rooted notion that providing a period of exclusivity for inventors is intended to rebound to the benefit of society as a whole, not simply to the benefit of the inventors. The patent protection should end, returning the market to a competitive state.

This foundational structure of the patent system—one that delicately balances innovation and competition—is crumbling, whittled away across time as one good idea after another creates a special carve-out. Each carve-out, standing on its own, presents an appealing cause. Together, however, the result is a complete undermining of the system for pharmaceutical innovation as the repeated addition of protections, one after another, pushes competition further into the future, threatening innovation in the process. The behavior is not limited to a few bad apples. Our research reveals that it is endemic to the pharmaceutical industry.

In short, this is not an image of innovation and competitive entry. It is an image of a system that provides for repeated creation of competition-free zones, pushing a competitive market further and further out into the future. The problem is not only pervasive and persistent, but it is also growing across time.

The impact created by these repeated competition zones is not some abstract problem that our grandchildren may face. Rather, the nation's pharmaceutical system is in crisis today, with prices soaring to heights that distort both individual and government budgets.[151] These dire circumstances bring calls for price controls, for government marching in to direct drug production, and for other strong measures.[152] The

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149 *Cf.*, Kapczynski et al., *supra* note 32, at 5 (finding that that late-filed secondary patents are more common for higher sales drugs).

150 See *EvaluatePharma World Preview 2017, Outlook to 2022*, EVALUATE 9 (June 2017), http://info.evaluategroup.com/rs/607-YGS-364/images/WP17.pdf.

151 See *supra* notes 22–24 and accompanying text.

152 See Meg Tirrell & Dan Mangan, *Clinton Calls Drug Price Hike 'Outrageous,' Vows Plan*, CNBC (Sept. 21, 2015), https://www.cnbc.com/2015/09/21/clinton-calls-drug-price-hike-outrageous-vows-plan.html (describing Hillary Clinton's calls 'to control the cost of skyrocketing prescription drugs'); *see also* Alison Kodjak, *One Way to Force Down Drug Prices: Have the U.S. Exercise Its Patent Rights*, NPR (Mar. 16, 2017), http://www.npr.org/sections/health-shots/2017/03/16/520390026/one-way-to-force-down-drug-prices-have-the-u-s-exercise-its-patent-rights (noting that Rep. Llyod Doggett, a Texas Democrat, is calling for the United States to exercise march-in rights); *see also* Renee Hickman, *Ohio Takes Drug Price Measure to Voting Booth*, BNA NEWS (July 19, 2017), https://www.bna.com/ohio-takes-drug-n73014461943/ (describing an upcoming drug pricing ballot measure in Ohio); *see also* Thomas Sullivan, *Both Houses of Congress Investigating Prescription Drug Prices*, POL'Y & MED. (Nov. 6, 2015), https://www.

US Government's history of directly managing pharmaceutical innovation, however, has been disappointing. In fact, prior to the Bayh-Dole Act of 1980, the federal government took responsibility for handing out licenses for innovation developed through government-funded research. Bayh-Dole shifted that responsibility from the federal government to universities, precisely because the government failed so miserably in this role. There is little reason to expect a different result this time.[153]

Competition is a powerful and effective tool, however, and paving the way for competition whenever it is possible remains the optimal approach. When the government itself bestows benefits that are stifling competition, society has both an obligation and an opportunity to act. One cannot, however, enter into such action lightly; it must be designed with thought and care. Pharmaceutical research and development are expensive, and companies must have sufficient incentive to travel down that risky road. Nevertheless, by incentivizing game-playing rather than innovation, society has clearly missed the mark.

V.A. One-and-done

This study offers a disappointing view of the state of pharmaceutical innovation, but this result is not inevitable. With sufficient political will—always a challenging task in the US landscape—our valued patent system can operate in the manner intended. The following section sketches out an approach that could roll back the repeated creation of competition-free zones documented in our research.

Specifically, one could implement of the principle of 'one-and-done' in which a drug would receive *one* period of exclusivity, and only one. The choice of which 'one' could be left entirely in the hands of the pharmaceutical company, with the election made at the moment of drug approval. Perhaps development and approval on the drug has gone swiftly and smoothly, so the remaining life of one of the drug's patent is of greatest value. Perhaps those processes languished through many setbacks, such that designation as an orphan drug or some other benefit would bring greater reward. The choice would be up to the company itself, based on its own calculation of the maximum benefit. The result, however, would be that a pharmaceutical company must choose whether its period of exclusivity should be a patent, or an orphan drug designation, or a period of data exclusivity for safety and efficacy data, or something else—just not all of the above and more.

Crafting the one-and-done implementation at the FDA level underscores the fact that these problems and solutions are designed for pharmaceuticals, not other types of technologies. Although there are similarities within the patent system for all

policymed.com/2015/11/both-houses-of-congress-investigating-prescription-drug-prices.html (describing 'a bipartisan Senate investigation into pharmaceutical drug pricing'); *see also* Andrew Pollack, *Drug Prices Soar, Prompting Calls for Justification*, New York Times (July 23, 2015), https://www.nytimes.com/2015/07/23/business/drug-companies-pushed-from-far-and-wide-to-explain-high-prices.html (discussing the efforts of various states to call for transparency and potentially even price controls); *see also* Joanna Shepherd, *The Prescription for Rising Drug Prices: Competition or Price Controls?*, 27 Health Matrix 315, 346 (2017) (remarking that '[r]ecent surges in drug spending have provoked anger and prompted calls for reform' and clarifying that the demands include price controls).

153 See Robin Feldman & Kris Nelson, *Open Source, Open Access, and Open Transfer: Market Approaches to Research Bottlenecks*, 7 Nw. J. Tech. & Intell. Prop. 14, 17 (2008) (explaining the history of the Bayh-Dole Act and describing the extraordinary translation of federal research dollars into new products for society that has occurred since passage of the Act).

inventions, given the drug approval processes—including the Hatch-Waxman system for approval of generic drugs and the Biosimilars pathway for approval of follow-on biologics—pharmaceuticals are different.

Much of one-and-done could be implemented through legislative changes to the FDA drug approval system, which would apply to patents granted going forward. Statutory amendments could specify that once a company elects a particular patent or exclusivity, competitors wishing to obtain approval of a generic version of the drug through the Hatch-Waxman system need only certify to that one exclusivity.

The election could be crafted so that it mandates relinquishment of any other patent or exclusivity claims as to the generic drug being approved. This approach would be somewhat analogous to an election that currently exists under the current Hatch-Waxman Act. When a generic applicant makes a Paragraph IV certification claiming that the brand-name company's patents are invalid or do not apply to the drug, the brand-name company has a period of time to challenge that certification in court. If the brand-name company fails to challenge the assertion, it relinquishes various rights, particularly, the right to an automatic 30-month stay of the generic's approval. Without the 30-month stay, the brand would have to prove likelihood of success on the merits and other preliminary injunction factors to keep the generic off the market during the period of the litigation.[154] Similarly, in the proposed system, the company's choice to designate a particular form of exclusivity upon approval could serve to relinquish its right to challenge the generic under any other exclusivity.

The compromise embodied in the original Hatch-Waxman system could provide a model for crafting the one-and-done system. Specifically, the Hatch-Waxman legislation included both the expedited system for generic approval and an expansion of the patent term to reflect delays in the federal approval system. Similarly, in implementing a one-and-done system, Congress could choose to expand the periods of the current exclusivities available, in recognition that pharmaceutical companies will no longer be able to tack so many periods of protection on to each other. One could argue that the current effects of the patent and exclusivities were never what Congress intended. Nevertheless, it may be politically expedient to follow the path blazed by Hatch-Waxman. In a similar vein, Congress could choose to standardize the periods of protection offered by various exclusivities, which currently range from 6 months to 7 years. As described in the section below on simplification, the complexity of these various systems provides opportunities for game-playing. Standardization may reduce those opportunities.

Some commentators may be tempted to claim that any relinquishment of patent or exclusivity rights constitutes a taking of private property. In particular, one scholar, Adam Mossoff, has asserted that patent rights are constitutionally protected property, and as such, would be subject to the Fifth Amendment Takings Clause.[155] Even Mossoff, however, acknowledges that 'modern courts and scholars … seem to agree in a rare case of unanimity that the historic record reflects no instance of a federal court holding that the Takings Clause applies to patents'.[156]

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154 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

155 See Adam Mossoff, *Patents as Constitutional Private Property: The Historical Protection of Patents Under the Takings Clause*, 87 B.U.L. Rev. 689, 691 (2007).

156 See Mossoff, *supra* note 155, at 691. Mossoff criticizes Supreme Court decisions from 1886 onward by referencing earlier Supreme Court and lower courts cases from the 1870s, as well as by arguing against those who

In a 2018 case upholding the inter partes review system at the Patent and Trademark Office, the Supreme Court specifically avoided ruling on the question of whether patents are property for the purpose of the Takings Clause.[157] In paragraph that begins by noting, '[w]e emphasize the narrowness of our holding' and presents a litany of what the decision does not address, the court cryptically concludes by noting that 'our decision should not be misconstrued as suggesting that patents are not property for purposes of the Due Process Clause or the Takings Clause'. The Justices then cite two cases related to sovereign immunity and whether the state can be sued for using a patented item without paying for it.[158] In contrast, the two dissenting Justices use language that would move the status of patents much closer into the realm of traditional property rights. This suggests that whether, and the extent to which, patents are treated as property for Constitutional purposes is likely to arise in future Supreme Court cases.

The notion of patents as full property rights—akin to the type of core property rights protected by the Constitution—would require ignoring significant aspects of patent history and theory. Patent rights are theoretically, doctrinally, and practically distinct from real property, making the notion of an absolute right to exclude particularly inapplicable[159]. More important, unlike real property, patent rights are granted by the government for limited times and for limited purposes, namely promoting the progress of the useful arts[160] for the benefit of society. The utilitarian roots of their theory and design bear little resemblance to natural rights theories of the types of property protected by the Constitution.

One particularly cogent modern description of the issue appears in a dissent to the 2015 Supreme Court decision in the *Teva* case, in which the dissenters reviewed the history of patent rights in contrast to core property rights.

> The Anglo-American legal tradition has long distinguished between 'core' private rights—including the traditional property rights represented by deeds—and other types of rights. These other rights [include] 'privileges'or'franchises,' 'which public authorities have created purely for reasons of public policy and which ha[ve] no counterpart in the Lockean state of nature. Notwithstanding a movement to recognize a core property right in inventions, the English common law placed patents squarely in the final category as franchises.[161]

As the text of the dissent also explained, our own 'Framers adopted a similar scheme'.[162]

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view passage of sovereign immunity legislation in 1887 as mooting the earlier cases. See Mossoff, *supra* note 155 at 701–710, 711–15.

157 See Oil States Energy Servs, LLC. v. Greene's Energy Group LLC., No. 16–712, slip op. at 16–17 (138 S. Ct. 1365).

158 *Id.* (citing United States v. Duell, 172 U.S. 576, 582, 586 (1899); Butterworth v. United States ex rel. Hoe, 112 U. S. 50, 59 (1884)).

159 See Robin Feldman, *Rethinking Patent Rights* (Harvard 2012). Even basic patent doctrines have, from time immemorial, provided for overlapping rights, such that more than one patent holder may have the right to exclude others from the exact same space. See Donald S. Chisum, 5 Chisum on Patents § 16.02 (2010) (citing Cantrell v. Wallick, 117 U.S. 694 (1886)).

160 See U.S. CONST. art. I, § 8, cl. 8 ("To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries").

161 Teva Pharm. USA, Inc., v. Sandoz, Inc., 135 S.Ct. 831, 848 n.2 (2015) (Thomas, J., dissenting) (citations omitted) (quoting Caleb Nelson, *Adjudication in the Political Branches*, 107 COLUM. L. REV. 559, 567 (2007)).

162 *Id.* at 847.

In short, patents are not core property rights, and attempting to characterize them as such threatens the reverence that the nation has traditionally held for core property rights. Although concerns may play out in the context of due process, the notion that the Takings Clause would prevent Congress from shortening the length of time or the interaction among various patent rights[163] would be misguided, at best.

V.B. Ruthless simplification

For those who like complexity, the intellectual property system for pharmaceuticals is a garden of delights. From the Hatch-Waxman legislation, to the Biosimilars Act, to the maze of regulatory exclusivities, and beyond, the judicial and regulatory processes surrounding intellectual property rights for drugs constitute among the most complex corners of our legal system.

Of course, some complexity in pharmaceuticals is inevitable. The intellectual property systems for drugs must, of necessity, interact with approval processes, and those approval processes must operate with exquisite awareness of public health and safety. These are heady responsibilities. Nevertheless, the system has become so complex and convoluted that it threatens to collapse in on itself.

And, of course, complexity breeds endless opportunities.[164] It ensures that the legislators and regulators will always be at least a step behind in an endless game of cat and mouse. Year after year, government actors must attempt to block strategic behaviors that have developed, even as the industry develops new ones.[165] In such a process, it is clear that our incentive structure is badly misaligned with societal goals.

Putting the system back on track will require ruthless simplification.[166] It means stripping away the intricate details that are so appealing to those who must form compromise among interest groups, but that sow the seeds of current and future strategic behavior. In short, what has become business as usual for the pharmaceutical industry must become a thing of the past.

The 180 day period of exclusivity for first-filing generics is a classic example of complexity that provides game-playing opportunities. It is an extremely complicated and intricate piece of legislation. In what is known as pay-for-delay, the system has provided a method for generics and branded pharmaceutical companies to form anticompetitive agreements in which the generic agrees to stay off the market in exchange for some form of payment.[167] A simplified approach, in which the period of exclusivity attaches only if the patent is actually invalidated, could reduce the game-playing. Frankly, although it

163 *Cf.* U.S. Patent & Trademark Off., Manual of Patent Examining Procedure § 804 (9th ed. 2018).

164 FELDMAN, *supra* note 8, at 160.

165 See *eg* FELDMAN & FRONDORF, *supra* note 2, at 31 (describing the Paragraph IV first-filer exclusivity that encourages generic companies to enter the market swiftly to challenge brand name drugs) (citing 21 U.S.C. §355(j)(5)(B)(iv)); *see also* FELDMAN & FRONDORF, *supra* note 2, at 143 (noting that the brand-name companies cannot receive more than one 30-month stay period on potential generic competitors); *see also* FELDMAN & FRONDORF, *supra* note 2, at 65 (noting that new legislation 'requires that citizen petitions with the potential to affect generic approval… be considered within 150 days'.) (citing 21 U.S.C. §355(q)(1)(F)); *Id* at 49–65 (describing examples of the complex second generation of pay-for-delay settlements, taking place even after courts try to shut down pay-for-delay settlements of the first generation).

166 For an example of simplification, see Hemphill, *supra* note 31, at 686–88 (suggesting in the context of complex pay-for-delay settlements the law government should suppress complexity by viewing contemporaneous value conferral as a payment and require firms to actually earn their exclusivity).

167 See FELDMAN & FRONDORF, *supra* note 2, at 34–66.

is akin to heresy to suggest, one could argue that the entire first filer exclusivity period should be eliminated. There may be sufficient market opportunities for generics without that incentive, particularly given the high price of branded pharmaceuticals, and the game-playing it has spawned may outweigh the benefits of having such as system.

V.C. Transparency[168]

Systemic changes such as One-and-Done and Ruthless Simplification require both time and political courage to promulgate and implement. Thus, additional adjustments will be necessary along the way. Chief among these is transparency. As one commentator noted in a 2017 FDA public meeting, transparency 'is the enemy of all this abuse'.[169] The power of pharmaceutical company behavior lies, in part, from the obscurity of those behaviors, making it difficult for legislators, regulators, and the public to tease out and address what is happening. No matter which approaches are chosen for addressing improper behavior in the pharmaceutical realm, transparency will be a critical component. Only then will society be able to quickly identify new strategic behaviors as they emerge and provide solutions before too much damage occurs.

Moreover, competition thrives on information. Those willing to offer better terms will find willing buyers—from the federal government to private insurers to HMOs—beating a path to their door and driving some measure of competition into a non-competitive market. That competitive environment can only exist if potential competitors have full and complete information. With this in mind, the following sections provide examples of areas in need of increased transparency. Although we focus these suggestions on transparency in relation to the topics studied in this article, we note that transparency in drug pricing will be critical as well, in order to take in the full range of modern games.[170]

V.C.i. Accessibility of Orange Book information

Accessibility of information is a problem throughout the FDA's many resources. We faced a number of obstacles conducting research, which are briefly outlined here, although they are detailed more extensively in our other publications and in sections above.[171]

First, there is considerable room for improvement within the Orange Book system, particularly for the information regarding ANDAs. One of the largest difficulties in that

[168] During the process of drafting this article, these transparency suggestions were included in comments to the FDA. Robin Feldman, *Comment on the FDA Notice: Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation Access; Public Meeting*, REGULATIONS.GOV (Sept. 19, 2017), https://www.regulations.gov/document?D=FDA-2017-N-3615-0071.

[169] David Balto, U.S. Food & Drug Admin. The Hatch-Waxman Amendments: Ensuring a Balance Between Innovation & Access, Comments at the Public Meeting (July 18, 2017) (transcript available at https://www.fda.gov/downloads/Drugs/NewsEvents/UCM571419.pdf).

[170] See FELDMAN & FRONDORF, *supra* note 2, at 15–16,143 (noting that secret negotiations between drug companies and pharmacy benefit managers ('PBM's) result in uncertain drug prices). A number of states have introduced transparency bills. See *eg* Lydia Ramsey, *'More is Possible': A Bunch of States Are Taking on High Drug Prices, and it Could Start Hitting Drugmaker Profits*, BUSINESS INSIDER (2017), http://www.businessinsider.com/states-with-drug-pricing-transparency-bills-2017-6/#maryland-is-tackling-generic-drug-price-hikes-1 (listing states with transparency bills, including Maryland, New York, California, and Vermont.)

[171] See FELDMAN & FRONDORF, *supra* note 2; *see* Feldman et al., *supra* note 31; *see supra* notes 78–80 and accompanying text; see *infra* note 173 and accompanying text.

realm lies in locating the date of an ANDA's filing, information that is invaluable to many researchers and members of the interested public.[172] For our research, we had to painstakingly read through every published approval letter to pull the dates of original filings, which were often casually mentioned.[173] For many approved drugs, we had to estimate the quarter year in which the application was published based on the number sequence, a complex and time-consuming process. Even worse, there are recent reports that approval letters will no longer include the original date of filing, making an approach like ours almost impossible for drugs going forward.[174] In addition, the citizen petition files do not always link to specific generic applications or offer indications of this information that is so critical for tracking the timing of citizen petitions in relation to the application process for a particular drug.[175]

Prior editions of the Orange Book are not readily available, although the FDA has stated that they will eventually be available in an archive.[176] There is also a lack of clarity when information is updated or changed. Specifically, when a patent or exclusivity is marked as a new addition in a cumulative supplement, the Orange Book does not identify which component of the listing warranted the new addition flag. It could be that the entire listing—patent number, expiration date, patent codes, and all—is new, but it could also be that just one element is new.

Timing issues exist with the updates to the Orange Book as well. While the FDA has begun updating the ASCII file version monthly, in the past it was not updated for months, even though hundreds of changes were occurring based on archived hard copies.[177] The information is difficult to interpret, especially in older versions. For example, files prior to December 11, 2009 do not include a data field indicating whether a drug product is a generic or a new drug.

In short, the Agency publishes substantial information online and in hardcopy, but a significant amount of information is missing.[178] This inaccessibility obscures the strategic behavior that is occurring, making it difficult for regulators, legislators, and the public to identify and address improper activity.[179]

V.C.ii. Accessibility of information in the Purple Book

Our study examined behavior in the market for small molecule drugs through the lens of information in the Orange Book. In 2010, Congress approved a separate system for approval of follow-on biologic drugs, known as the Biosimilars Act. Information on biosimilars is listed in the so-called Purple Book, in colorful contrast to the Orange Book. While the Orange Book has long been a highly useful tool for various stakeholders addressing many aspects of small molecule drugs and their approved counterpart

172 Feldman et al., *supra* note 32, at 90; FELDMAN & FRONDORF, *supra* note 2, at 115.

173 Feldman et al., *supra* note 32, at 66.

174 FELDMAN & FRONDORF, *supra* note 2, at 119 n.11 (citing Bob Pollock, *Do You Notice Something Missing? What the Heck!*, LACHMAN CONSULTANTS (Mar. 31, 2016), http://www.lachmanconsultants.com/2016/03/do-you-notice-something-missing-what-the-heck/).

175 FELDMAN & FRONDORF, *supra* note 2, at 115.

176 See *supra* note 79.

177 See *supra* notes 82–110.

178 See *supra* notes 82–83.

179 FELDMAN & FRONDORF, *supra* note 2, at 115–16, 119.

generic drugs,[180] the relatively new Purple Book was intended to be its equivalent for biologics, listing biologics and corresponding licensed biosimilars.[181] Unfortunately, the Purple Book has serious shortcomings as an information vehicle. Although these shortcomings may be driven by the fact that the Biologics Act does not disclose particular information for the purposes of the judicial and regulatory challenges involved in the Act, the FDA could, of course, choose to provide the information, and Congress could mandate it.

For example, the Purple Book does not include patent information for the reference biological product.[182] Although the Biologics Act does not require that a drug company publishes patent information up front,[183] that information may emerge to some extent during the process of approving what are known as biosimilars and interchangeables. As of now, it appears that the FDA has no plans to include patent information as it emerges in the biosimilar approval process.[184]

Most important, the information available in the Purple Book is difficult to access. While the FDA has an easy-to-use, reasonably sophisticated website for the Orange Book—where a user can search by active ingredient, proprietary name, patent, applicant holder, or application number—in most cases there is no similar mechanism for the Purple Book.[185] In fact, the Purple Book's two lists are only available in PDF format and are not easily searchable.[186]

Biosimilars have extraordinary potential to lower pharmaceutical costs and expand access for consumers. If the FDA wishes to allow companies, academics, and other stakeholders to tap into this potential, the Purple Book must be updated to increase the amount of information available and to improve the accessibility of this information. At the very least, the Purple Book should be of the same caliber as the Orange Book; and it should aspire to even better.

V.D. Paving a better road

One-and-Done and Ruthless Simplification, coupled with transparency measures, could go a long way towards returning the system of pharmaceutical innovation to its proper competitive pathway. There will, of course, be much wailing and gnashing of teeth. The pharmaceutical industry has become comfortably accustomed to working

180 Evert Uy Tu & Jeffrey A. Wolfson, *FDA Throws the (Purple) Book at Biosimilars—Purple v. Orange*, HAYNES-BOONE (2014), http://www.haynesboone.com/Alerts/fda-throws-the-purple-book-at-biosimilars-purple-v-orange (accessed Nov. 1, 2018).

181 *Id.*

182 *Id.*

183 See *generally* Biologics Price Competition and Innovation Act, 42 U.S.C § 201 et. seq. (2009); *see* Kurt Karst, *The 'Purple Book' Makes its Debut!*, FDA LAW BLOG (Sep. 9, 2014), http://www.fdalawblog.net/2014/09/the-purple-book-makes-its-debut/ (noting that 'the [Biologics Act] does not require the FDA to publish a list of licensed biological products, including applicable patents and non-patent exclusivities.').

184 Daniel M. Scolnick, *FDA's 'Purple Book' for Biologics – Patents Not Included*, PEPPER HAMILTON LLP (Sept. 15, 2014), https://www.lexology.com/library/detail.aspx?g=daeb199c-c1f1-4704-9cb8-38ca6ee24514.

185 Tu & Wolfson, *supra* note 180.

186 *Id.*; *Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations*, U.S. FOOD & DRUG ADMIN. (last updated Sept.5, 2017 and Sept. 1, 2017, respectively), https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm.

with a system that provides space for creating non-competitive environments. The industry will not relinquish this environment with ease and grace, and the nation is likely to hear impassioned pleading that pharmaceuticals cannot withstand any reform of the current system.[187] Along similar lines, the CEO of the pharmaceutical company Allergan published a 2017 Op-Ed in the Wall Street Journal arguing that the 2011 patent reforms, which created a new post-grant review process for patents, left the company with no choice but to transfer their patents to Indian tribes to avoid having the patents reviewed.

When companies plead with government for benefits by arguing that they cannot withstand competition, one should be deeply skeptical. Our challenge as a society is to restore the balance provided by the patent system itself, in which the inventor of a truly innovative product receives a limited period time to attempt to garner a return, following which, open competition reigns supreme. The system has strayed far from that ideal.

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187 See *eg* Brent Saunders, *Reverse Patent Trolls are Harming Drug Innovation—and Patients,* WALL STREET JOURNAL (Oct. 8, 2017), https://www.wsj.com/articles/reverse-patent-trolls-are-harming-drug-innovationand-patients-1507487600 (Op-Ed by CEO of Allergan arguing that the 2011 patent reforms, which created a more effective post-grant review process at the Patent and Trial Appeal Board, left them with no choice but to transfer their patents to Indian tribes to avoid having their patents reviewed).