

# The Drug Repurposing Ecosystem: Intellectual Property Incentives, Market Exclusivity, and the Future of “New” Medicines

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*The pharmaceutical industry is in a state of fundamental transition. New drug approvals have slowed, patents on blockbuster drugs are expiring, and costs associated with developing new drugs are escalating and yielding fewer viable drug candidates. As a result, pharmaceutical firms have turned to a number of alternative strategies for growth. One of these strategies is “drug repurposing”—finding new ways to deploy approved drugs or abandoned clinical candidates in new disease areas. Despite the efficiency advantages of repurposing drugs, there is broad agreement that there is insufficient repurposing activity because of numerous intellectual property protection and market failures. This Article examines the system that surrounds drug repurposing, including serendipitous discovery, the application of “big data” methods to prioritize promising repurposing candidates, the unorthodoxly regulated off-label prescription practices of providers, and related prohibitions on pharmaceutical firms’ off-label marketing. The Article argues that there is a complex ecosystem in place and that additional or disruptive IP*

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*or market exclusivity incentives may harm as much as help in promoting repurposing activity. To illustrate this threat, the Article traces the trajectory of metformin, a common diabetes drug that shows promise for conditions ranging from polycystic ovary syndrome to breast cancer. From the initial reasons for Bristol-Myers Squibb to refuse to invest in promising alternative uses, to the institutions, researchers, and regulators who identified possibilities for metformin treatment, this Article aims to map the role of intellectual property protection, market exclusivity, and search for capital that led to metformin's ascent as a repurposed drug. The Article contributes a concrete understanding to an important problem in pharmaceutical law and policy, one for which scholars have quickly suggested more powerful patent and market exclusivity protection when doing so may undermine the very processes now leading to effective alternative uses for existing drugs.*

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## INTRODUCTION

After applying a sophisticated algorithm to screen 6,000 compounds either approved by the U.S. Food and Drug Administration (FDA) or far along in clinical development, researchers from two U.S. universities and the National Institutes of Health found existing drug compounds that can stop the Zika virus both from replicating in the body and from damaging fetal brain cells that lead to birth defects in newborns.<sup>2</sup> One of the drugs, niclosamide, is already on the market as a treatment for tapeworm.<sup>3</sup> The breakthrough is part of a trend in the development trajectory of new medicines: instead of developing new small molecule compounds, with their associated long approval timelines and high rates of failure, researchers are turning to already-approved medications in the hope that rapidly advancing computer analysis techniques may match information from existing compounds to diseases in need of new treatments. Separate studies suggest that niclosamide may be effective in treating cancer as well as methicillin-resistant *Staphylococcus aureus* (MRSA), a bacterium resistant to most antibiotics

Of course, just because niclosamide shows promise at the cellular level does not necessarily mean that it would be effective (or at what dosage) at treating Zika if humans actually used it for that purpose. Nor does it resolve, given the possibility that it would be prescribed to pregnant women, additional safety concerns particular to them.<sup>4</sup> In order for niclosamide to be approved, expensive clinical trials must be undertaken and the regulatory process for its alternative use approved by FDA. If niclosamide were new, the normal mechanism that would cover clinical trial and other development costs would be the patent system: the original patent holder—Bayer—would be able to charge high prices on the drug, license the compound to others,

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<sup>2</sup> See Miao Xu, et. al., *Identification of Small Molecule Inhibitors of Zika Virus Infection and Induced Neural Cell Death via a Drug Repurposing Screen*, 22 NATURE MED. 1101, 1101 (2016).

<sup>3</sup> Kathleen Haughney, *FSU Research Team Makes Zika Drug Breakthrough*, FSU NEWS (Aug. 29, 2016), <http://news.fsu.edu/news/science-technology/2016/08/29/fsu-research-team-makes-zika-drug-breakthrough/> [<https://perma.cc/5DP2-L6YN>].

<sup>4</sup> Although there are no controlled studies supporting use by pregnant women during pregnancy, animal studies have revealed no evidence of harm to the fetus. See *Niclosamide (Oral)*, MAYO CLINIC, <http://www.mayoclinic.org/drugs-supplements/niclosamide-oral-route/before-using/drg-20065068> [<https://perma.cc/8KR7-P85P>].

or sell rights to the patent until the patent expired, at which time generic manufacturers would enter the market and the price would decline by ninety percent or more.<sup>5</sup> But, niclosamide was patented in the U.S. in 1960.<sup>6</sup> If the patent had already expired by the time of the drug's approval, then Bayer, which had received approval by FDA to market niclosamide under the trade name Niclocide, would be able to rely upon "regulatory" exclusivity, or the five-year period granted for new small molecule medicines. But, niclosamide was first approved by FDA on May 14, 1982.<sup>7</sup> So, with no ability to recover clinical investments through the patent system or through special regulatory exclusivity, who would pay to prove that this promising, already-approved treatment might save unborn children from severe birth defects and lifelong disability?

This problem—what Rebecca Eisenberg calls the "problem of new uses"—has vexed firms, legislators and regulators for most of the last decade.<sup>8</sup> The 21st Century Cures Act, one of the last laws signed by President Obama, contained provisions applicable to new uses of existing drugs up until the last legislative session, when the major parties could not reach an agreement.<sup>9</sup> The provisions applicable to new uses had been circulating in Congress for five years or more.<sup>10</sup>

In reality, the debate over new uses for existing drugs has not arisen because of public health threats like Ebola or Zika, but rather because pharmaceutical firms face a fundamental transformation of their business model.<sup>11</sup> While expenditures on

<sup>5</sup> See *Price Declines After Medicines Lose Exclusivity in the U.S.*, IMS INST. FOR HEALTHCARE INFORMATICS 2 (2016), [https://www.imshealth.com/files/web/IMSH%20Institute/Healthcare%20Briefs/Price\\_Declines\\_after\\_Branded\\_Medicines\\_Lose\\_Exclusivity.pdf](https://www.imshealth.com/files/web/IMSH%20Institute/Healthcare%20Briefs/Price_Declines_after_Branded_Medicines_Lose_Exclusivity.pdf) [https://perma.cc/4CC4-CRCJ] (providing evidence of price reduction in a drug after generic entry).

<sup>6</sup> U.S. Patent No. 3,079,297 (filed May 31, 1960).

<sup>7</sup> *Niclocide (Niclosamide) Product Details*, U.S. Food & Drug Admin. Orange Book, [https://www.accessdata.fda.gov/scripts/cder/ob/results\\_product.cfm?App\\_Type=N&Appl\\_No=018669](https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?App_Type=N&Appl_No=018669) [https://perma.cc/S6XC-TVXS].

<sup>8</sup> Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL'Y L. & ETHICS 717, 717-18 (2005).

<sup>9</sup> See Juliet Eilperin & Carolyn Y. Johnson, *Obama, Paying Tribute to Biden and Bipartisanship, Signs 21st Century Cures Act Tuesday*, WASH. POST (Dec. 13, 2016) [https://www.washingtonpost.com/news/powerpost/wp/2016/12/13/obama-paying-tribute-to-biden-and-bipartisanship-signs-21st-century-cures-act-tuesday/?utm\\_term=.3c6cf7dc6b7e](https://www.washingtonpost.com/news/powerpost/wp/2016/12/13/obama-paying-tribute-to-biden-and-bipartisanship-signs-21st-century-cures-act-tuesday/?utm_term=.3c6cf7dc6b7e) [https://perma.cc/9JM6-PKS3].

<sup>10</sup> See, e.g., MODERN Cures Act, H.R. 3497, 112th Cong. (2011).

<sup>11</sup> See Iain Cockburn, *Is the Pharmaceutical Industry in a Productivity Crisis?*, in INNOVATION POLICY AND THE ECONOMY 1 (Lerner & Stern eds., 2007); Kristopher Hult and Tomas Philipson, *Should Investors Pay Attention to the Alleged Productivity Crisis in Pharma?*, FORBES (Apr. 3, 2015), <https://www.forbes.com/sites/tomasphilipson/2015/04/03/should-investors-pay-attention-to-the-alleged-productivity-crises-in-pharma> [https://perma.cc/72TX-YGL8].

pharmaceutical research and development have accelerated rapidly over the last several years, the number of drug approvals, including new molecular entities and new biologics, has declined steadily since the mid-1990s. During the period from 1978 to 1980, the average number of the FDA category of new molecular entities was forty-three. By the period from 1998 to 2000, the average number had dropped to thirty-three.<sup>12</sup> That number fell to twenty-two between 2005 and 2010, although approvals have edged up in recent years as a result of accelerated regulatory pathways.<sup>13</sup> Of approvals, however, roughly half offered therapeutic qualities similar to an already approved drug.<sup>14</sup> In the same period, research and development investments, as reported by member firms of the Pharmaceutical Research and Manufacturers of America (PhRMA), increased from \$8.4 billion per year in 1990 to \$48.6 billion in 2011.<sup>15</sup> As a consequence of modest new approvals, new patented products are not replacing revenues supported by patents expiring on existing drugs.<sup>16</sup> Moreover, the return from each new drug has declined.<sup>17</sup> The growing reach and strength of insurance firms and pharmaceutical benefit management companies has further pressured pharmaceutical firms' profit margins.<sup>18</sup>

The financial pressures facing pharmaceutical firms have resulted in both internal and external reorganizations. Pharmaceutical firms are now far more likely either to outsource

<sup>12</sup> A. Demain and J. Spizek, *The Antibiotic Crisis*, in *ANTIMICROBIAL DRUG DISCOVERY* 29 (George Tegos & Eleftherios Mylonakis eds., 2012).

<sup>13</sup> *Summary of NDA Approvals & Receipts, 1938 to the Present*, U.S. FOOD & DRUG ADMIN. (Jan. 18, 2013), <https://www.fda.gov/aboutfda/whatwedo/history/productregulation/summaryofndaapprovalsreceipts1938tothepresent/default.htm> [<http://perma.cc/RQK2-YER8>].

<sup>14</sup> Elina Petrova, *Innovation in the Pharmaceutical Industry: The Process of Drug Discovery and Development*, in *INNOVATION AND MARKETING IN THE PHARMACEUTICAL INDUSTRY* 23-24 (Stefan Stremersch & Min Ding eds. 2013) ("Notably, more than half of the new brands of drugs introduced in 2010 were not novel chemical entities or biopharmaceuticals, but improved versions and altered formulations.").

<sup>15</sup> See *2015 Profile*, PHRMA 2 (Apr. 2015), [http://phrma-docs.phrma.org/sites/default/files/pdf/2015\\_phrma\\_profile.pdf](http://phrma-docs.phrma.org/sites/default/files/pdf/2015_phrma_profile.pdf) [<http://perma.cc/NZ3Z-3SLX>].

<sup>16</sup> Mark Kessel, *The Problem with Today's Pharmaceutical Business—An Outsider's View*, 29 *NATURE BIOTECHNOLOGY* 27, 27 (2011) ("Blockbuster drugs are coming off patent or being taken off the market for safety reasons and there are no replacement drugs on the horizon to make up the shortfall in profits."); Andrew Jack, *Pharma Tries to Avoid Falling Off "Patent Cliff,"* *FINANCIAL TIMES* (Apr. 6, 2012), <https://www.ft.com/content/572ea510-9452-11e1-bb47-00144feab49a> [<https://perma.cc/V5LD-E3KB>].

<sup>17</sup> Ernst R. Berndt et al., *Decline in Economic Returns from New Drugs Raises Questions About Sustaining Innovations*, 34 *HEALTH AFF.* 245, 251-52 (2015).

<sup>18</sup> *Id.*

one of the major expenses of drug development—clinical trials—to contract research organizations (CROs) or to undertake trials in less expensive jurisdictions.<sup>19</sup> The industry has also consolidated to achieve cost synergies. Of the forty-two members of PhRMA active in 1988, only eleven remain today.<sup>20</sup> Major pharmaceutical firms are also using acquisition of highly specialized biotechnology firms to open access to new products. Since 1994, GlaxoSmithKline and Sanofi have undertaken, respectively, over \$78 billion and \$100 billion in acquisitions and have made explicit, public announcements about targeting smaller biotechnology firms.<sup>21</sup> Pharmaceutical firms are also shifting their investment priorities, on the one hand becoming as much marketing and sales firms as research firms and on the other directing more research dollars toward biologics, or therapies derived from living organisms.<sup>22</sup> The former investment allows pharmaceutical firms to capture off-patent revenues diminished by competition from generics firms. The latter investment is promising from a medical standpoint, but also a more difficult market for generics firms to enter.<sup>23</sup>

Among the strategies that have emerged as pharmaceutical industry innovation, financing, and organization transforms is investment in finding new ways to use approved drugs or abandoned clinical candidates.<sup>24</sup> Drug repurposing—also known as repositioning, reusing, or rediscovery—is an attractive option

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<sup>19</sup> Editorial Board, *Sponsorship, Authorship, and Accountability*, 345 *NEW ENG. J. MED.* 825, 825 (2001) (“Over the past few years CROs have received the lion’s share of clinical-trial revenues. For example, in 2000 in the United States, CROs received 60 percent of the research grants from pharmaceutical companies, as compared with only 40 percent for academic trialists.”).

<sup>20</sup> *Consolidation Efforts Transform the Pharmaceutical Industry*, *BLOOMBERG* (May 1, 2014), <http://www.bloomberg.com/infographics/2014-05-01/pharma-mergers.html> [<https://perma.cc/25WU-XXHE>].

<sup>21</sup> *Id.*

<sup>22</sup> Kessel, *supra* note 16 (“The traditional business model at big pharma relies on (i) identifying promising new blockbuster drugs; (ii) conducting large, expensive clinical trials; and (iii) if successful, promoting the drugs with extensive marketing and sales presence in developed countries.”); Steve Brozak, *Big Pharma Learned the Wrong Marketing Lesson*, *FORBES* (May 25, 2014), <https://www.forbes.com/forbes/welcome/?toURL=https://www.forbes.com/sites/stephen-brozak/2013/05/25/big-pharma-learned-the-wrong-marketing-lesson> [<https://perma.cc/E6PX-W4HR>] (“In the past several years, big pharma companies have also begun advertising directly to consumers on television and in print, telling potential patients, ‘ask your doctor’ to prescribe a variety of powerful medicines that can often have multiple and potentially dangerous side-effects.”).

<sup>23</sup> Benjamin P. Falit et al., *Biosimilar Competition in the United States: Statutory Incentives, Payers, and Pharmacy Benefit Managers*, 34 *HEALTH AFF.* 294, 294-295 (2015).

<sup>24</sup> Ann M. Thayer, *Drug Repurposing*, *CHEMICAL & ENGINEERING NEWS*, Oct. 1, 2012, at 15, 15.



for several reasons.<sup>25</sup> Repurposing requires shorter cycle times, sometimes only one-third the time required for new drug development and approval.<sup>26</sup> Traditional drug development usually requires twelve to fifteen years.<sup>27</sup> Repurposing is much faster, taking only three to twelve years.<sup>28</sup> Many of the drugs subject to repurposing investigations can also go directly to preclinical testing and clinical trials.<sup>29</sup> Second, drug repurposing has much lower development costs.<sup>30</sup> New drug development costs tens of billions of dollars every year, but only results in about twenty-seven new drug approvals annually.<sup>31</sup> With repurposing, on the other hand, many of the drugs have already been put through costly preclinical and early clinical testing.<sup>32</sup> For firms, this leads to faster, higher profits, especially if they are facing expiring patents, high costs, and low productivity.<sup>33</sup> For non-profit organizations and research institutions, the low cost of repurposing is an opportunity to treat neglected diseases or address other unmet medical needs.<sup>34</sup> Third, repurposing has higher success rates than traditional drug development.<sup>35</sup> Computer-generated screening processes have been used to identify hundreds of compounds with potential for repurposing.<sup>36</sup>

Despite the timing and circumstances under which drug repurposing has drawn greater interest from pharmaceutical manufacturers, the National Institutes of Health, non-profit research centers, and prescribing physicians, the “problem” of new uses for old drugs has been relatively quickly characterized

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<sup>25</sup> *Id.*

<sup>26</sup> See Benjamin Roin, *Solving the Problem of New Uses by Creating Incentives for Private Industry to Repurpose Off-Patent Drugs*, MICH. ST. L. REV. (forthcoming) (manuscript at 47), <http://nrs.harvard.edu/urn-3:HUL.InstRepos:11189865> [<https://perma.cc/A4VF-C3QA>].

<sup>27</sup> JP Hughes et al., *Principles of Early Drug Discovery*, 162 BR. J. PHARMACOLOGY 1239 (2011) (“Developing a new drug from original idea to the launch of a finished product is a complex process which can take 12-15 years . . .”).

<sup>28</sup> Thayer, *supra* note 24.

<sup>29</sup> Guangxu Jin and Stephen T.C. Wong, *Toward Better Drug Repositioning: Prioritizing and Integrating Existing Methods into Efficient Pipelines*, 19 DRUG DISCOVERY TODAY 637, 637 (2014).

<sup>30</sup> Thayer, *supra* note 24.

<sup>31</sup> Roin, *supra* note 26.

<sup>32</sup> Thayer, *supra* note 24.

<sup>33</sup> *Id.*

<sup>34</sup> *Id.*

<sup>35</sup> *Id.*

<sup>36</sup> See, e.g., Michael J. Keiser et al., *Predicting New Molecular Targets for Known Drugs*, 462 NATURE 175, 175-81 (2009).

as one of market failure.<sup>37</sup> As a result of the aforementioned trends, venture capital firms are unwilling to invest in new drug development, and new-use discovery offers different, sometimes complicated incentives.<sup>38</sup> Scholars and industry advocates argue that a robust market for repurposed drugs is undermined because generics firms game federal labeling requirements tied to market exclusivity, and physicians prescribe for off-label off-patent indications (that is, prescribe a drug for a condition or a person, like a child, not covered by the FDA's authorization).<sup>39</sup> Others argue that firms holding marketing approvals for specific indications need tailored legal or monetary incentives to use existing data to support new drug applications.<sup>40</sup> Public funding is, as always, inadequate.<sup>41</sup>

Without explicitly stating so, the consensus in the economics, medical, and even legal literature is that in order to obtain more drug repurposing of the kind society needs, the incentives for repurposing drugs should look *more* like those for de novo drug development: better patent protection, more market exclusivity, and tightly regulated conditions for entry by generic pharmaceutical manufacturers.<sup>42</sup> This Article challenges that consensus through two means. First, there has been no systematic or rational method by which the current level of drug repurposing may be assessed as being sub-optimal or optimal. Indeed, the majority of calls for additional incentives come from those with a financial stake in those incentives materializing.

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<sup>37</sup> See, e.g., Roin, *supra* note 26 (“Once [patent] rights expire, pharmaceutical companies quickly lose their market share to generics. As a result, their incentive to develop new indications also expires, though many indications may remain untested and often undiscovered.”).

<sup>38</sup> Declan Butler, *Translational Research: Crossing the Valley of Death*, 453 NATURE 840, 841 (2008); John C. Reed, *NCATS Could Mitigate Pharma Valley of Death: National Center for Advancing Translational Science Essential to Capitalize on Basic Research*, 31 GENETIC ENGINEERING & BIOTECHNOLOGY NEWS 6, 6 (2011) (“[P]rivate companies and venture capitalists are increasingly reluctant to fund the crucial early stages of preclinical development—the research necessary to ‘translate’ promising discoveries made in laboratories into optimized candidate therapeutics ready for testing in clinical trials.”).

<sup>39</sup> See, e.g., Roin, *supra* note 26.

<sup>40</sup> Diana W. Shineman et al., *Overcoming Obstacles to Repurposing for Neurodegenerative Disease*, 1 ANNALS CLINICAL & TRANSLATIONAL NEUROLOGY 512, 516 (2014).

<sup>41</sup> See Shumei Kato et al., *Challenges and Perspectives of Drug Repurposing Strategies in Early Phase Clinical Trials*, 2 ONCOSCIENCE 576, 576 (2015).

<sup>42</sup> Scott J. Weir et al., *Repurposing Approved and Abandoned Drugs for the Treatment and Prevention of Cancer Through Public-Private Partnership*, 72 CANCER RES. 1056, 1056-57 (2012) (“[R]egulatory approval often requires expensive and complex clinical trials, but limited returns on investment make it difficult to attract private sector financing and expertise. New paths to exclusivity and pricing/reimbursement strategies are needed to promote private sector engagement.”).

Second, drug repurposing occurs through a more complex process that involves relevant actors—both public and private—in a more interconnected way. In other words, there is a drug repurposing ecosystem in place that has generated extraordinary breakthroughs—by one account, producing one-third of the major breakthrough drugs of the last half-century.<sup>43</sup> Before deploying additional intellectual property or market exclusivity protection that may interrupt this system, clinicians, scholars, and policymakers should understand how that ecosystem functions.

This Article aims to map the complex system through which approved drugs enter and circulate within the healthcare system with the objective of understanding what market, if any, has failed and, if so, what the mechanisms are that have contributed toward that failure. Existing narratives take narrow views of relevant players and their incentives, embedding an incomplete model of pharmaceutical innovation that is inattentive not only to public, private, and hybrid organizations promoting drug repurposing, but also to the regulatory environment in which that innovation occurs. If the drug repurposing system is not effectively understood, the legal and monetary incentives now ascending the list of solutions to the drug repurposing “problem” may, at best, result in a wasteful giveaway of scarce resources and, at worst, disrupt the systems of prescription, research, observation, public, private and regulatory support that undergird current, reasonably robust, repurposing activity.<sup>44</sup>

Against the backdrop of the drug repurposing ecosystem, this Article examines the trajectory of metformin, a common diabetes drug; its introduction into, and promotion within, the U.S. market by Bristol-Myers Squibb; the physician-regulator-financing networks that steered it toward new disease treatment; and finally, how proposed “solutions” to the drug repurposing market may affect those networks in a way that would undermine, not encourage, new indication research and development.

Metformin’s industrial and market history are an ideal case study for the current drug repurposing debate. Introduced into the U.S. market after the most useful patent on it had expired, metformin enjoyed only the five-year market exclusivity window

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<sup>43</sup> Aaron Kesselheim et al., *The Roles of Academia, Rare Diseases, and Repurposing in the Development of the Most Transformative Drugs*, 34 HEALTH AFF. 286 (2015).

<sup>44</sup> See Bernard H. Munos & William W. Chin, *A Call for Sharing: Adapting Pharmaceutical Research to New Realities*, 1 SCI. TRANS. MED. 1, 1-3 (2009).

granted under the Hatch-Waxman Act. After that period ended, under now-prominent theories, there should have been little, if any, research into alternative uses because there would be no or uncertain economic reward for doing so. Yet metformin has become one of the most actively deployed drugs for off-label uses and for alternative use research. Clinical trials now under way investigate its promise for Alzheimer's disease, cancer, nonalcoholic fatty liver disease, polycystic ovary syndrome (the most common cause of female infertility), and weight loss, among others.<sup>45</sup> This Article analyzes how and why metformin became a prominent focus of academics, regulators, and private capital without the incentives now advocated in the legal and medical literature.

Part I of this Article assesses the existing literature addressing the “problem” of discovering new uses of approved medicines. Part II explains the process now in place for new drug development, as well as which aspects of that system industry advocates endorse for new use research. Part III identifies and discusses relevant actors, variables, and influences that shape firms' decisions to seek new indications or to partner with organizations that do. Part IV analyzes the history of metformin and the process by which the ecosystem described in Part II developed. Part V applies the lessons learned in the industrial and market history of metformin and applies them to current proposals advocating extension of patent or other market exclusivities. Part VI provides a brief conclusion.

## I. THE DRUG REPURPOSING “PROBLEM”

“Drug repurposing” refers to the research undertaken to support deployment of both FDA-approved and -unapproved compounds to disease profiles for which they were not initially

<sup>45</sup> See, e.g., Stephen Arnold, *A Trial of the Anti-Diabetes Drug Metformin for Alzheimers*, BRIGHTFOCUS.ORG, <http://www.brightfocus.org/alzheimers/grant/effect-insulin-sensitizer-metformin-alzheimers-disease-biomarkers> [https://perma.cc/RJX9-EJ7Y]; Kathy Boltz, *Clinical Trial Data on Metformin for Cancer are Showing Conflicting Results*, ONCOLOGYNURSEADVISOR.COM (Jan. 2014), <http://www.oncologynurseadvisor.com/web-exclusives/clinical-trial-data-on-metformin-for-cancer-are-showing-conflicting-results/article/331688> [https://perma.cc/7YZX-G43E]; *Find a Study on PCOS*, NAT'L INST. HEALTH, <https://www.nichd.nih.gov/health/topics/PCOS/clinicaltrials/Pages/default.aspx> [https://perma.cc/24M8-JM7A]; *Frequently Asked Questions About Infertility*, AM. SOC. REPRODUCTIVE MED., <http://www.reproductivefacts.org/faqs/frequently-asked-questions-about-infertility/q02-what-causes-infertilitynew-page/> [https://perma.cc/QSH8-QLEV] (noting that PCOS is the most common cause of female infertility); *Treatment of Nonalcoholic Fatty Liver Disease in Children*, CLINICALTRIALS.GOV (Sept. 27, 2012), <https://www.clinicaltrials.gov/ct2/show/NCT00063635> [https://perma.cc/WN55-QZ23].

considered. For the latter category of drugs, they are better understood in the context of repurposing to be “rescued.”<sup>46</sup> There are, for example, thousands or tens of thousands of compounds that drug companies archive after clinical trials or even proof-of-concept for a specific disease fail to support a new drug application.<sup>47</sup> This class of compounds in need of rescuing is different than repurposed drugs, which are compounds that enjoy FDA approval (for at least one indication), a long market life, and show promise through clinical observations, university-based research, or testing through newly available data aggregation and analysis technologies.<sup>48</sup> In a 2009 *Nature* article, Michael Keiser and his collaborators predicted new off-targets for 878 purchasable FDA-approved small molecule drugs.<sup>49</sup> This Article focuses on these kinds of repurposed drugs and the incentives for their development.

There is a consensus among scholars studying drug repurposing that there is a fundamental problem—insufficient and inadequate research into new uses of approved drugs—although they do not agree as to the scope, depth, or contours of that problem. A 2014 report by the Ewing Marion Kauffman Foundation captures the view of many industry participants and researchers in asserting that there are not effective ways to give market exclusivity to new uses. According to the Foundation’s report,

exclusivities provided by patents and the Orphan Drug Act . . . may be nominally applicable to [new uses, but] such exclusivities can be undermined by physician decisions to prescribe the generic version of the old drug ‘off-label’ for the new indication. Lack of exclusivity (typically afforded by the composition of matter patents for new drugs) creates challenges for innovator firms, generic

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<sup>46</sup> Thomas A. Hemphill, *The NIH Promotes Drug Repurposing and Drug Rescue*, RES.-TECH. MGMT. (Sept.-Oct. 2012); Univ. of Oxford, *Human Trials Suggest ‘Rescued’ Drug Could be Safer Treatment for Bipolar Disorder: Initial Human Trial Promising for ‘Failed’ Drug Ebselen*, SCIENCEDAILY (Dec. 8, 2015), [www.sciencedaily.com/releases/2015/12/151208134125.htm](http://www.sciencedaily.com/releases/2015/12/151208134125.htm) [<https://perma.cc/DW7P-M599>].

<sup>47</sup> Thayer, *supra* note 24 (“A few thousand drug candidates are estimated to languish in pharma company cold storage, and the number only grows as more compounds fail in development or get dropped for business reasons.”).

<sup>48</sup> Indeed, as Arti Rai and Grant Rice argue, there isn’t really a problem with this class of drugs since use patents would effectively cover them. Arti Rai & Grant Rice, *Use Patents Can Be Useful: The Case of Rescued Drugs*, 6 SCI. TRANSLATIONAL MED. 248 (2014).

<sup>49</sup> Keiser et al., *supra* note 36.

manufacturers, and investors, making it difficult to fund drug development activities required for market approval.<sup>50</sup>

MIT's Ben Roin argues that the problem is, in essence, an "information" problem because pharmaceutical companies do not know when their drugs are being prescribed for new uses. If they could, he suggests, they could impose the kinds of exclusivities described by the Kauffman Foundation.<sup>51</sup> Don Frail, Vice-President of Science at Astra-Zeneca, has argued that firms should receive twelve years of data exclusivity for approved new uses.<sup>52</sup>

Diana Shineman and her coauthors suggest a royalty structure for pharmaceutical firms to sponsor Phase III clinical trials for new use indications for generic drugs, as well as incentives provided through the government payment structure.<sup>53</sup> Steven M. Paul and Freda Lewis-Hall state the "market failure" problem in its most succinct industry-sympathetic form: "because the pharmaceutical industry will be the main source of repurposed drugs, any impediments to Pharma's active (and enthusiastic) participation must be anticipated and removed."<sup>54</sup> Arti Rai suggests that the problem is essentially a lack of public support for new use research, especially costly Phase II and Phase III clinical trials.<sup>55</sup>

Legislative proposals circulating in Congress give a designated data exclusivity period in exchange for patent rights to encourage pharmaceutical firms to undertake research related to repurposing.<sup>56</sup> Drafts of the 21st Century Cures Act

<sup>50</sup> *A New Market Access Path for Repurposed Drugs*, EWING MARION KAUFFMAN FOUND. (May 2014), [http://www.kauffman.org/~media/kauffman\\_org/research%20reports%20and%20covers/2014/05/new\\_market\\_access\\_path\\_for\\_repurposed\\_drugs.pdf](http://www.kauffman.org/~media/kauffman_org/research%20reports%20and%20covers/2014/05/new_market_access_path_for_repurposed_drugs.pdf) [https://perma.cc/69W9-8CX5].

<sup>51</sup> Roin, *supra* note 26.

<sup>52</sup> Beachy et al., *Drug Repurposing and Repositioning: Workshop Summary*, NAT'L ACADEMIES PRESS 10 (2014), <http://www.ncbi.nlm.nih.gov/books/NBK202175/pdf/TOC.pdf> [https://perma.cc/3RP4-NKZ4].

<sup>53</sup> Diana W. Shineman et. al., *Overcoming Obstacles to Repurposing for Neurodegenerative Disease*, 1 ANNALS CLINICAL & TRANSLATIONAL NEUROLOGY 512, 516 (2014).

<sup>54</sup> Steven M. Paul & Freda Lewis-Hall, *Drugs in Search of Diseases*, 5 SCI. TRANSL. MED. 186, 186 (2013).

<sup>55</sup> Arti Rai, *Use Patents, Carve-Outs, and Incentives—A New Battle in the Drug-Patent Wars*, 367 NEW ENG. J. MED. 491, 492 (2012).

<sup>56</sup> John Graham, *21st Century Cures: Waking Up Dormant Drug Therapies*, FORBES (Feb. 19, 2015), <http://www.forbes.com/sites/theapothecary/2015/02/19/21st-century-cures-waking-up-dormant-drug-therapies/> [https://perma.cc/B3YP-LLU3].

included fifteen-year exclusivity for drugs that met “unmet medical needs” and two-year exclusivity for enhancements to approved drugs like “greater patient adherence” and limitation of side effects.<sup>57</sup> Under the Hatch-Bennett Dormant Therapies Act,

the innovator [would] waive any patents that extend beyond the 15-year marketing exclusivity, in exchange for extending patents that expire within 15 years . . . . According to the bill, [a drug] is dormant if “The medicine is being investigated or is intended to be investigated for an indication to address one or more unmet medical needs . . . .”<sup>58</sup>

These provisions represent the broad agreement that repurposing incentives should start to look more like incentives in place for *de novo* drug development.

To a lesser extent, scholars describe drug repurposing as an institutional-design problem rather than an incentive-based one. For example, some scholars have argued that collaborative efforts between manufacturers, academic institutions, and small biotechnology firms are hampered by the high costs of negotiating agreements over technology transfer and intellectual property rights. The organization Cures Within Reach, for example, avoids support of research for unapproved compounds because legal, intellectual, and publication barriers make doing so cost prohibitive.<sup>59</sup>

## II. DRUG DEVELOPMENT PROCESSES, INCENTIVES, AND PLAYERS

While it remains largely unstated in the aforementioned sources, it may be surmised that scholars and legislators broadly suggest that repurposing incentives should look more like the system in place for new drug development. Certainly, when pharmaceutical firms consider repurposing candidates, the same market perspectives apply. “The class [of repurposing candidates] offering the most novelty is off-target pharmacology—finding a

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<sup>57</sup> Alexander Gaffney, *10 Proposals Worth Paying Attention to in the 21st Century Cures Act*, REG. AFF. PROFESSIONALS SOC’Y (Jan. 30, 2015), <http://raps.org/Regulatory-Focus/News/2015/01/30/21208/10-Proposals-Worth-Paying-Attention-to-in-the-21st-Century-Cures-Act/> [<https://perma.cc/6WBE-5R9V>].

<sup>58</sup> Graham, *supra* note 56.

<sup>59</sup> Deborah Collyer, *How To Solve Diseases with Existing Drugs*, ONE HEALTH OF A LIFE (Apr. 28, 2016), <https://collyar.wordpress.com/2016/04/28/how-to-solve-diseases-with-existing-drugs> [<https://perma.cc/D52W-S4HG>]; Thayer, *supra* note 24.

new target in a new disease with an old drug.”<sup>60</sup> A somewhat less novel class is on-target repurposing, hitting a known target in a new disease.<sup>61</sup> Under both systems, good drug prospects must be identified and acquired, and new uses still must meet all of the FDA’s regulatory requirements to be approved.<sup>62</sup>

Some detail as to what those regulatory requirements entail will shed light on why drug repurposing is an appealing alternative to developing new drugs from scratch. The costs involved in clinical development have increased substantially in recent decades.<sup>63</sup> The average cost to develop one new drug nearly doubled from 2000 to 2005 alone.<sup>64</sup> A brief overview of the drug development process will help explain why these costs are high and continue to escalate.

The first phase with which new drug development normally begins is identifying a candidate target for drug action followed by preclinical chemical synthesis to identify a family of molecules as candidate new chemical entities (NCEs).<sup>65</sup> Researchers—increasingly at universities and small startups—determine the candidate NCE’s basic properties, including safety in cells and animals, and its pharmacodynamics and pharmacokinetic characteristics. These tests predict the NCE’s effect in humans so that a lead candidate and a safe dose for human trials may be identified. “An additional component of the preclinical research phase is to test the drug both *in vitro* and on relevant animal species for pharmacological activity and toxicity.”<sup>66</sup>

When *in vitro* and animal studies have been completed, the sponsor firm may file an Investigational New Drug (IND) application with the FDA’s Center for Drug Evaluation and Research (“CDER”)—the unit responsible for regulating new chemical entities (i.e., a drug that contains no active moiety that has been approved by the FDA in any other application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act) at which point it becomes “a new drug subject to

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<sup>60</sup> Thayer, *supra* note 24, at 5.

<sup>61</sup> See Michael Pollastri & Robert Campbell, *Target Repurposing for Neglected Diseases*, 3 FUTURE MED CHEMISTRY 1307 (2011).

<sup>62</sup> Thayer, *supra* note 24.

<sup>63</sup> Jesse Goodman, *Addressing Emerging Challenges in the Pharmaceutical Product Development Ecosystem*, in FOOD AND DRUG REGULATION IN AN ERA OF GLOBALIZED MARKETS 4-5 (Sam Halabi ed., 2015).

<sup>64</sup> *Id.*

<sup>65</sup> *Investigational New Drug (IND) Application*, FOOD & DRUG ADMIN. (2014), <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm> [<https://perma.cc/2BBW-P3QX>] [hereinafter *IND Application*].

<sup>66</sup> Goodman, *supra* note 63.



specific requirements of the drug regulatory system.”<sup>67</sup> The FDA requires the IND application to present data and analysis that pertain to three general issues: pharmacology and toxicology studies, the properties of and manufacturing process for the drug, and a proposed protocol for human trials which includes safeguards to ensure that human test subjects are not exposed to any unnecessary risks.<sup>68</sup> Once an IND is authorized, the sponsor typically embarks on a three-phase clinical development process intended to lead to approval.

Phase I trials are designed to assess the safety, immunogenicity and dose-response of the drug in, typically, twenty to one-hundred healthy volunteers.<sup>69</sup> Phase II studies involve several hundred healthy volunteers.<sup>70</sup> They are designed to identify the most appropriate dose or doses for further studies, as well as to identify safety issues that may not have been apparent in the smaller number of subjects included in Phase I. A control group is often included and administered a placebo while the test group receives the drug. Phase III trials enroll up to thousands or tens of thousands of human subjects in order to detect sometimes rare adverse events.<sup>71</sup> Phase III studies are typically referred to as “pivotal” and are designed to establish the efficacy and safety of the product, and support its approval, for the intended indication(s) and in the intended population(s).<sup>72</sup> They are typically randomized and well-controlled studies comparing the drug against a placebo or standard of care and measuring effects on meaningful clinical endpoints.

At the conclusion of clinical testing, if studies support a favorable benefit-to-risk profile, the drug manufacturer submits a New Drug Application (NDA). The NDA is extensive and costly to generate. It includes comprehensive information on chemistry, manufacturing processes and specifications, clinical data supporting each dosage and dosing form/route the manufacturer intends to use, proposed packaging and labeling, and the results of all relevant preclinical (e.g., laboratory and animal studies of drug effects, including toxicology) and clinical testing. The NDA also typically provides plans both for safety surveillance, which may be needed to address any safety signals or questions identified during development, as well as any planned Phase IV

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<sup>67</sup> *IND Application*, *supra* note 65.

<sup>68</sup> 21 CFR § 312.23(a)(8) (2017).

<sup>69</sup> *See* 21 C.F.R. § 312.23 (2017).

<sup>70</sup> *Id.*

<sup>71</sup> *Id.*

<sup>72</sup> Goodman, *supra* note 63.

studies intended to be performed post-marketing. The complete application is reviewed by CDER by a multidisciplinary team that typically includes biologists, physicians, statisticians and epidemiologists, chemists, manufacturing experts, pharmacologists, and other scientists. Finally, the FDA conducts an inspection of the manufacturer's facilities. Upon final approval, the manufacturer brings the drug to market. However, the manufacturer must continue to submit safety and manufacturing updates to the FDA to ensure that the product performs as expected, and must also complete and submit the results of any Phase IV studies.

**A. *The Conventional Pharmaceutical Model: Small Molecules, Specific Targets, Widespread Disease***

Just as with de novo drug development, large pharmaceutical firms are understandably sensitive to the potential returns on research and development investments.<sup>73</sup> New approved drugs are profitable if firms can charge high prices for new drugs, develop drugs for widespread diseases (or risk factors for disease), or both.<sup>74</sup> Pharmaceutical research and development priorities over the course of the last three decades have therefore focused on conditions like high cholesterol, asthmatic airway passages, depression, and ulcerous digestive systems.<sup>75</sup> Similarly, large pharmaceutical firms have prioritized research into single molecules that may be tailored to target cellular flaws causing or associated with specific diseases, aiming to patch or destroy the flaw without harming healthy cells, again, in large populations.<sup>76</sup> As a result, considerable research and development resources are committed to screening vast numbers of compounds to find one that might target one cellular protein, genetic flaw, or gene per se.

Over the course of the 1980s, 1990s, and 2000s, this model generated extraordinary returns for pharmaceutical companies

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<sup>73</sup> Steven M. Paul et al., *How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge*, 9 NAT'L REV. DRUG DISCOVERY 203, 203 (2010).

<sup>74</sup> Kevin Outterson et al., *Repairing the Broken Market for Antibiotic Innovation*, 34 HEALTH AFF. 277, 278 (2015).

<sup>75</sup> Daniel J. DeNoon, *The 10 Most Prescribed Drugs*, WEBMD NEWS ARCHIVE (Apr. 20, 2011), <http://www.webmd.com/news/20110420/the-10-most-prescribed-drugs> [<https://perma.cc/F5GZ-JWP9>].

<sup>76</sup> Antti Jekunen, *Decision-making in Product Portfolios of Pharmaceutical Research and Development—Managing Streams of Innovation in Highly Regulated Markets*, 8 DRUG DESIGN, DEV. & THERAPY 2009, 2010 (2014) (“A drug development company typically has many projects, and a leading drug molecule and several other molecules that form a pipeline.”).

and their investors. At its peak in 2006, Pfizer's Lipitor sales topped \$13 billion annually; Bristol-Myers Squibb's antidepressant Abilify reached over \$7 billion in 2011, and AstraZeneca's Seroquel brought in over \$6 billion in revenues the same year.<sup>77</sup> Yet the model, by its nature, is limited, and current trends suggest that the "low-hanging fruit" of small molecule-specific target-widespread disease has been picked.<sup>78</sup> Jie Jack Li summarized the situation in his 2013 work, *Blockbuster Drugs: the Rise and Decline of the Pharmaceutical Industry*:

The last 10 years have seen dramatic changes in the pharmaceutical industry. Many patents, especially for blockbuster drugs, have expired. Yet new blockbuster drugs are few and far between, certainly not enough to fill the gap of lost revenues due to patent expirations. The industry has panicked, making many knee-jerk decisions with dubious consequences. One is merger mania . . . . Another trend we are seeing is outsourcing . . . . It seems that the golden age for small-molecule blockbuster drugs is behind us. However, blockbuster drugs for *biologics* are on the rise.<sup>79</sup>

Li is correct that reducing clinical research costs through outsourcing, mergers and divestitures, and investment in biologics is part of the shifting industry landscape. "Biologics" differ from small molecule drugs in that they are manufactured in a living system such as a microorganism, or plant or animal cells. They are generally complex molecules or combinations of molecules. In 2013, seven of the top eight bestselling drugs were biologics—e.g., AbbVie's Humira, Pfizer's Enbrel, and Roche's Avastin—generating a combined \$58 billion.<sup>80</sup> There are several

<sup>77</sup> Simon King, *The Best Selling Drugs of All Time; Humira Joins The Elite*, FORBES (Jan. 28, 2013 9:58 AM), <http://www.forbes.com/sites/simonking/2013/01/28/the-best-selling-drugs-of-all-time-humira-joins-the-elite> [<https://perma.cc/5QPG-BLJN>].

<sup>78</sup> Cockburn, *supra* note 11, at 14 ("Many commentators have suggested that the pharmaceutical industry is facing sharply diminishing marginal returns to R&D. Drews (1998), for example, characterizes drug development during the 1970s and '80s as a matter of making minor chemical improvements to existing compounds directed at a static set of about 500 well-proven physiological 'targets' an activity that surely runs quickly into diminishing returns.").

<sup>79</sup> Jie Jack Li, BLOCKBUSTER DRUGS: THE RISE AND DECLINE OF THE PHARMACEUTICAL INDUSTRY 171-72 (2013).

<sup>80</sup> Rob Wright, *Can Big Pharma Survive in a Big Biotech World?*, LIFESCIENCELEADER BLOG (May 15, 2014), <http://www.lifescienceleader.com/doc/can-big-pharma-survive-in-a-big-biotech-world-0001> [<https://perma.cc/7LVE-EETZ>].

advantages to investing in biologics: U.S. law gives approved biologics a twelve-year market exclusivity period (new small molecules receive only five—practically six to seven given the delays that accompany generics applications) and, because they are more fundamentally tied to the means by which they are manufactured, they are more difficult for generics firms to cheaply imitate.<sup>81</sup>

But those are not the only transitions underway in major pharmaceutical firms. Since 1997, when the FDA eased rules on direct-to-consumer advertising, large pharmaceutical firms have invested heavily in advertising and marketing, spending much more—in some cases twice as much—on detailing, sampling, educational programming, promotional mailings, web advertisements, and very large in-house sales forces as they spend on research and development.<sup>82</sup> Pharmaceutical firms continue to spend on marketing branded drugs when a lower-cost generic has entered the market.<sup>83</sup>

Pharmaceutical firms also turned to drug rescuing and repurposing.<sup>84</sup> “There is a greater emphasis [on repurposing] now as companies try to squeeze more revenue out of their existing assets.”<sup>85</sup> While there are other factors that explain the ascent of drug repurposing—like the application of sophisticated “big data” analytics to large sources of small molecule information like the FDA’s “Approved Drug Products With Therapeutic Equivalence Evaluations,” or “Orange Book”—drug repurposing is in large measure part of a broad industry response to its changing business climate.

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<sup>81</sup> W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1024, 1028 (2015).

<sup>82</sup> Richard Anderson, *Pharmaceutical Industry Gets High on Fat Profits*, BBC (Nov. 6, 2014), <http://www.bbc.com/news/business-28212223> [<https://perma.cc/7ZWF-4V7L>]; Bulletin of the World Health Organization, *Direct-to-Consumer Advertising Under Fire*, WORLD HEALTH ORG. (Aug. 2009), <http://www.who.int/bulletin/volumes/87/8/09-040809/en> [<https://perma.cc/35LV-6X8G>]; *Persuading the Prescribers: Pharmaceutical Industry Marketing and its Influence on Physicians and Patients*, PEW CHARITABLE TRUSTS (Nov. 11, 2013), <http://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients> [<https://perma.cc/6G45-TD7M>].

<sup>83</sup> Fernando Antoñanzas et al., *Innovation, Loyalty and Generic Competition in Pharmaceutical Markets*, 2 SERIEs 75, 78 (2011).

<sup>84</sup> Thayer, *supra* note 24 (“Revisiting shelved compounds is an undertaking without much downside and one that can help companies feeling the pressures of expiring patents, high costs, and low productivity. Some firms have cut back on early R&D and have made repurposing a part of their core business.”).

<sup>85</sup> *Id.* (citing Richard K. Harrison, Scientific Director at Thomson Reuters).

### ***B. Origins and Players in Pharmaceutical Innovation***

Even if repurposing has become a larger share of large pharmaceutical firm activity, the core of the business remains drug development and approval. The development of new drug compounds (or application of existing drugs to new indications) is itself the result of a complex matrix of financial support, organizational structure, and access to knowledge that influences how and why major pharmaceutical firms undertake drug research and development in-house, collaborate with public or private researchers outside the firm, support drug research and development in universities, or acquire smaller, nimbler firms for their compounds and/or researchers.<sup>86</sup> There is no effective method by which to precisely identify where in this matrix drug discovery and development occurs (and competitive markets mean it will always change), but analysis of certain features of these research bodies helps clarify the institutional design questions most relevant to the drug repurposing debate.

A substantial portion of a large pharmaceutical company's research and development budget, seventy-five percent or more, is devoted to Phase II, Phase III, and post-approval studies required to prove the efficacy, safety, and value to regulators, payers, physicians, and patients.<sup>87</sup> The disproportionate allocation of resources to development, approval and, essentially, marketing, still leaves substantial support for new drug or new use research—but even so, structural features of in-house research limit the innovative (or repurposing) potential of in-house efforts. Researchers within large pharmaceutical firms will frequently have a portfolio of diseases upon which they work, marginalizing possible new uses for diseases with which they are less familiar, or which are not firm priorities.<sup>88</sup> A researcher working on a promising molecule to treat heart failure, for

<sup>86</sup> Ronald Gilson, *Locating Innovation: The Endogeneity of Technology, Organizational Structure and Financial Contracting*, 109 COLUM. L. REV. 885 (2009).

<sup>87</sup> John LaMattina, *Should Pharma Companies Give Up Discovery Research?*, FORBES.COM (Sept. 10, 2013), <http://www.forbes.com/sites/johnlamattina/2013/09/10/should-pharma-companies-give-up-discovery-research> [<https://perma.cc/E8QB-XDZQ>]; see also *Canada's Research-Based Pharmaceutical Companies (Rx&D) 2015 Pre-Budget Submission House of Commons Standing Committee on Finance*, PARLIAMENT CAN. (Aug. 6, 2014), [http://www.parl.gc.ca/Content/HOC/Committee/412/FINA/WebDoc/WD6615327/412\\_FINA\\_PBC2014\\_Briefs/CanadasResearchBasedPharmaceuticalCompaniesRxD-e.pdf](http://www.parl.gc.ca/Content/HOC/Committee/412/FINA/WebDoc/WD6615327/412_FINA_PBC2014_Briefs/CanadasResearchBasedPharmaceuticalCompaniesRxD-e.pdf) [<https://perma.cc/53WP-9U6W>] (“In 2013, Rx&D members invested more than \$1 billion in R&D—with 75% of this activity devoted to clinical trials—and approximately \$322 million toward patient and community contributions.”).

<sup>88</sup> Jekunen, *supra* note 76, at 2011 (“In general these [drug development teams] are aligned by disease area, with each disease area-responsible direct empowered to make go/no-go decisions.”).

example, will not typically be thinking of its potential applicability for cancer.

Relatedly, internal cognitive biases like “sunk costs” and over-optimism also limit repurposing activity.<sup>89</sup> Once a researcher or a research team has made progress toward the applicability of a candidate to a specific disease target, there is a tendency to hesitate to end the project when results become less promising. Data that may be ambiguous or even negative is read as supporting initial hypotheses with respect to the candidate molecule, and more positive data is moved up the firm hierarchy.<sup>90</sup> Both of these biases act to limit the inherent capacity of pharmaceutical firms to repurpose as part of the development process.

Inherent biases play an important role, but even as a consciously adopted strategy, repurposing exposes firms to avoidable risks related to the principal market for an approved drug. Research into new uses may expose adverse events that might undermine the profitability of the drug for the use that initially earned FDA approval.<sup>91</sup> This disincentive to repurpose—undermining the market potential of a currently profitable drug or exposing the manufacturer to large tort liability—is rarely mentioned in the current debate and may provide a significant explanation for why less repurposing activity is under way.

Pharmaceutical firms therefore participate in a wide range of research support activities that comprise varying portions of their new drug pipeline. The degree of investment in academic research or drugs nearing early clinical studies also varies according to the broader risk-analysis and disease specializations of firms. Investments in early stage, academic research are inherently speculative with a low probability of success.<sup>92</sup> Alternatively, pharmaceutical firms may invest in research programs showing indications of working in patients.<sup>93</sup> Doing so increases the chances that competitors will also bid for

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<sup>89</sup> Randolph Case, *Managing Risk in Pharmaceutical R&D*, 53 RES-TECH. MGMT. 24, 24 (2015); Richard W. Peck et al., *Why Is It Hard to Terminate Failing Projects In Pharmaceutical R&D?*, 14 NATURE REVIEWS DRUG DISCOVERY 663, 663-664 (2015).

<sup>90</sup> Donald C. Langevoort, *Organized Illusions: A Behavioral Theory of Why Corporations Mislead Stock Market Investors (and Cause Other Social Harms)*, 146 U. PA. L. REV. 101, 125 (1997).

<sup>91</sup> Thayer, *supra* note 24.

<sup>92</sup> See Jose-Maria Fernandez, Roger M Stein & Andrew W. Lo, *Commercializing Biomedical Research Through Securitization Techniques*, 30 NATURE BIOTECHNOLOGY 964 (2012).

<sup>93</sup> LaMattina, *supra* note 87.

promising compounds.<sup>94</sup> Investments made later in the development process are subject to higher upfront payments and royalties that would not be associated had compounds been developed internally.<sup>95</sup>

The distribution of pharmaceutical company investments is borne out by the data on new approvals. A study of 252 new drugs approved by the FDA between 1998 and 2007 found that drugs initially discovered in biotechnology companies or universities accounted for approximately half of the drugs that responded to unmet medical needs and represented innovative rather than me-too approvals.<sup>96</sup> A more recent study by HBM Partners, a healthcare investment firm, concluded that 64% of drugs approved since 2006 have originated in small biotechnology companies.<sup>97</sup>

Drug repurposing activity mirrors this general distribution of investment and risk. Repurposing has occurred within diversifying forms of private, public, and hybrid research initiatives as large pharmaceutical manufacturers seek collaborative partnerships to exploit new uses for old drugs. Indeed, this ascendant method of filling drug pipelines has even facilitated agreements between large competitors. In 2015, AstraZeneca and Sanofi agreed to give each other “free access to 210,000 usually closely guarded compounds . . . as a ‘cheap and quick way’ of diversifying” the companies’ drug portfolios.<sup>98</sup>

### ***C. The Nexus Between Drug Approval and Market Exclusivity***

Whether through in-house development, partnership, or acquisition, pharmaceutical firms currently recoup their research, development, acquisition, and marketing costs through the prices they are able to charge based on the ability to exclude others and, to some extent, convince buyers to purchase brand name drugs even when generic forms are available.<sup>99</sup> There are two principal forms of market exclusivity that firms obtain when the FDA grants approval of a new drug application or a

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<sup>94</sup> *Id.*

<sup>95</sup> *Id.*

<sup>96</sup> Robert Kneller, *The Importance of New Companies for Drug Discovery: Origins of a Decade of New Drugs*, 9 NATURE REVIEWS DRUG DISCOVERY 867 (2010).

<sup>97</sup> Jennifer Alsever, *Big Pharma Innovation in Small Places*, FORTUNE (May 13, 2016) <http://fortune.com/2016/05/13/big-pharma-biotech-startups> [<https://perma.cc/ED6K-3VQ7>].

<sup>98</sup> Denise Roland, *Drug Companies Seek Edge by Sharing Secrets*, WALL ST. J., Nov. 20, 2015.

<sup>99</sup> See Yaniv Heled, *Patents v. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both*, 18 MICH. TELECOMM. & TECH. L. REV. 419 (2012).

supplemental<sup>100</sup> new drug application requesting approval of an existing approved drug for a new indication.<sup>101</sup>

## 1. Patents

First, firms gain the normal market exclusivity that applies for the life of a patent that runs from the time the patent was filed with the U.S. Patent and Trademark Office, currently between ten and twelve years.<sup>102</sup> In the pharmaceutical context, two typical kinds of patents protect innovations: composition-of-matter patents and use patents.<sup>103</sup> Composition-of-matter patents protect

all compositions of two or more substances . . . and all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids.<sup>104</sup>

These are the most valuable kinds of pharmaceutical patents since they allow the patent holder to exclude all others who wish to use the basic structure of the molecule they have developed, regardless of purpose.

Use patents, or method-of-use patents, cover the use of the molecule to treat a specific disease or diseases. The discovery of a new indication for an old drug can form the basis for a method-of-use patent if the discovery is novel, unexpected, and potentially beneficial. The new-use claims may apply to both patent-protected and patent-expired drugs if the new use has not been previously disclosed or covered in the original patents pertaining to the drug. For use patents, the brand manufacturer

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<sup>100</sup> Usage of the term “supplemental” may be misleading; it is commonly used to refer to the approval pathway under 505(b)(2) described below, but there are also continuing obligations to “supplement” NDAs for changes in labeling, manufacturing, and so on.

<sup>101</sup> See Henry G. Grabowski et al., *The Roles of Patents and Research and Development Incentives in Biopharmaceutical Innovation*, 34 HEALTH AFF. 302 (2015).

<sup>102</sup> See Kate S. Gaudry, *Evergreening: A Common Practice to Protect New Drugs*, 29 NAT. BIOTECHNOLOGY 876 (2011); Alfred Engelburg, *How Government Policy Promotes High Drug Prices*, HEALTH AFF. BLOG (Oct. 29, 2015) (“According to the Pharmaceutical Manufacturers Association, it takes at least 10 years to develop a new drug. It is no surprise that the typical monopoly period on an existing drug is also 10-12 years.”); see also Frank R. Lichtenberg, *Time Release: The Effect of Patent Expiration on U.S. Drug Prices, Marketing, and Utilization by the Public*, CTR. FOR MED. PROGRESS MANHATTAN INST. (Oct. 20, 2009), <https://www.manhattan-institute.org/html/time-release-effect-patent-expiration-us-drug-prices-marketing-and-utilization-public-5938.html> [http://perma.cc/G856-9YSR].

<sup>103</sup> Rai & Rice, *supra* note 48.

<sup>104</sup> *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980) (quoting *Shell Development Co. v. Watson*, 149 F. Supp 279, 280 (D.C. Cir. 1957) (citation omitted)).



must provide a description of the methods, which is referred to as the “use code narrative” when included in the FDA Orange Book. For example, a use patent may read: “A method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin.”<sup>105</sup> Repurposed drugs typically target a new patient population or a new indication; or include a new dosage form, dosing regimen, or route of administration. In short, any time the label instructs the patient or physician to do something, that method is potentially patentable.<sup>106</sup>

Use patents are weaker and therefore more costly to enforce.<sup>107</sup> They are weaker not only because of basic vulnerabilities in patentability criteria—for example, non-obviousness—but also because generics firms may seek FDA approval only for expired patent uses, even though they (and prescribers) know that, once the generic is on the market, it will be prescribed for more than just that indication. Indeed, one study found that only 12 of 170 molecules approved by FDA between 1996 and 2004 relied exclusively on use patents.<sup>108</sup> There is a general consensus that method-of-use patents “generally do not provide sufficient exclusivity protection once the basic compound patent expires.”<sup>109</sup>

This is consistent with the overall scheme of Congress in the Hatch-Waxman Act to balance the rights of innovators against the right of people to affordable medications. Courts interpreting this so-called “skinny labeling” tactic of generics firms have determined that holding generics firms accountable for infringement actually committed by prescribers would allow a pioneer manufacturer to extend its monopoly “by regularly filing a new patent application claiming a narrow method of use not covered by its [New Drug Application].”<sup>110</sup>

Otherwise, use patents would serve as the principal mechanism by which drug repurposing could provide extensive and valuable monopolies to pharmaceutical manufacturers.

<sup>105</sup> *Novo Nordisk A/S v. Caraco Pharm. Lab., Ltd.*, 719 F.3d 1346, 1349 (Fed. Cir. 2013).

<sup>106</sup> Ned Israelsen, *New Patents for Old Drugs: Label-Based Strategies in the United States*, PHARMA FOCUS ASIA, <http://www.pharmafocusasia.com/strategy/new-patents-old-drugs> [<http://perma.cc/5ZDB-6JJQ>].

<sup>107</sup> Rai, *supra* note 55.

<sup>108</sup> See C. Scott Hemphill & Bhaven N. Sampat, *When Do Generics Challenge Drug Patents?*, 8 J. EMPIRICAL LEGAL STUD. 613, 625 (2011).

<sup>109</sup> Paul & Lewis-Hall, *supra* note 54, at 187.

<sup>110</sup> *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1359 (Fed. Cir. 2003).

## 2. Statutory and Regulatory Market Exclusivity

Second, even where a drug is not patentable or a patent has expired, federal law allows firms to exclude others (typically generics firms) from using the data that supports their new drug applications: five years for new pharmaceutical chemical entities, seven years for drugs designated to treat “orphan” diseases, three years for new indications for pharmaceutical drugs, and twelve years for biologic products.<sup>111</sup> These exclusivities are, in turn, intertwined with statutory and regulatory approval pathways.<sup>112</sup>

In the United States, there are three common pathways available by which to obtain approval for drug products: FDCA Act sections 505(b)(1), 505(b)(2), and 505(j).<sup>113</sup> The section 505(b)(1) (“new drug application”) pathway applies to novel chemical entities and requires significant nonclinical and clinical pharmacology and toxicology test data support.<sup>114</sup> The section 505(j) (“abbreviated new drug application”) pathway applies to generic drugs and requires clinical bioequivalence studies to show that two drug products are equivalent.<sup>115</sup>

The section 505(b)(2) (“supplemental new drug application” or “sNDA”) pathway focuses on a new formulation or new use of an already approved drug product.<sup>116</sup> In this pathway, previous data submissions supporting safety and efficacy of known drugs may be used so that only studies supporting the safety and/or efficacy of the new indication are necessary.<sup>117</sup> Using the section 505(b)(2) pathway, the applicant may be able to use prior pharmacology and toxicology studies related to the drug. The application may reference published studies available in the academic literature, approved product labels, or product monographs.<sup>118</sup> A similar pathway also exists for the filing of

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<sup>111</sup> Emily Michiko Morris, *The Myth of Generic Pharmaceutical Competition Under the Hatch-Waxman Act*, 22 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 245, 253, 256-57 (2012); see CDER Small Bus. & Indus. Assistance, *Patents and Exclusivity*, FDA/CDER SBIA Chronicles (May 19, 2015), <https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm447307.pdf> [http://perma.cc/8TWN-9Y82].

<sup>112</sup> See Diana W. Shineman et al., *Overcoming Obstacles to Repurposing for Neurodegenerative Disease*, 1 ANNALS CLINICAL TRANSLATIONAL NEUROLOGY 512, 513 (2014).

<sup>113</sup> 21 U.S.C. § 355 (2012).

<sup>114</sup> 21 U.S.C. § 355(b)(1) (2012); 21 C.F.R. § 314.50 (2017).

<sup>115</sup> 21 U.S.C. § 355(j) (2012).

<sup>116</sup> 21 U.S.C. § 355(b)(2) (2012).

<sup>117</sup> 21 C.F.R. § 314.3(b) (2012).

<sup>118</sup> Mahadeo A. Sukhai et al., *New Sources of Drugs for Hematologic Malignancies*, 117 BLOOD 6747, 6752 (2011) (“In this pathway, the previous findings of safety and efficacy of known drugs can be leveraged so that only studies necessary to support the safety and/or efficacy of the new indication need to be conducted. Therefore, using the

investigational new drug applications for clinical trials of known drugs for new indications. As such, even patent-protected drugs may be evaluated for new indications without submitting the chemistry and manufacturing files in the investigational new drug or even obtaining the approval of the original sponsors, if the drug product is used in compliance with the approved product label. In addition to a new use claim, an applicant may also include development of a new formulation in order to obtain market exclusivity.

When a brand manufacturer obtains FDA approval for a new drug product or method of treatment, it submits to the FDA a list of relevant patents, both composition-of-matter and method-of-use, and their expiration dates. For method-of-use patents, the brand manufacturer also provides the aforementioned use code narratives. The FDA does not investigate or verify the identified patents or uses, but publishes the information in the Orange Book.<sup>119</sup> Patent considerations are relevant for drug approval under the section 505(b)(2) pathway, as a 505(b)(2) approval may be delayed because of patent or exclusivity protection.

Separately, firms may achieve market exclusivity for repurposed drugs by showing their efficacy in treating rare diseases. The Orphan Drug Act encourages pharmaceutical firms to develop compounds for the treatment of rare diseases, where “orphan” is defined as a prevalence of less than two hundred thousand people.<sup>120</sup> The Orphan Drug Act offers economic and other incentives to develop therapies for rare disease. For example, when reviewing orphan drug applications, the FDA accepts smaller cohort sizes for registration trials and waives certain fees associated with the development and approval of orphan drugs.<sup>121</sup> Orphan drug candidates also attract significant grants and qualify for tax credits. Approval of

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505(b)(2) mechanism, the sponsor may be able to capitalize on the prior pharmacology and toxicology studies related to the drug rather than repeating these studies.”).

<sup>119</sup> See *Approved Drug Products with Therapeutic Equivalence Evaluations*, FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm> [<https://perma.cc/XHJ2-R2XT>]; Courtenay C. Brinckerhoff, *U.S. Courts Look at Method of Use Patents in Generic Drug/ANDA Litigation*, KLUWER PATENT BLOG (May 21, 2012), <http://klwepatentblog.com/2012/05/21/u-s-courts-look-at-method-of-use-patents-in-generic-druganda-litigation> [<http://perma.cc/BX9B-89JC>].

<sup>120</sup> 21 U.S.C. § 360bb(a)(2) (2008); Caroline Asbury, *The Orphan Drug Act: The First 7 Years*, 265 JAMA 893, 896 (1991).

<sup>121</sup> Aaron Kesselheim, *Innovation and the Orphan Drug Act, 1983-2009: Regulatory and Clinical Characteristics of Approved Orphan Drugs*, in RARE DISEASES AND ORPHAN PRODUCTS: ACCELERATING RESEARCH AND DEVELOPMENT 26 (MJ Field & TF Boat eds., 2010).

orphan drugs provides market exclusivity for seven years.<sup>122</sup> Before the introduction of the Orphan Drug Act in the United States in 1983, only 38 treatments were approved by the FDA for rare conditions. Since passage of the law, more than 350 new treatments have been approved.<sup>123</sup> In 2015, Congress introduced the “Orphan Product Extensions Now Accelerating Cures & Treatments Act,” or OPEN Act, which would have made available an additional six months of market exclusivity for repurposed treatments if the sponsor company established that the therapy was designated to treat a rare disease and obtained a rare disease indication from the FDA on the drug label.<sup>124</sup>

The Orphan Drug Act has also encouraged some firms to intentionally position drugs for orphan indications and then rely on off-label prescribing for non-orphan indications to supplement revenues. It has also allowed some firms to obtain orphan designation for known drugs already widely prescribed but unapproved for an orphan designation.<sup>125</sup> The market exclusivity granted for orphan indications creates the same incentives as other forms of intellectual property and data protection. That is, when market exclusivities are inexpensive to enforce, firms do so. For example, URL Pharma received orphan drug designation for colchicine for the treatment of familial Mediterranean fever and a label indication for the treatment of gout.<sup>126</sup> Although colchicine had been used for many years for the treatment of these conditions, randomized Phase III data were not available to support the indication.<sup>127</sup> In exchange for producing the data demonstrating clinical efficacy, the FDA granted URL Pharma three years of market exclusivity for the treatment of gout and seven years of market exclusivity for the treatment of familial Mediterranean fever. The price of colchicine rose fifty-fold after these approvals and URL’s legal

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<sup>122</sup> Bill Walsh, *The Tier IV Phenomenon—Shifting the High Cost of Drugs to Consumers*, AARP (March 9, 2009), <http://assets.aarp.org/rgcenter/health/tierfour.pdf> [<https://perma.cc/JY6G-WFYX>].

<sup>123</sup> Sinead Murphy et al., *Unintended Effects of Orphan Product Designation for Rare Neurological Diseases*, 72 ANNALS NEUROLOGY 481, 481 (2012).

<sup>124</sup> Orphan Product Extensions Now Accelerating Cures and Treatments Act of 2015, H.R. 971, 114th Cong. (2015).

<sup>125</sup> Shannon Gibson & Barbara von Tigerstrom, *Orphan Drug Incentives in the Pharmacogenomic Context: Policy Responses in the US and Canada*, 2 J. L. & BIOSCIENCES 263, 281 (2015).

<sup>126</sup> Aaron Kesselheim & Daniel Solomon, *Incentives for Development—The Curious Case of Colchicine*, 362 NEW ENG. J. MED. 2045, 2046 (2010). According to the authors, colchicine was grandfathered in because it existed before the FDCA.

<sup>127</sup> *Id.* at 2045.

efforts against other manufacturers to enforce its exclusivity rights.<sup>128</sup>

Indeed, in a letter inviting U.S. Government Accountability Office (GAO) investigation of the law, Senators Orrin Hatch, Chuck Grassley, and Tom Cotton wrote that “some pharmaceutical manufacturers might be taking advantage of the multiple designation allowance in the orphan drug approval process.”<sup>129</sup> That letter in turn was motivated in some measure by a Kaiser Health News investigation finding that

[m]ore than 70 [orphan-disease designated drugs] were drugs first approved by the Food and Drug Administration for mass market use. These medicines, some with familiar brand names, were later approved as orphans. In each case, their manufacturers received millions of dollars in government incentives plus seven years of exclusive rights to treat that rare disease, or a monopoly.<sup>130</sup>

In 2012, the Generating Antibiotic Incentives Now (GAIN) provisions were signed into the law as part of the Food and Drug Administration Safety and Innovation Act.<sup>131</sup> GAIN grants an additional five years of exclusivity for a new antibiotic designated as a “qualified infectious disease product,” defined as “an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections.” The five years of market protection are added to any existing exclusivity, including that which may be applicable under Hatch-Waxman, orphan drug, or pediatric exclusivity (six months, as discussed *infra*).

### III. THE DRUG REPURPOSING ECOSYSTEM

As the above discussion reveals, the process of developing new drugs is itself extraordinarily complex; relies upon a set of incentives with essentially unknown influence; and, more recently, is deeply affected by the changing environment for

<sup>128</sup> *Id.* at 2046.

<sup>129</sup> Letter from Sen. Orrin Hatch et al. to Gene L. Dodaro, Comptroller Gen., U.S. Gov’t Accountability Office (Mar. 3, 2017), <https://kaiserhealthnews.files.wordpress.com/2017/03/gao-request-oda-signed1-002.pdf> [<https://perma.cc/8R8P-E27V>].

<sup>130</sup> Sarah Jane Tribble & Sydney Lupkin, *Drugs For Rare Diseases Have Become Uncommonly Rich Monopolies*, MORNING ED. (Jan. 17, 2017, 4:59 AM), <http://www.npr.org/sections/health-shots/2017/01/17/509506836/drugs-for-rare-diseases-have-become-uncommonly-rich-monopolies> [<https://perma.cc/2YVX-PK5M>].

<sup>131</sup> GAIN Act, Pub. L. 112-144 (2012).

large pharmaceutical innovator firms. Indeed, the costs of developing a single *new* drug is among the most controversial and heated topic in the public health literature, with abundant, disputed evidence all around.<sup>132</sup>

*Repurposing* drugs involves an even greater number of players, with more diverse incentives, working in far more ambiguous zones of formal regulation. Market exclusivity incentives—whether through the patent system or idiosyncratic regulatory regimes—cannot, at least on currently available evidence, be assumed to work in the same way as *de novo* drug development incentives. Indeed, there has been no study to date asserting that the amount of repurposing activity is suboptimal. The studies that *do* exist suggest that currently approved drugs may show promise in other disease areas, *not* that they will be safer or more efficacious. Given these uncertainties, it is not clear that deploying the kinds of incentives used for *de novo* drug development will generate the kinds of repurposing activity society needs and, indeed, doing so may substantially interrupt the processes that now bring many repurposed drugs to market.

In contrast to *de novo* drug development, the process by which new indications for approved drugs are discovered involves a larger set of actors who are, in turn, more integrated into the healthcare system and function under a different set of incentives less formalized than the market exclusivity mechanisms identified above. To date, new indication discovery has been largely driven by serendipitous observations made by academic researchers, clinicians, and pharmaceutical firm researchers.<sup>133</sup> Pharmaceutical firms have encouraged this disaggregated new indication system through technically illegal but widespread “off-label marketing” and, relatedly, legal, practices like disseminating third-party medical literature about alternative indications for approved drugs.<sup>134</sup>

### A. *Serendipity and Clinical Observations*

To some extent, drug repurposing is embedded in the research and treatment process itself. Alexander Fleming was engaged in research on influenza when one of his staphylococcus

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<sup>132</sup> Jerry Avorn, *The \$2.6 Billion Pill—Methodologic and Policy Considerations*, 372 *NEW ENG. J. MED.* 1877, 1877 (2015).

<sup>133</sup> Divya Sardana et al., *Drug Repositioning for Orphan Diseases*, 12 *BRIEF BIOINFORM.* 346, 347 (2011).

<sup>134</sup> 21 U.S.C. §§ 331(a), 352(a), 352(f) (2012); Marc J. Scheineson & Guillermo Cuevas, *United States v. Caronia: The Increasing Strength of Commercial Free Speech and Potential New Emphasis on Classifying Off-Label Promotion as “False and Misleading”*, 68 *FOOD & DRUG L.J.* 201, 206 (2013).

culture plates became contaminated and developed a mold that created a bacteria-free circle.<sup>135</sup> Fleming recognized the possible significance of the bacteria-free circle, and by isolating the mold in pure culture he found that it produced a substance that has a powerful destructive effect on many of the common bacteria that infect human beings.<sup>136</sup> He named the antibacterial substance liberated into the fluid in which the mold was grown “penicillin,” after *Penicillium notatum*, the contaminant of the staphylococcus colony that led to the discovery.<sup>137</sup> The most famous episode of modern serendipitous drug discovery is sildenafil, a drug Pfizer scientists were attempting to use as a treatment for angina.<sup>138</sup> Although it failed to relieve angina pain, some patients experienced erections as a side effect. Independently, researchers at Johns Hopkins were working with the effect of nitric oxide on the physiological relaxation of blood vessels.<sup>139</sup> They discovered that the enzyme responsible for nitric oxide in the body is localized in the penis and suggested that nitric oxide was the transmitter for penile erection.<sup>140</sup> Because the action of nitric oxide was mediated by organic molecules similar to that of sildenafil, the side effect of penile erection reported by cardiac patients in the Pfizer study was explained by the findings of the Hopkins group. Together, the discoveries led to the drug’s indication for male erectile disorder, and the blockbuster sildenafil (Viagra) for Pfizer.

Serendipitous discoveries that approved drugs may be used for different diseases are even more common. Thalidomide was a drug initially marketed as a sedative and antiemetic, widely taken by pregnant women for the treatment of morning sickness with the catastrophic result of thousands of children suffering severe birth defects.<sup>141</sup> A few years later, it was administered to a patient with mania and leprosy mainly for its sedative effect.<sup>142</sup> The patient’s cutaneous symptoms nearly completely resolved with the treatment, resurrecting thalidomide’s promise as an anti-inflammation agent. Its postulated mechanisms of

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<sup>135</sup> Thomas Ban, *The Role of Serendipity in Drug Discovery*, 8 DIALOGUES IN CLINICAL NEUROSCIENCE 335, 339 (2006).

<sup>136</sup> *Id.*

<sup>137</sup> *Id.*

<sup>138</sup> Hossein Ghofrani et al., *Sildenafil: From Angina to Erectile Dysfunction to Pulmonary Hypertension and Beyond*, 5 NAT. REV. DRUG DISCOVERY 689, 689 (2006).

<sup>139</sup> Ban, *supra* note 135, at 342.

<sup>140</sup> *Id.*

<sup>141</sup> J.N. Gordon & P.M. Goggin, *Thalidomide and Its Derivatives: Emerging From the Wilderness*, 79 POSTGRAD. MED. J. 127, 130 (2003).

<sup>142</sup> *Id.* at 127.

action led to academic research into alternative uses, especially the treatment of tumors.<sup>143</sup>

The tyrosine kinase inhibitor imatinib—Novartis’s blockbuster cancer drug marketed as Gleevec—has been studied as a therapeutic agent for the treatment of rheumatoid arthritis. The rationale for those trials was based in part on clinical observations demonstrating improved rheumatoid symptoms in patients who received imatinib for their coexisting chronic myelogenous leukemia.<sup>144</sup> Between 2000 and 2009, eleven known drugs received a new anticancer indication based on similar clinical observations.<sup>145</sup> “Except for the use of thalidomide for the treatment of multiple myeloma, the other 10 drugs represented label extensions of known chemotherapeutic agents.”<sup>146</sup> Thus, identification of new indications through clinical evaluation is a common form of drug repurposing.

### ***B. Big Data and In Silico Screening***

An emerging but as-of-yet less prominent means of identifying and developing new drug uses is the application of sophisticated algorithms based on current drug labels, as well as computer-modeled projections, for new uses based on the known mechanisms of action for current approved drugs. These methods are sometimes referred to as *in silico* methods because they involve computer simulation (in contrast to *in vitro* or *in vivo* methods otherwise used in medical research).<sup>147</sup> This process has been facilitated by pressures imposed by public and academic institutions to make knowledge more readily available. In 2001, academic journals began to require that authors using microarrays deposit their data into repositories.<sup>148</sup> Since then, more than one million microarray datasets have become available, and the number is doubling every two years.<sup>149</sup> Other kinds of molecular, clinical and epidemiological data are becoming available at similar rates.

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<sup>143</sup> *Id.* at 129.

<sup>144</sup> See Jorg H. W. Distler et al., *Treatment of Pulmonary Fibrosis for Twenty Weeks With Imatinib Mesylate in a Patient With Mixed Connective Tissue Disease*, 58 ARTHRITIS & RHEUMATISM 2538, 2541-42 (2008).

<sup>145</sup> Sukhai et al., *supra* note 118, at 6750.

<sup>146</sup> *Id.*

<sup>147</sup> Stefan S. Tunev, *Differences Between in Vitro, in Vivo, and in Silico Studies*, MARSHAL PROTOCOL KNOWLEDGE BASE, [http://mpkb.org/home/patients/assessing\\_literature/in\\_vitro\\_studies](http://mpkb.org/home/patients/assessing_literature/in_vitro_studies) [<http://perma.cc/ABP6-SVX4>].

<sup>148</sup> Monya Baker, *Gene Data to Hit Milestone*, 487 NATURE 282, 282-83 (2012).

<sup>149</sup> *Id.*



Cheminformatics approaches rely on the analysis and entry of chemical compound characteristics, and analyze those characteristics across commercially or publicly available databases or compendia of molecular targets like the National Institute of Neurological Disorders and Stroke (NINDS)/Microsource US drug collection or the Prestwick Chemical library.<sup>150</sup> The Keiser study noted above, for example, compared

3,665 US Food and Drug Administration (FDA)-approved and investigational drugs against hundreds of targets, defining each target by its ligands.”<sup>151</sup> Chemical similarities between drugs and ligand sets predicted thousands of unanticipated associations. Overall, 23 new drug-target associations were confirmed.<sup>152</sup>

Sivanesan Dakshanamurthy, at Georgetown’s Lombardi Cancer Institute, and his coauthors developed a computational method called “train, match, fit, streamline” (TMFS) to map new drug-target interaction space and predict new uses. The TMFS method combines shape, topology, and chemical signatures, including docking score and functional contact points of the ligand, to predict potential drug-target interactions. Using the TMFS method, they ran molecular fit computations on 3,671 FDA approved drugs across 2,335 human protein crystal structures to discover promising repurposing opportunities for an antihookworm agent to treat cancer and combined therapies to treat otherwise unresponsive rheumatoid arthritis.<sup>153</sup>

Other approaches aim at exploiting other forms of drug and indication relationships, such as matching clinical side effects and additional disease indications. GlaxoSmithKline researchers Lun Yang and Pankaj Agarwal, for example, argued in a 2011 article—which overlapped in significant part with a GSK patent on their discovery methods—that clinical side effects provide a human phenotypic profile for any given drug, and that profile

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<sup>150</sup> Ruili Huang et al., *The NCGC Pharmaceutical Collection: A Comprehensive Resource of Clinically Approved Drugs Enabling Repurposing and Chemical Genomics*, 3 SCI. TRANSL. MED. 80 (2011); *Workshop & Conference Proceedings*, NAT’L INST. NEUROLOGICAL DISORDERS & STROKE, [http://www.ninds.nih.gov/news\\_and\\_events/proceedings/Drug\\_Screening\\_Consortium\\_2002.htm](http://www.ninds.nih.gov/news_and_events/proceedings/Drug_Screening_Consortium_2002.htm) (last visited Nov. 20, 2017) [<http://perma.cc/L6A7-SX23>].

<sup>151</sup> See Keiser et al., *supra* note 36.

<sup>152</sup> *Id.*

<sup>153</sup> S. Dakshanamurthy et al., *Predicting New Indications for Approved Drugs Using a Proteochemometric Method*, 55 J. MED. CHEMISTRY 6832 (2012).

can suggest additional disease indications.<sup>154</sup> They extracted 3,175 side effect-disease relationships by combining the relationships from drug labels and the drug-disease relationships from PharmGKB, an NIH-initiated central knowledge sharing site that curates and mediates data and researchers examining complex relationships between genes, variants, drugs, diseases and pathways.<sup>155</sup> Yang and Agarwal found that many relationships provided explicit repositioning hypotheses, such as drugs causing hypoglycemia that were potential candidates for diabetes.<sup>156</sup> Sean Ekins and Antony Williams reviewed thirty-four studies over a six-year period and determined that “a conservative estimate indicates at least 109 previously approved drugs have shown activity in vitro against additional diseases different than those for which the drugs were originally approved.”<sup>157</sup>

No matter how effective big data methods become at identifying promising compounds and even facilitating animal testing data, they cannot, yet, directly establish either an economically rational or a normative preference system for selecting promising compounds for Phase II and Phase III trials. Those trials comprise the most expensive aspects of FDA approval and have been estimated to fail at 80% and 50% rates respectively.<sup>158</sup> A single Phase III trial for Alzheimer’s Disease may cost up to \$300-\$400 million.<sup>159</sup> The current debate largely revolves around putting in place incentives so that firms behave as they do with de novo drug development and the most profitable drugs’ new uses rise to the top for clinical testing and regulatory approval.

### C. *Public and Foundation Supported New Use Research*

Publicly funded trial options for drug repurposing, as with all drug development, are limited.<sup>160</sup> The NIH’s National Center for Advancing Translational Sciences has established a program

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<sup>154</sup> Lun Yang & Pankaj Agarwal, *Systematic Drug Repositioning Based on Clinical Side-Effects*, 6 PLOS ONE e28025, at 1 (Dec. 21, 2011), <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0028025> [<http://perma.cc/FR2Z-DSQH>].

<sup>155</sup> *Id.* at 2.

<sup>156</sup> *Id.* at 6.

<sup>157</sup> Antony Williams, *Finding Promiscuous Old Drugs for New Uses*, 28 PHARM. RES. 1785 (2011).

<sup>158</sup> John Arrowsmith, *Trial Watch: Phase II Failures: 2008-2010*, 10 NATURE REVIEWS DRUG DISCOVERY 328, 328-329 (2011); John Arrowsmith, *Trial Watch: Phase III and Submission Failures: 2007-2010*, 10 NATURE REVIEWS DRUG DISCOVERY 87 (2011).

<sup>159</sup> Shineman et. al., *supra* note 53, at 513.

<sup>160</sup> See Rebecca English et al., TRANSFORMING CLINICAL RESEARCH IN THE UNITED STATES: CHALLENGES AND OPPORTUNITIES: WORKSHOP SUMMARY 73 (2010).

called Discovering New Therapeutic Uses for Existing Molecules (the “NCATS Program”).<sup>161</sup> Firms participating in NCATS contribute compounds that advanced in clinical studies but were unsuccessful for their original indication.<sup>162</sup> The NCATS Program allows researchers to submit proposals to investigate a compound for use in a particular disease area through two- and three-year grants that fund through Phase IIA.<sup>163</sup> A successful researcher owns any new intellectual property rights generated by his or her work, while the contributing company owns the first right to develop the product.<sup>164</sup>

When clinical trials for new uses are publicly funded, it is often indirectly. Because non-profit organizations, including university researchers, encounter difficulty in acquiring potential drugs from pharmaceutical firms because of extensive legal, intellectual, and publication complexities, among other hurdles, they purchase readily available approved drugs and test them for other uses.<sup>165</sup> If clinical trials are successful, researchers can publish their results and doctors can elect to prescribe the drug off-label.<sup>166</sup> The Food and Drug Administration’s Rare Disease Repurposing Database; the National Institutes of Health’s pharmaceutical collection held by its Therapeutics for Rare & Neglected Diseases program; and the World Intellectual Property Organization’s Re:Search, a database of available intellectual property assets held to support research on neglected tropical diseases, are also used to facilitate access to publicly funded clinical trials for new uses.<sup>167</sup>

<sup>161</sup> National Center for Advancing Translational Sciences, *NCATS, Programming and Initiatives*, NAT’L INST. HEALTH, <https://ncats.nih.gov/about/center> [<http://perma.cc/P68T-N7QV>].

<sup>162</sup> *Five More Pharmaceutical Companies Join NIH Initiative to Speed Therapeutic Discovery*, NATIONAL INSTITUTES OF HEALTH, <https://www.nih.gov/news-events/news-releases/five-more-pharmaceutical-companies-join-nih-initiative-speed-therapeutic-discovery> [<http://perma.cc/H75R-PR8M>].

<sup>163</sup> *See id.*

<sup>164</sup> *Collaborative Research Agreement Between Pharmaceutical Research & Development, L.L.C. (The Company) and Academic Medical Center*, NAT’L CTR. FOR ADVANCING TRANSLATIONAL SCI., <https://ncats.nih.gov/sites/default/files/NTU-CRA-JnJ.pdf> [<http://perma.cc/79W2-W5WR>].

<sup>165</sup> Thayer, *supra* note 24.

<sup>166</sup> *See id.*

<sup>167</sup> K. Xu & T.R. Coté, *Database Identifies FDA-Approved Drugs with Potential To Be Repurposed for Treatment of Orphan Diseases*, 12 BRIEF BIOINFORM 341 (2011); *NIH Therapeutics for Rare and Neglected Diseases Program Announces Next Round of Drug Development Projects*, NAT’L INST. HEALTH, <http://www.nih.gov/news/health/nov2011/nhgri-15.htm> [<https://perma.cc/U2QG-D8ZA>]; WIPO RE:SEARCH, <http://www.wipo.int/research/en/> [<https://perma.cc/UAF7-ZQJJ>].

Public agencies not only directly fund repurposing work, but facilitate knowledge and resource sharing partnerships. Auranofin, a rheumatoid arthritis agent first approved in 1985, has shown promise treating Chronic Lymphocytic Leukemia (CLL).<sup>168</sup> CLL qualifies as a rare disease under the Orphan Drug Act.<sup>169</sup> The treatment was developed through the Learning Collaborative, a partnership between the Institute for Advancing Medical Innovation (IAMI) at the University of Kansas Medical Center (KUMC), the Leukemia & Lymphoma Society (LLS), and the National Center for Advancing Translational Sciences (NCATS) at NIH.<sup>170</sup>

There are also a limited number of private foundations that support new use research, like Cures within Reach, the Alzheimer's Drug Discovery Foundation, and the Michael J. Fox Foundation.<sup>171</sup>

#### D. Industry-University Partnerships

Firms that have adopted active repurposing programs have also looked to both traditional and new partnerships with academic research centers. Swiss pharmaceutical firm, Roche, for example, interviewed its own researchers company-wide to develop a list of more than 350 compounds, the Roche Repurposing Compound Collection.<sup>172</sup> It then entered into an agreement with the Harvard-MIT Broad Institute to design experiments that might help Roche link a compound with a patient population.<sup>173</sup> Roche shares information about its compounds under a staggered arrangement. "Collaborators will first get the compounds and their molecular weights. If they uncover any interesting findings, more information will be shared."<sup>174</sup>

Industry-academic partnerships are traditionally not so comprehensive and directed at new use research. In more

<sup>168</sup> Nora Yang, *Auranofin for Chronic Lymphocytic Leukemia*, NAT'L INST. HEALTH (Sept. 7, 2017), <https://ncats.nih.gov/trnd/projects/complete/auranofin-chronic-lymphocytic-leukemia> [https://perma.cc/6UYT-76BE].

<sup>169</sup> Kesselheim, *supra* note 121.

<sup>170</sup> Yang, *supra* note 168.

<sup>171</sup> See ALZHEIMER'S DISEASE DISCOVERY FOUND., <https://www.alzdiscovery.org/cognitive-vitality/article/promise-in-off-label-drugs-for-alzheimers> [https://perma.cc/8FQU-3X5A]; CURES WITHIN REACH, <http://www.cureswithinreach.org/> [https://perma.cc/YEP8-8A33]; MICHAEL J. FOX FOUND. FOR PARKINSON'S RESEARCH, <https://www.michaeljfox.org/foundation/news.html> [https://perma.cc/3KWK-5MQD].

<sup>172</sup> Ann M. Thayer, *Roche Collaborates with Broad Institute*, 90 CHEMICAL & ENGINEERING NEWS 19 (2012), <https://cen.acs.org/articles/90/i49/Roche-Collaborates-Broad-Institute.html> [http://perma.cc/4W2M-TYMW].

<sup>173</sup> *Id.*

<sup>174</sup> *Id.*

orthodox relationships, pharmaceutical firms encounter unexpected results and reach out to academic specialists to undertake further investigation. Dasatinib, an agent used to inhibit tumor growth, was originally developed from a Bristol-Myers Squibb program targeting the tyrosine kinase Lck.<sup>175</sup> During the study of dasatinib, researchers noticed that the drug had off-target effects against other tyrosine kinases, including Abl, which is involved in Philadelphia chromosome-positive leukemia.<sup>176</sup> BMS reached out to Charles Sawyer at the University of California, Los Angeles to adapt dasatinib for Abl, which led to FDA approval for its use in treating imatinib-resistant Philadelphia chromosome-positive leukemia.<sup>177</sup>

Indeed, repurposing has given birth to its own industry, where secondary firms “hire away molecules, perhaps 10 to 20 at a time, choosing only those that weren’t abandoned for safety reasons and aren’t protected by composition of matter patents.”<sup>178</sup> Repurposing methods themselves are a thriving source of patent activity.<sup>179</sup>

### ***E. Liability and Cost Factors Influencing New Use Research Priorities***

Although the literature is overwhelmingly focused on the promise of developing new uses for old drugs through incentives like commercialization rights, data exclusivity, and intellectual property rights, there has been little discussion or research into the relief from adverse incentives like product liability.<sup>180</sup> Incentives like market exclusivity and tax incentives may not work where relief from product liability may. Even in the latter case, if a drug has a global market potential (as most do), firms may not invest in repurposing if a principal use in a global market might be undermined.

In many cases, pharmaceutical firms refuse to develop new uses not because they will not reap a proportionate award

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<sup>175</sup> DRUG REPURPOSING AND REPOSITIONING: WORKSHOP SUMMARY 34 (Sarah H. Beachy et al. eds., 2014).

<sup>176</sup> *Id.*

<sup>177</sup> *Id.* at 34-35; Nell P. Shah et al., *Overriding Imatinib Resistance with a Novel ABL Kinase Inhibitor*, 305 SCIENCE 399 (2004); Moshe Talpaz et al., *Dasatinib in Imatinib-Resistant Philadelphia Chromosome-Positive Leukemias*, 354 NEW ENG. J. MED. 2531 (2006).

<sup>178</sup> Thayer, *supra* note 24.

<sup>179</sup> Cf. U.S. Patent Application No. 14/239,564, Publication No. 20140193517 (published Jul. 10, 2014) (Pankaj Agarwal, Lun Yang, applicants).

<sup>180</sup> *But see* Keving Outterson and Aaron Kesselheim, *Improving Antibiotic Markets for Long Term Sustainability* 11 YALE J. HEALTH L. POLY & ETHICS 101, 122-23 (2011) (describing eight-sector incentive scheme).

through a new approval (although that may also be the case), but because research into new uses may expose side effects detrimental to the drug's primary market. Merck, for example, discovered cardiovascular side effects for Vioxx while testing the drug's potential for treating colon polyps, after FDA had approved it as an analgesic.<sup>181</sup> Repurposing may create or eliminate toxicity issues, since it may be delivered differently or at a different dose for the new use.<sup>182</sup> Indeed, there is evidence that Merck was aware of cardiovascular side effects with Vioxx during clinical trials for its analgesic properties.<sup>183</sup>

Despite the importance of product liability disincentives (which may raise both safety issues and market signal issues—even if no lawsuit is filed, product weaknesses can affect revenue), there are few scholars in the drug repurposing debate that propose any kind of relief from tort liability as a way of encouraging pharmaceutical firms to undertake new use research or to more openly share drug data including clinical trial data.<sup>184</sup> If it is true that pharmaceutical firms fear liabilities arising from new-use research, the incentives now imagined to be necessary for more off-label research—like more robust protection of method-of-use patents—may not generate the kind of repurposing activity advocates say society will realize as a result of those incentives.

Nor would relief from product liability be a logical or practical approach to encouraging new use research. Product

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<sup>181</sup> Barry Meier, *Merck Canceled an Early Study of Vioxx*, N.Y. TIMES (Feb. 8, 2005), <http://www.nytimes.com/2005/02/08/business/merck-canceled-an-early-study-of-vioxx.html> [https://perma.cc/Z5S8-Q35B]; see Statement of Sandra Kweder, Vioxx and Drug Safety, Senate Finance Committee, Nov. 18, 2004 (“Merck contacted FDA on September 27, 2004, to request a meeting to discuss with the Agency the Data Safety Monitoring Board's decision to halt Merck's long-term study of Vioxx in patients at increased risk of colon polyps. Merck and FDA officials met the next day, September 28, and during that meeting the company informed FDA of its decision to remove Vioxx from the market voluntarily. The data presented demonstrated an increase in risk in cardiovascular risk and stroke starting at the eighteen-month time point compared to placebo.”), <https://www.finance.senate.gov/imo/media/doc/99575.pdf> [https://perma.cc/2DAX-NUXB].

<sup>182</sup> See Thayer, *supra* note 24; Alex Berenson et al., *Despite Warnings, Drug Giant Took Long Path to Vioxx Recall*, N.Y. TIMES (Nov. 14, 2004), <http://www.nytimes.com/2004/11/14/business/despite-warnings-drug-giant-took-long-path-to-vioxx-recall.html> [https://perma.cc/E7EZ-98GE]. Litigation documents suggest Merck knew even earlier than this, but it was this study that prompted Merck's communications to FDA.

<sup>183</sup> Joseph S. Ross, et. al., *Guest Authorship and Ghostwriting in Publications Related to Rofecoxib: A Case Study of Industry Documents From Rofecoxib Litigation*, 299 JAMA 1800 (2008); Joseph S. Ross, et. al., *Pooled Analysis of Rofecoxib Placebo-Controlled Clinical Trial Data: Lessons for Postmarket Pharmaceutical Safety Surveillance*, 169 ARCHIVES INTERNAL MED. 1976 (2009).

<sup>184</sup> Efthimios Parasidis, *Patients Over Politics: Addressing Legislative Failure in the Regulation of Medical Products*, 2011 WISC. L. REV. 929 (2011).

liability provides an important layer of review for drugs that may escape the FDA's attention, in addition to making victims whole for drugs that cause severe adverse events.<sup>185</sup> Nothing about repurposed drugs would alter this important aspect of pharmaceutical regulation.

### *F. Off-Label Marketing*

In addition to product liability, the current debate is largely silent on the drug repurposing that is already common and widespread: the marketing of drugs by pharmaceuticals for indications that have not been approved by the FDA, or “off-label marketing.”<sup>186</sup> Typically, the FDA approves a drug for specific uses based on substantial evidence of effectiveness.<sup>187</sup> That evidence is statutorily defined as

evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.<sup>188</sup>

When FDA approves a new drug or approves an already marketed drug for a new indication, it only does so for claims

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<sup>185</sup> David Vladeck & David Kessler, *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, 96 Geo. L.J. 461, 463(2008) (“State damages litigation helps uncover and assess risks that are not apparent to the agency during a drug’s approval process . . . The agency also wanted to avoid the “harsh implications” of eliminating judicial recourse for consumers injured by dangerous drugs.”).

<sup>186</sup> Ryan Abbott & Ian Ayres, *Evidence and Extrapolation: Mechanisms for Regulating Off-Label Uses of Drugs and Devices*, 64 DUKE L.J. 378, 391 (2014) (“Under the current regulatory regime, manufacturers opt for back-door approaches to developing off-label revenue streams because of the “enormous amount of time and money” required to seek FDA approval for a new use.”); *In re Gilead Sciences Securities Litigation*, 536 F.3d 1049, 1051 (9th Cir. 2008) (“Generally, [FDA] regulations prohibit the marketing of drugs for non-FDA-approved uses, commonly referred to as ‘off-label’ uses. For example, it would be considered off-label for a company to market a FDA-approved HIV/AIDS drug as also being effective for fighting Hepatitis B infection if such use of the drug had not been reviewed and approved by the FDA and included in the drug’s FDA-approved package labeling.” (internal quotation marks and alterations omitted)).

<sup>187</sup> Russell Katz, *FDA: Evidentiary Standards for Drug Development and Approval*, 1 NEURORX 307 (2004).

<sup>188</sup> 21 U.S.C. § 355(d) (2012).

which are supported by evidence meeting this high standard.<sup>189</sup> While firms may develop or become aware of other uses for their medications that fall outside of the FDA's specific authorization, the agency prohibits them from marketing the drugs for these off-label uses. When firms do so, they are, strictly speaking, "misbranding" drugs in violation of federal law.<sup>190</sup>

The FDA's ban does not extend to doctors, however, who may prescribe drugs for off-label uses when patient needs or the standard of care requires it.<sup>191</sup> Despite the flexibility given to physicians to prescribe for unapproved uses, medical training itself, including residency, offers little guidance on best practices for off-label prescription practices, and the American Medical Association and other professional organizations have offered little advice on the matter.<sup>192</sup> Ambiguity is even entrenched in federal reimbursement programs like Medicare and Medicaid—which, under the law, should not reimburse for off-label uses except as recognized in specific compendia, but which, in practice, routinely reimburse for off-label use even outside those sources.<sup>193</sup>

Off-label marketing and prescription therefore operate in a vast legal gray zone. According to some estimates, off-label prescriptions account for 20% of all prescriptions, totaling more than \$40 billion in sales annually.<sup>194</sup> 80% of all drug prescriptions for children are off-label, and between 80 and 90% of all drug prescriptions for rare diseases are off-label.<sup>195</sup> Pharmaceutical firms may not market off-label uses; physicians may, and arguably must, when the standard of care requires it. In between, the information is shaped by multiple actors with

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<sup>189</sup> *Id.*

<sup>190</sup> 21 C.F.R. §202.1(e)(4)(i)(a); *United States ex rel. Polansky v. Pfizer*, 822 F.3d 613 (2d Cir. 2016).

<sup>191</sup> Scheineson & Cuevas, *supra* note 134, at 202-03.

<sup>192</sup> Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J. L. MED. & ETHICS 476, 480 (2009).

<sup>193</sup> J. Cohen et al., *Off-Label Use Reimbursement*, 64 FOOD & DRUG L.J. 391, 394 (2009).

<sup>194</sup> Abbott & Ayres, *supra* note 186, at 388 ("Off label use is common: 'for the 3 leading drugs in each of the 15 leading drug classes, off-label use accounts for approximately 21% of prescriptions.' Moreover, off-label uses may be the norm in some areas of practice such as oncology, pain management, and palliative care, and in some patient populations, such as children, the elderly, and the severely ill. For example, about 80% of all drug prescriptions for children are off-label, and between 80 and 90 percent of all drug prescriptions for rare diseases are off label."); Michael Bobelian, *J&J's \$2.2 Billion Settlement Won't Stop Big Pharma's Addiction to Off-Label Sales*, FORBES (Nov. 12, 2013), <http://www.forbes.com/sites/michaelbobelian/2013/11/12/jjs-2-2-billion-settlement-wont-stop-big-pharmas-addiction-to-off-label-sales> [https://perma.cc/DJA8-CZV4].

<sup>195</sup> James O'Reilly & Amy Dalal, *Off Label or Out of Bounds: Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANNALS HEALTH L. 295, 298 (2003).



different incentives. Academic researchers are free to study approved drugs for new uses and publish their findings. Physicians may request information from pharmaceutical firms (who know best the literature on alternative uses of their products and who in some cases pay for published studies) who may, under those circumstances, lawfully provide it.<sup>196</sup>

It is, in fact, the off-label market that causes the most difficulty in the drug repurposing context. Proponents of additional incentives for new use research argue that research investments will never be recouped because physicians may prescribe generic versions of an approved drug even where a valid, new method-of-use patent has been granted on a second indication by the original drug applicant.<sup>197</sup> The FDA and scholars sympathetic to the prohibition it enforces believe that the policy saves patients from injury or death caused by medical treatments unsupported by adequate evidence as to safety or efficacy, while allowing physicians flexibility to effectively treat patients.<sup>198</sup>

Indeed, it is an underexplored question in the current literature as to whether incentives for formal, legal approval of alternative uses may nevertheless fail to overcome the incentives for illegal marketing.<sup>199</sup> The off-label market represents a key channel of many drugs' revenue streams.<sup>200</sup> In 2007, Bristol-Myers Squibb paid \$515 million to settle various civil allegations, including its promotion of the antipsychotic drug, aripiprazole (Abilify).<sup>201</sup> Two years later, Eli Lilly paid

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<sup>196</sup> Aaron S. Kesselheim, *Off-Label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J. L. & MED. 225, 256 (2011).

<sup>197</sup> Roin, *supra* note 26 (“Pharmaceutical companies almost never have access to the information they need to enforce a new-use patent. When physicians prescribe a drug to a patient to treat a particular indication, the patient’s medical condition is confidential information. Physicians sometimes disclose the prescribed indication to pharmacists and insurers, especially when required as a condition for insurance coverage. However, they almost never share that information with pharmaceutical companies. Without access to patient-level information, pharmaceutical companies cannot enforce their new-use patents to charge insurers when physicians prescribe an off-patent drug for a patented indication.”).

<sup>198</sup> JERRY AVORN, POWERFUL MEDICINES: THE BENEFITS, RISKS, AND COSTS OF PRESCRIPTION DRUGS (2004); Philip M. Rosoff & Doraine Lambelet Coleman, *The Case for Legal Regulation of Physicians’ Off-Label Prescribing*, 86 NOTRE DAME L. REV. 649, 653 (2011).

<sup>199</sup> Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427-28 (2008).

<sup>200</sup> The manufacturers hold an extraordinary amount of information about their products. See U.S. Dep’t of Health and Human Services, U.S. FDA, GUIDANCE FOR INDUSTRY RESPONDING TO UNSOLICITED REQUESTS FOR OFF-LABEL INFORMATION ABOUT PRESCRIPTION DRUGS AND MEDICAL DEVICES 2 (2011).

<sup>201</sup> Press Release, U.S. Dep’t of Justice, *Bristol-Myers Squibb to Pay More Than \$515 Million to Resolve Allegations of Illegal Drug Marketing and Pricing*,

\$1.415 billion for its off-label marketing of Zyprexa.<sup>202</sup> GlaxoSmithKline agreed to plead guilty to criminal charges and pay \$3 billion to settle various government claims, including the unlawful promotion of some of its drugs, like the anti-depressant Paxil.<sup>203</sup> In its pursuit of Johnson & Johnson's Risperdal marketing activities, the U.S. government alleged that the firm made payments to physicians to influence them to write prescriptions for off-label uses, provided misleading information about the drug's safety and efficacy for alternative uses, and paid kickbacks to a large provider of pharmaceuticals to nursing homes to boost Risperdal's off-label sales.<sup>204</sup> Sales of Risperdal increased from \$172 million in 1994 to \$1.726 billion in 2005; in 2000, it was J&J's second-best selling drug.<sup>205</sup> A significant portion of the sales earned during this era—about 75% as of May 2002—came from off-label prescriptions.<sup>206</sup>

Over the last three years, a series of federal court decisions have ensured that—constitutionally protected—off-label marketing will increase rather than decrease. In 2013, the U.S. Court of Appeals for the Second Circuit invalidated the prosecution of a pharmaceutical firm's representative's off-label marketing on the basis that the government could not criminalize truthful, non-misleading speech.<sup>207</sup> On August 7, 2015, Judge Paul Engelmayer of the U.S. District Court for the Southern District of New York granted a motion for a preliminary injunction against the FDA for threatening to prosecute Amarin Pharmaceuticals for off-label marketing of its triglyceride-lowering medication based on commercial speech that was otherwise protected by the First Amendment.<sup>208</sup> Both cases, *Caronia* and *Amarin*, strongly suggest firms will become more aggressive in challenging FDA limitations on their off-label marketing activity. In *United States ex rel. Polansky v. Pfizer*, the Second Circuit questioned in dicta the fundamental

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[https://www.justice.gov/archive/opa/pr/2007/September/07\\_civ\\_782.html](https://www.justice.gov/archive/opa/pr/2007/September/07_civ_782.html)  
[<https://perma.cc/58AW-Z3SN>].

<sup>202</sup> Press Release, U.S. Dep't of Justice, *Eli Lilly and Company Agrees to Pay \$1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa*, <https://www.justice.gov/archive/opa/pr/2009/January/09-civ-038.html> [<https://perma.cc/RZ7T-VNHK>].

<sup>203</sup> Bobelian, *supra* note 194.

<sup>204</sup> *Id.*

<sup>205</sup> *Id.*

<sup>206</sup> *Id.*

<sup>207</sup> Scheineson & Cuevas, *supra* note 134, at 201.

<sup>208</sup> *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196 (S.D.N.Y. 2015).

tie between off-label promotion and liability under the federal False Claims Act.<sup>209</sup>

### G. *Evergreening*

Off-label marketing represents, in essence, the unregulated ways in which pharmaceutical firms repurpose drugs. The formal, *regulated* means by which firms repurpose drugs—often the aforementioned section 505(b)(2) pathway—are difficult in concept and practice to distinguish from “evergreening.” Evergreening refers to a wide range of pharmaceutical firm strategies for extending the exclusive market for a drug, including, most relevantly here, patenting peripheral aspects of drugs, like their coating or normal metabolites, in order to extend market exclusivity.<sup>210</sup> Most reforms will face the principle obstacle of drawing the distinction between modifications that represent the improvements in medical therapy that repurposing advocates desire and those intended to artificially extend the period for which firms can charge high prices on the underlying drug. GlaxoSmithKline, for example, secured ten patents unrelated to Paxil’s active ingredient, the last of which would have expired in 2019 had those patents gone unchallenged.<sup>211</sup> In the current debate, the line between practices largely criticized as efforts to raise drug prices and efforts praised as new-use research is impliedly sharp and distinct, whereas the distortions rendered by new use incentives would almost certainly create entanglements between “valid” and “invalid” assertions of data exclusivity or intellectual property protection. As Arti Rai and Grant Rice have noted, “all types of use patents get caught up in debates over patent ‘evergreening.’”<sup>212</sup>

Evergreening strategies are adopted not only in the patent context, but also in the various market exclusivity regimes administered by FDA. The manufacturers of loratidine (Claritin) and metformin (Glucophage) petitioned Congress for extended market exclusivity based on those regimes, and in the case of ranitidine (Zantac), a legal technicality gave the

<sup>209</sup> See *United States ex rel. Polansky v. Pfizer*, 822 F.3d 613, 619-20 (2d Cir. 2016); *Pacira Pharms., Inc. v. FDA*, No. 15-7055 (S.D.N.Y. Sept. 8, 2015).

<sup>210</sup> Cynthia M. Ho, *Should All Drugs be Patentable? A Comparative Perspective*, 17 *VAND. J. ENT. & TECH. L.* 295, 297 (2015).

<sup>211</sup> C. Scott Hemphill & Bhaven N. Sampat, *Evergreening, Patent Challenges, and Effective Market Life in Pharmaceuticals*, 31 *J. HEALTH ECON.* 327, 328 (2012).

<sup>212</sup> Rai & Rice, *supra* note 48.

manufacturer nearly seven more years of market protection.<sup>213</sup> Indeed, a relatively comprehensive study undertaken by the Federal Trade Commission cited occasions where companies registered duplicative or otherwise inappropriate modifications *precisely* to prevent lower-cost generic alternatives from being marketed.<sup>214</sup> Such patenting strategies are part of a larger set of tactics, which also include new formulations and other product line extensions that can lengthen market exclusivity for therapies facing generic entry.

#### IV. METFORMIN AND THE DRUG REPURPOSING ECOSYSTEM

Because the process by which drugs become repurposed is complex, perhaps too complex to design accurate aggregate studies, case study methodology provides an effective research method by which to understand multiple variables that may not be easily adapted to other research designs:

[C]ase studies are pertinent when . . . research addresses either a descriptive question—“What is happening or has happened?”—or an explanatory question—“How or why did something happen?” As contrasting examples, alternative research methods are more appropriate when addressing two other types of questions: an initiative’s effectiveness in producing a particular outcome (experiments and quasi-experiments address this question) and how often something has happened (surveys address this question). However, the other methods are not likely to provide the rich descriptions or the insightful explanations that might arise from doing a case study.<sup>215</sup>

Metformin provides a representative case for what has been posed as the drug repurposing problem. One of the leading treatments for type II diabetes mellitus in the United States,

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<sup>213</sup> *Glaxo Patent on Zantac Gets Extension*, N.Y. TIMES (Apr. 22, 1995), <http://www.nytimes.com/1995/04/22/business/glaxo-patent-on-zantac-gets-extension.html> [https://perma.cc/YQ66-PC3Z].

<sup>214</sup> Generic Drug Entry Prior to Patent Expiration: An FTC Study, FED. TRADE COMMISSION A-44, A-45 (July 2002).

<sup>215</sup> ROBERT K. YIN, *A (Very) Brief Refresher on the Case Study Method*, in APPLICATIONS OF CASE STUDY RESEARCH 5 (2012), [http://www.sagepub.com/sites/default/files/upm-binaries/41407\\_1.pdf](http://www.sagepub.com/sites/default/files/upm-binaries/41407_1.pdf) [https://perma.cc/5WR4-SKSC].

metformin—marketed as Glucophage by Bristol-Myers Squibb—was approved for marketing in 1995. Because its composition-of-matter patent had expired, metformin enjoyed only the five-year exclusivity extended to it by the Hatch-Waxman Act. Although it became an immediate blockbuster for Bristol-Myers Squibb and its licensing partner, Merck KGaA, neither firm has endeavored to move metformin into Phase II or Phase III trials for metformin’s many promising alternative uses: nonalcoholic fatty liver disease, polycystic ovary syndrome, Alzheimer’s disease, obesity, and cancer. According to the narrative now prevailing in the scholarly literature, 1) those firms have not sought to exploit metformin’s alternative uses because there is no incentive to do so, and 2) without incentives extended to firms like BMS and Merck KGaA, society will not realize many promising treatments made available through repurposing.

### A. *Metformin’s Origins*

Metformin (dimethyl biguanide) is one of three biguanides originally derived from the French lilac.<sup>216</sup> In its natural form, it has been used to treat symptoms of diabetes since medieval times.<sup>217</sup>

Its pharmacology and toxicology were studied in Paris and its structure was identified in Edinburgh.<sup>218</sup> In 1922, metformin was synthesized in Dublin and shown to lower blood glucose with fewer gastrointestinal adverse effects than its predecessors.<sup>219</sup> However, in the same year, insulin was used for the first time, distracting interest from other glucose-lowering drugs.<sup>220</sup>

Jean Sterne, a physician and clinical pharmacologist who trained in diabetology under Francis Rathery at the Hôpital de la Pitie in Paris,<sup>221</sup> held positions in 1956 at Aron Laboratories (later acquired by Lipha Pharmaceuticals, which was in turn acquired by Merck KGaA) and the Hôpital Laennec in Paris. Sterne selected metformin for clinical development and proposed

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<sup>216</sup> Ripudaman S. Hundal & Silvio E. Inzucchi, *Metformin: New Understandings, New Uses*, 63 DRUGS 1879, 1879 (2003).

<sup>217</sup> *Id.*

<sup>218</sup> Gillian Shenfield, *Metformin: Myths, Misunderstandings and Lessons from History*, 36 AUSTRALIAN PRESCRIBER 38 (2013).

<sup>219</sup> *Id.*

<sup>220</sup> *Id.*

<sup>221</sup> Gauri R. Patade & A. Rosalind Marita, *Metformin: A Journey from the Countryside to the Bedside*, 1 J. OBESITY & METABOLIC RES. 127, 127-30 (2014).

the name “Glucophage” (glucose eater).<sup>222</sup> His results were published in 1957.<sup>223</sup>

In Sterne’s trials, metformin lowered blood glucose in patients with type II diabetes, but not in people without diabetes.<sup>224</sup> Unlike sulfonylureas—first generation diabetes drugs—metformin did not stimulate insulin release, but instead increased its peripheral uptake and also reduced the release of glucose from the liver.<sup>225</sup> The other two biguanides, phenformin and buformin, were found to be more potent and, in fact, phenformin was given FDA marketing authorization by Ciba-Geigy (now Novartis) in 1959.<sup>226</sup> Increasing rates of lactic acidosis in diabetes patients taking phenformin led to a steep decline in prescriptions by 1973 and formal FDA cancellation of Ciba-Geigy’s new drug application in 1979.<sup>227</sup>

The window between the steep decline in phenformin prescriptions and its ultimate cancellation coincided with a critical period of growth in type II diabetes as a national public health problem. Between 1973 and 1978, the number of Americans diagnosed with type II diabetes increased by one million in absolute numbers and rose from 2.04% to 2.37% of the U.S. population.<sup>228</sup> Even in the 1970s, the trends that eventually led to 20% or more of population living with type II diabetes were apparent: more sedentary routines, higher caloric intakes, and increasing obesity.<sup>229</sup> Because these trends have become global, so has the potential market for effective diabetes drugs.<sup>230</sup>

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<sup>222</sup> Clifford J. Bailey & Caroline Day, *Metformin: Its Botanical Background*, 21 PRACT. DIABETES INT’L 115 (2004).

<sup>223</sup> *Id.*

<sup>224</sup> Shenfield, *supra* note 218.

<sup>225</sup> *Id.*

<sup>226</sup> See Phenformin Hydrochloride; Withdrawal of Approval of New Drug Application; Final Decision, 44 Fed. Reg. 20,967 (Apr. 6, 1979).

<sup>227</sup> *Id.*; see Shun C. Kwong & Jeffrey Brubacher, *Phenformin and Lactic Acidosis: A Case Report and Review*, 16 J. EMERGENCY MED. 881 (1998).

<sup>228</sup> Div. of Diabetes Translation, *Long-term Trends in Diabetes*, NAT’L DIABETES SURVEILLANCE SYS. (Apr. 2017), [http://www.cdc.gov/diabetes/statistics/slides/long\\_term\\_trends.pdf](http://www.cdc.gov/diabetes/statistics/slides/long_term_trends.pdf) [<https://perma.cc/64DJ-VE87>].

<sup>229</sup> See *id.*; Frank B. Hu, *Globalization of Diabetes: The Role of Diet, Lifestyle, and Genes*, 34 DIABETES CARE 1249 (2011).

<sup>230</sup> Hu, *supra* note 229.

## ***B. The Entry and Expansion of Metformin in the Healthcare System***

### **1. The Industrial Partnership Behind Glucophage**

Type II diabetes was therefore precisely the kind of disease that represented strong market potential for any given pharmaceutical firm, and the exit of phenformin from the U.S. market opened the possibility for a non-insulin therapy. Metformin had enjoyed a long life without phenformin's adverse effects in France, Sweden and, after 1977, Canada.<sup>231</sup> Despite the promising role metformin might play in the U.S. market, the patents on the composition of metformin were not only held by others, but were either expired or close to expiring.<sup>232</sup> Hatch-Waxman did not become law in the U.S. until 1984, around the same time that Lipha enjoyed increasing success with Glucophage in Europe and other markets around the world. Lipha commenced clinical trials for an oral therapy of metformin in 1987. It sought a marketing partner in the United States because the Hatch-Waxman exclusivity window was so narrow that it needed a partner with an established market presence. Indeed, the merger between Bristol-Myers and Squibb largely combined the marketing strengths of the former with the research strengths of the latter.<sup>233</sup> In 1994, Bristol-Myers Squibb (BMS) licensed the right to market metformin from Lipha.<sup>234</sup> It obtained FDA approval in 1995 under the requirement that it conduct robust Phase IV surveillance because of continuing fears over lactic acidosis.<sup>235</sup> In exchange, Lipha received the right to market BMS's hypertension drug Fosinopril in France.<sup>236</sup>

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<sup>231</sup> O.J. Lucis, *The Status of Metformin in Canada*, 128 CANADIAN MED. ASSOC. J. 24, 24 (1983).

<sup>232</sup> U.S. Patent No. 3,960,949 (filed July 9, 1974).

<sup>233</sup> BERT ROSENBLUM, *MARKETING CHANNELS: A MANAGEMENT VIEW* 609 (2011).

<sup>234</sup> *Business Brief—Bristol-Myers Squibb Co.: Rights to Diabetes Drug are Acquired from Lipha*, WALL ST. J. (Apr. 28, 1994); *FDA Advisory Panel Recommends Lipha Pharma Diabetes Drug*, DOW JONES NEWS SERV. (Mar. 18, 1994).

<sup>235</sup> *Id.*; see also Bristol-Myers Squibb, Co., Annual Report (Form 10-K) at 2 (Mar. 31, 1994); Ralph A. DeFronzo et al., *Efficacy of Metformin in Patients with Non-Insulin-Dependent Diabetes Mellitus*, 333 NEW ENG. J. MED. 541, 541 (1995); Harry C.S. Howlett & Clifford J. Bailey, *A Risk-Benefit Assessment of Metformin in Type II Diabetes Mellitus*, 20 DRUG SAFETY 489 (1999); see also Ronald Innerfield, *Letter to the Editor: Metformin-Associated Mortality in U.S. Studies*, 334 NEW ENG. J. MED. 1612-13 (1996) (noting FDA post-marketing surveillance protocol).

<sup>236</sup> Royal Soc'y of Chemistry, *Lipha, France/US—Signs Agreement with Bristol-Myers Squibb*, BULL. INT'L D'INFORMATION DROIT ET PHARMACIE (May 4, 1995).

## 2. The Marketing Behind Glucophage as Blockbuster

BMS undertook one of the largest and most expansive marketing campaigns in history, one that aimed not only to increase awareness of Glucophage, but to expand awareness of type II diabetes. While early marketing for Glucophage focused on health care providers and public awareness campaigns for medical treatment of diabetes, the FDA's flexibility on direct-to-consumer advertising gave BMS more outlets for promoting metformin sales.<sup>237</sup> BMS began reaching out to consumers through sources aimed primarily towards women, such as *Ladies' Home Journal*, *Good Housekeeping*, *Better Homes and Gardens*,<sup>238</sup> and *Star Style*.<sup>239</sup> BMS also sought to reach a slightly wider audience through sources such as the *National Enquirer* and *Star* magazine.<sup>240</sup>

Glucophage was introduced on the market in 1995.<sup>241</sup> It turned almost immediately into a blockbuster.<sup>242</sup> In 1997, sales of Glucophage increased by seventy-four percent,<sup>243</sup> and it became the leading branded product in the United States for the treatment of type II diabetes.<sup>244</sup> Glucophage maintained its status as the leading branded type II diabetes medication in 1998,<sup>245</sup> with sales increasing another forty-nine percent.<sup>246</sup> In 1999, Glucophage's sales increased an additional fifty-three percent,<sup>247</sup> exceeding one billion

<sup>237</sup> Bristol-Myers Squibb, Co., Annual Report (Form 10-K) 27 (Mar. 31, 1997); Gary Humphreys, *Direct-to-Consumer Advertising Under Fire*, 87 BULL. WORLD HEALTH ORG. (2009), <http://www.who.int/bulletin/volumes/87/8/09-040809/en/> [<https://perma.cc/GPH8-5R4K>] ("Direct-to-consumer advertising of drugs has been legal in the USA since 1985, but only really took off in 1997 when the Food and Drug Administration (FDA) eased up on a rule obliging companies to offer a detailed list of side-effects in their infomercials (long format television commercials. Since then the industry has poured money into this form of promotion, spending just under US\$5 billion last year alone.").

<sup>238</sup> See STARCH COMPARABLE ADVERTISEMENTS, JANUARY-JUNE 1999 (1999), <http://industrydocuments.library.ucsf.edu/tobacco/docs/zjnm0186> [<https://perma.cc/8UMC-YCBA>].

<sup>239</sup> See MCCALL'S STARSTYLE 91 (Feb. 2000), <http://industrydocuments.library.ucsf.edu/tobacco/docs/hzck0070> [<http://perma.cc/DK99-HBKK>].

<sup>240</sup> See NATIONAL ENQUIRER/STAR 7 (Aug. 11, 1998), <http://industrydocuments.library.ucsf.edu/tobacco/docs/hgwx0061> [<https://perma.cc/QTC7-KEPK>].

<sup>241</sup> Bristol-Myers Squibb, Co., Annual Report (Form 10-K) at 22 (Mar. 29, 1995).

<sup>242</sup> *Id.* at 22; Bristol-Myers Squibb, Co., Annual Report (Form 10-K) at 22-23 (Mar. 28, 1996).

<sup>243</sup> Bristol-Myers Squibb, Co., *supra* note 237, at 27.

<sup>244</sup> *Id.* at 27.

<sup>245</sup> Bristol-Myers Squibb, Co., Annual Report (Form 10-K) 23 (Mar. 31, 1998).

<sup>246</sup> *Id.* at 27.

<sup>247</sup> Bristol-Myers Squibb, Co., Annual Report (Form 10-K) 24 (Mar. 30, 1999).



dollars.<sup>248</sup> It also increased its market share from approximately twenty-seven percent to over thirty-one percent,<sup>249</sup> and was the third-highest-selling drug marketed by BMS.<sup>250</sup> Glucophage sales continued to increase in by thirty-two percent in 2000,<sup>251</sup> and it remained one of BMS's top-selling medications<sup>252</sup> through 2001.<sup>253</sup> In 2001, Glucophage's annual sales surpassed two billion dollars.<sup>254</sup> The entrance of generics onto the market caused a steep decline in the sales of all Glucophage formulations the following year.<sup>255</sup>

### 3. The Evergreening of Glucophage

In preparation for Glucophage's loss of Hatch-Waxman exclusivity, BMS undertook a number of measures. First, it increased its marketing budget in an attempt to increase demand specifically for Glucophage.<sup>256</sup> Second, BMS also sought to increase sales from Glucophage by creating "improved formulations" of the drug, developing two new drugs suitable for marketing in 1999.<sup>257</sup> In short, it evergreened.

The first formulation was an extended-release version of Glucophage, Glucophage XR.<sup>258</sup> The extended release formula required only one dose per day, which could improve treatment compliance of patients by simplifying their drug regimens.<sup>259</sup> Its slow-release mechanism also caused fewer side effects for patients who did not tolerate standard Glucophage well.<sup>260</sup> Glucophage XR was one of the most heavily advertised medications in 2001, with advertising costs exceeding eighty million dollars.<sup>261</sup> The second, Glucovance,<sup>262</sup> combined

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<sup>248</sup> *Id.* at 20, 24.

<sup>249</sup> *Id.* at 24.

<sup>250</sup> *Id.* at 48.

<sup>251</sup> Bristol-Myers Squibb, Co., Annual Report (Form 10-K) 21 (Mar. 30, 2000).

<sup>252</sup> *Id.* at 2.

<sup>253</sup> See Bristol-Myers Squibb, Co., Annual Report (Form 10-K) at 14 (Apr. 2, 2001) [hereinafter, Bristol-Myers Squibb, Co., 2001 Annual Report]; see also Bristol-Myers Squibb, Co., Annual Report (Form 10-K) at 29 (Apr. 1, 2002) [hereinafter Bristol-Myers Squibb, Co., 2002 Annual Report].

<sup>254</sup> Bristol-Myers Squibb, Co., 2002 Annual Report, *supra* note 253, at 14.

<sup>255</sup> *Id.* at 29.

<sup>256</sup> See Wendy L. Bonifazi, *Hard Sell: Drug Makers are Spending Billions on 'Direct-to-Consumer' Ads. But Just How Effective are the Products?*, WALL ST. J. (Mar. 25, 2002, 12:01 AM ET), <https://www.wsj.com/articles/SB1016657742405551120>.

<sup>257</sup> Bristol-Myers Squibb, Co., *supra* note 247, at 23.

<sup>258</sup> *Id.*

<sup>259</sup> Otesa Middleton, *Bristol-Myers: FDA OKs New Once-a-Day Form of Glucophage*, DOW JONES NEWS SERV. (Oct. 16, 2000).

<sup>260</sup> Bonifazi, *supra* note 256.

<sup>261</sup> *Id.*

metformin with glyburide.<sup>263</sup> Glyburide is a sulfonylurea drug which increases insulin secretion in type II diabetics, and treatment with both glyburide and metformin can be superior to treatment with either drug alone<sup>264</sup> by treating both insulin resistance and insulin deficiency at the same time, with fewer medications.<sup>265</sup> BMS's marketing schemes focused largely on persuading doctors and patients to move from standard Glucophage to one of these new formulations.<sup>266</sup>

Both Glucophage XR and Glucovance received FDA approval in 2000, and were launched the same year.<sup>267</sup> At the end of the year, sales were \$50 million and \$110 million, respectively.<sup>268</sup> The approval also earned BMS additional exclusivity on each drug—until October 2003 for Glucophage XR and July 2003 for Glucovance.<sup>269</sup> Sales increased substantially in 2001 for the individual medications, with both drugs earning over three hundred million dollars, and the Glucophage franchise overall had a forty-two percent increase in sales.<sup>270</sup> In 2002, sales of both Glucophage XR and Glucovance exceeded sales of standard Glucophage.<sup>271</sup> However, Glucophage franchise sales dropped sixty-seven percent thereafter due to a decrease in sales of standard Glucophage, Glucophage XR, and Glucovance.<sup>272</sup> BMS offered coupons for the new indications in popular outlets like the *New York Times* and the *Wall Street Journal* as well as on its website, along with a range of diabetes management tools.<sup>273</sup>

BMS made an additional move to expand profitability of the Glucophage franchise through seeking an extension of the exclusivity periods by completing clinical studies of Glucophage on children.<sup>274</sup> 21 U.S.C. § 355a permits an applicant, at the request of the FDA, to gain six additional months of market exclusivity for an already-marketed drug in exchange for performing clinical studies in pediatric patients<sup>275</sup> to assess the

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<sup>262</sup> Rebecca Thomas, *SMARTMONEY.COM: Buffing Up the Blockbusters*, DOW JONES NEWS SERV. (Aug. 7, 2000).

<sup>263</sup> Bristol-Myers Squibb, Co., *supra* note 247, at 20.

<sup>264</sup> DeFronzo et al., *supra* note 235.

<sup>265</sup> Thomas, *supra* note 262.

<sup>266</sup> Middleton, *supra* note 259.

<sup>267</sup> Bristol-Myers Squibb, Co., *supra* note 247, at 20.

<sup>268</sup> Bristol-Myers Squibb, Co., *supra* note 251, at 20.

<sup>269</sup> Bristol-Myers Squibb, Co., 2001 Annual Report, *supra* note 253, at 3.

<sup>270</sup> *Id.* at 16.

<sup>271</sup> Bristol-Myers Squibb, Co., 2002 Annual Report, *supra* note 253, at 3.

<sup>272</sup> *Id.* at 29.

<sup>273</sup> ROSENBLUM, *supra* note 233, at 614.

<sup>274</sup> *Bristol-Myers' Glucophage Gets Extended FDA Exclusivity*, DOW JONES NEWS SERV. (Mar. 20, 2000).

<sup>275</sup> 21 U.S.C. § 355a(b)(1).

safety, efficacy, and pharmacokinetic profile of the drug in children.<sup>276</sup> BMS performed pediatric studies on Glucophage, receiving approval for a six-month extension of exclusivity in 2000, which extended the termination of Glucophage's exclusivity period<sup>277</sup> from March 2000<sup>278</sup> to September 2000.<sup>279</sup> BMS subsequently earned a six-month pediatric extension for Glucovance as well, extending its exclusivity from July 2003 until January 2004.<sup>280</sup>

Initially, BMS argued that its successful pediatric studies were sufficient to merit a new indication, and, as a result, it was entitled not only to the six-month pediatric extension but also to an additional three-year exclusivity period for a new indication.<sup>281</sup> At the time, pending legislation might have granted BMS a three-year exclusivity extension for children's versions of Glucophage. However, BMS was lobbying for a total extension covering both adults and children.<sup>282</sup> Some members of Congress were supportive of BMS's position based on the same rationale that underpins current arguments in favor of incentives for new-use research.<sup>283</sup> Although pediatric studies are comparatively low-cost—about \$500,000 to \$15 million—they can be risky and burdensome for drug companies.<sup>284</sup> Liability and informed consent present problems in pediatric studies, and adverse reactions in participants can lead to negative publicity and damage drug sales for all age groups.<sup>285</sup> Others regarded BMS's efforts as a “very serious” abuse of Hatch-Waxman procedures,<sup>286</sup> and ultimately prevailed in limiting BMS to an additional six months for all patients and indications.<sup>287</sup>

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<sup>276</sup> *Bristol-Myers' Glucophage Gets Extended FDA Exclusivity*, *supra* note 274.

<sup>277</sup> *Id.*

<sup>278</sup> Bristol-Myers Squibb, Co., *supra* note 245, at 3.

<sup>279</sup> *Bristol-Myers' Glucophage Gets Extended FDA Exclusivity*, *supra* note 274.

<sup>280</sup> Bristol-Myers Squibb, Co., Annual Report (Form 10-K) at 9 (Mar. 28, 2003).

<sup>281</sup> 147 Cong. Rec. H 10,200-212 (Nov. 13, 2001).

<sup>282</sup> *Why You Still Can't Buy Cheaper Generics*, WASH. POST, Nov. 13, 2001, at F02.

<sup>283</sup> 147 CONG. REC. H10,200 (Dec. 18, 2001).

<sup>284</sup> Christopher-Paul Milne & Jon B. Bruss, *The Economics of Pediatric Formulation Development for Off-Patent Drugs*, 30 CLIN. THERAPEUTICS 2138 (2008); Rachel Zimmerman, *Child Play: Pharmaceutical Firms Win Big on Plan to Test Adult Drugs on Kids—By Doing Inexpensive Trials, They Gain 6 More Months Free from Generic Rivals—FDA: Law Does Some Good*, WALL ST. J., Feb. 5, 2001, at A1.

<sup>285</sup> *Id.*

<sup>286</sup> 147 CONG. REC. H10,200-212 (Nov. 13, 2001).

<sup>287</sup> *Bristol-Myers' Glucophage Gets Extended FDA Exclusivity*, *supra* note 274.

#### 4. Off-Label Marketing of Glucophage

The evidence as to Bristol-Myers Squibb's off-label marketing of Glucophage is indirect.<sup>288</sup> A 1998 FDA warning letter determined that BMS had issued misleading claims to physicians both as to metformin's effect on insulin resistance and as to its efficacy for promoting weight loss.<sup>289</sup> BMS's settlement with the U.S. Department of Justice for off-label marketing of Abilify included claims related to improper physician inducements to prescribe Glucophage, although no specific allegation tied those inducements to off-label uses.<sup>290</sup>

#### 5. Glucophage's Global Market

BMS expanded Glucophage (the branded name of generic metformin) into international markets.<sup>291</sup> In March 2013, BMS began collaborating with Merck KGaA (which had absorbed Lipha in 1996) to co-promote Glucophage in China through a profit-sharing agreement.<sup>292</sup> They distributed several formulations of Glucophage, including Glucovance, Glucophage XR, and a Glucophage Powder packaged in sachets.<sup>293</sup> BMS and Merck also collaborated to provide diabetes-related health and medical information to patients, as well as education for healthcare professionals.<sup>294</sup> BMS also markets a combination drug, Xigduo, in the European Union.<sup>295</sup> Xigduo combines metformin with dapagliflozin.<sup>296</sup>

<sup>288</sup> Aaron S. Kesselheim et al., *Strategies and Practices in Off-Label Marketing of Pharmaceuticals: A Retrospective Analysis of Whistleblower Complaints*, 8 PLOS MED. e1000431, at 1 (2011).

<sup>289</sup> Letter from Mark W. Askine, Regulatory Review Officer, to Stephen J. Lenart (Mar. 9, 1998), <http://wayback.archive-it.org/7993/20170112071222/http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM168270.pdf> [https://perma.cc/2J6D-2T2N].

<sup>290</sup> Press Release, U.S. Dep't of Justice, Bristol-Myers Squibb to Pay More Than \$515 Million to Resolve Allegations of Illegal Drug Marketing and Pricing (Sept. 28, 2007), [http://www.justice.gov/archive/opa/pr/2007/September/07\\_civ\\_782.html](http://www.justice.gov/archive/opa/pr/2007/September/07_civ_782.html) [https://perma.cc/R329-VQS7].

<sup>291</sup> See *Merck Serono Signs Diabetes Partnership with BMS in China*, PMLIVE (Mar. 20, 2013), [http://www.pmlive.com/pharma\\_news/merck\\_serono\\_signs\\_diabetes\\_partnership\\_with\\_bms\\_in\\_china\\_468347](http://www.pmlive.com/pharma_news/merck_serono_signs_diabetes_partnership_with_bms_in_china_468347) [https://perma.cc/3ZSR-DULE]; Lisa Nainggolan, *Canagliflozin/Metformin Combo Finally Approved in US*, MEDSCAPE (Aug. 11, 2014), <http://www.medscape.com/viewarticle/829695> [https://perma.cc/A64E-HD2L].

<sup>292</sup> *Merck KGaA—Q2 2015*, CHINA PHARMACEUTICALS & HEALTHCARE REP. 165 (Feb. 20, 2015).

<sup>293</sup> *Merck Serono Signs Diabetes with BMS in China*, *supra* note 291.

<sup>294</sup> *Id.*

<sup>295</sup> Nainggolan, *supra* note 291.

<sup>296</sup> *Id.*

Between BMS's marketing authorization and the end of its Glucophage, Glucophage XR, and Glucovance exclusivity windows, the percentage of the American population living with type II diabetes increased from 2.89% to 4.93%; in absolute numbers, the cases increased from 7.63 million to over 14 million.<sup>297</sup> The number of Americans living with diabetes has increased at an accelerated rate since 2003, now totaling approximately 22 million Americans.

### C. *The Ecosystem of Metformin Repurposing*

The result of metformin's introduction and substantial expansion was a large population of individuals on a metformin regimen that were often afflicted by other illnesses or conditions common in type II diabetes patients.<sup>298</sup> Metformin is the most widely prescribed antihyperglycemic drug in the United States, either alone or in combination with other drugs.<sup>299</sup> The entry of metformin into the diabetes treatment portfolio available to treating physicians and academic researchers immediately drew the attention of the National Institute of Diabetes and Digestive and Kidney Diseases, which from 1997 onward sponsored a number of conferences and workshops investigating metformin's mechanisms of action.<sup>300</sup> Metformin repurposing occurred not through private sector incentives, but through university research made possible by large numbers of patients and free sharing of information; serendipitous discoveries made in the process of that research; and observant physicians who noticed and reported the alternative possibilities for metformin based on patient outcomes.

As a result of metformin's trajectory in the academic, clinical, and health care systems, it has been discovered that it promotes

<sup>297</sup> Div. of Diabetes Translation, *supra* note 228.

<sup>298</sup> Diabetes Prevention Program Research Grp., *Reduction in the Incidence of Type II Diabetes with Lifestyle Intervention or Metformin*, 346 NEW ENG. J. MED. 393, 393-403 (2002).

<sup>299</sup> Christian Hampp et al., *Use of Antidiabetic Drugs in the U.S., 2003-2012*, DIABETES CARE (Mar. 12, 2014), <http://care.diabetesjournals.org/content/diacare/early/2014/03/04/dc13-2289.full.pdf> [<https://perma.cc/MS63-UZU7>] ("In 2012, 154.5 million prescriptions were dispensed for antidiabetic drugs, 78.4% of which were for noninsulin antidiabetic drugs (Table 1). About one in every two noninsulin antidiabetic drug prescriptions was for single-ingredient metformin, which was used by 11.8 million of 16.3 million noninsulin antidiabetic drug users (72.3%).").

<sup>300</sup> *Metformin Pharmacogenomics*, NAT'L INST. DIABETES & DIGESTIVE & KIDNEY DISEASES (June 6, 2012), <http://www.niddk.nih.gov/news/events-calendar/Pages/metformin-pharmacogenomic.aspx> [<https://perma.cc/YX7A-2B7T>]; *Diabetes Prevention Program (DPP)*, NAT'L INST. DIABETES & DIGESTIVE & KIDNEY DISEASES, <http://www.niddk.nih.gov/about-niddk/research-areas/diabetes/diabetes-prevention-program-dpp/Pages/default.aspx> [<https://perma.cc/Z47P-DKPE>].

weight reduction (at least in the short-term); decreases hyperinsulinaemia; improves lipid profiles; enhances endothelial function;<sup>301</sup> and is associated, although not uniformly, with a reduced risk of cardiovascular-related death.<sup>302</sup> Unlike phenformin and buformin, metformin has a much lower risk of lactic acidosis, and the few recorded cases have only occurred in patients for whom metformin was contraindicated due to conditions such as renal insufficiency or abnormal liver function.<sup>303</sup> In addition, there are no known negative effects from use during the first trimester of pregnancy, though metformin use during the third trimester may increase the risk of pre-eclampsia and perinatal mortality.<sup>304</sup>

Metformin's precise mechanism of action remains unclear.<sup>305</sup> Recent studies suggest that it primarily acts by decreasing glucose production in the liver.<sup>306</sup> In addition, metformin seems to stimulate glucose uptake by skeletal muscle, adipose tissue, and the small intestines.<sup>307</sup> It may also ameliorate the negative effect of high glucose and lipid levels on insulin action and the secretion of insulin by pancreatic cells.<sup>308</sup> Metformin has been explored as a treatment for various conditions other than type II diabetes, including polycystic ovary syndrome,<sup>309</sup> HIV-associated metabolic abnormalities, and dementia.<sup>310</sup> These alternative uses, none of which have been approved by the FDA, represent the quagmire that alternative uses pose: the absence of incentives to invest in Phase II and Phase III trials for these alternative indications, the argument goes, deprives patients of potentially life-enhancing and life-saving treatments.

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<sup>301</sup> Hundal & Inzucchi, *supra* note 216, at 1880.

<sup>302</sup> Aaron C. Pawlyk et al., *Metformin Pharmacogenomics: Current Status and Future Directions*, 63 *DIABETES* 2590, 2591 (2014).

<sup>303</sup> Robert I. Misbin, *The Phantom of Lactic Acidosis due to Metformin in Patients with Diabetes*, 27 *DIABETES CARE* 1791 (2004).

<sup>304</sup> Carlo M. Rotella et al., *Metformin Beyond Diabetes: New Life for an Old Drug*, 2 *CURRENT DIABETES REV.* 307, 311 (2006).

<sup>305</sup> Li Gong et al., *Metformin Pathways: Pharmacokinetics and Pharmacodynamics*, 22 *PHARMACOGENET GENOMICS* 820, 823 (2012) (“The molecular mechanisms underlying metformin action appear to be complex and remain a topic of considerable debate.”).

<sup>306</sup> *Id.*; see also Pawlyk et al., *supra* note 302.

<sup>307</sup> Pawlyk et al., *supra* note 302, at 2592.

<sup>308</sup> Marc L. Reitman & Eric E. Schadt, *Pharmacogenetics of Metformin Response: A Step in the Path Toward Personalized Medicine*, 117 *J. CLINICAL INVESTIGATION* 1226 (2007).

<sup>309</sup> Hundal & Inzucchi, *supra* note 216, at 1887; Rotella et al., *supra* note 304, at 310.

<sup>310</sup> Karen Kreeger, *The Many Faces of Metformin*, *PENN MED. NEWS BLOG: ARCHIVES* (Jan. 30, 2013), <http://news.pennmedicine.org/blog/2013/01/the-many-faces-of-metformin.html> [<https://perma.cc/A8N8-5CKE>]; see also Megan Brooks, *Metformin Cuts Dementia Risk in Type II Diabetes*, *MEDSCAPE MED. NEWS* (July 16, 2013), <http://www.medscape.com/viewarticle/807886> [<https://perma.cc/5CT9-TB6T>].

## 1. Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is the most common cause of female infertility in the United States.<sup>311</sup> Patients with polycystic ovary syndrome frequently suffer from insulin resistance and hyperinsulinaemia—both also commonly found in type II diabetics—which is thought to contribute significantly to the disease by increasing ovarian androgen secretion and decreasing the production of sex-hormone binding globulin which removes excess testosterone from the system.<sup>312</sup> Doctors treating women afflicted by polycystic ovary syndrome noticed that the condition affected obese women at higher rates and, for those also suffering from type II diabetes, treatment with metformin appeared to decrease body weight, insulin levels, and testosterone levels and lowered progesterone response to human chorionic gonadotropin.<sup>313</sup> In doing so, treatment also improves menstrual cycles and ovulatory function.<sup>314</sup> Continuation of metformin throughout pregnancy for polycystic ovary syndrome patients has been associated with a decline in miscarriage rate.<sup>315</sup>

Routine clinical observation of metformin's performance in treating polycystic ovary syndrome prompted academic researchers to investigate which aspects of metformin's properties targeted which biological mechanisms. Beginning with a series of studies undertaken by John Nestler at the Medical College of Richmond (Virginia Commonwealth University) in 1997 and funded by the National Institutes of Health, clinical researchers showed that metformin decreased insulin levels and that hyperinsulinemia stimulates cytochrome P450c17 $\alpha$ , a key enzyme in ovarian androgen production.<sup>316</sup> A subsequent study by Nestler and his collaborators also used

<sup>311</sup> *Infertility*, U.S. CENTERS FOR DISEASE CONTROL & PREVENTION, <http://www.cdc.gov/reproductivehealth/infertility/> [https://perma.cc/5AKQ-SAK3] (“PCOS is a hormone imbalance problem that can interfere with normal ovulation. PCOS is the most common cause of female infertility.”).

<sup>312</sup> Hundal & Inzucchi, *supra* note 216, at 1887.

<sup>313</sup> *Id.*

<sup>314</sup> See Richard Fleming et al., *Ovarian Function and Metabolic Factors in Women with Oligomenorrhea Treated with Metformin in a Randomized Double Blind Placebo-Controlled Trial*, 87 J. CLINICAL ENDOCRINOLOGY & METABOLISM 569, 569-74 (2002); see also Sandro Gerlo et al., *Randomized, Double Blind Placebo-Controlled Trial: Effects of Myo-inositol on Ovarian Function and Metabolic Factors in Women with PCOS*, 11 EUR. REV. MED. & PHARMACOLOGICAL SCI. 347 (2007).

<sup>315</sup> Daniela J. Jakubowicz et al., *Effects of Metformin on Early Pregnancy Loss in the Polycystic Ovary Syndrome*, 87 J. CLINICAL ENDOCRINOLOGY & METABOLISM 524 (2002).

<sup>316</sup> John E. Nestler & Daniela J. Jakubowicz, *Decreases in Ovarian Cytochrome P450c17 $\alpha$  Activity and Serum Free Testosterone after Reduction of Insulin Secretion in Polycystic Ovary Syndrome*, 335 NEW ENG. J. MED. 617, 617-18 (1996).

metformin to prove that hyperinsulinemia and insulin resistance were features of PCOS in both obese and non-obese women.<sup>317</sup> After these studies, Nestler and his collaborators then studied the effect of metformin on ovulation in PCOS patients. They found that, after thirty-four days of metformin treatment, non-diabetic participants had increases in both spontaneous ovulation and clomiphene-induced ovulation compared to participants not receiving metformin. The result of these findings, published in the *New England Journal of Medicine*, caused the widespread off-label prescription of metformin to treat polycystic ovary syndrome.<sup>318</sup>

Despite the long-standing rationale for using metformin in PCOS studies and prescribing it for off-label use in the treatment of PCOS, Corrine Welt at Massachusetts General Hospital has argued that metformin may not function in the traditionally understood way.<sup>319</sup> In a fourteen-week study of non-diabetic PCOS patients, Welt found that, while participants did experience decreased testosterone levels and increased ovulation, there was no indication that metformin improved insulin sensitivity.<sup>320</sup> The research did find that metformin improved glucose-mediated glucose disposal, acute insulin response to glucose, and fasting glucose levels, suggesting that metformin may have a direct effect on the ovaries, liver, and muscles through mitochondrial complex I inhibition.<sup>321</sup>

Although there appears to be a wealth of research suggesting that metformin is an effective treatment for PCOS, clinical practice guidelines do not recommend metformin as a first-line treatment for any aspect of PCOS.<sup>322</sup> This primarily appears to be due to the fact that there are more efficacious treatments with fewer risks than those posed by metformin.<sup>323</sup> For example, lifestyle modification is more beneficial in the improvement of

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<sup>317</sup> John E. Nestler & Daniela J. Jakubowicz, *Lean Women with Polycystic Ovary Syndrome Respond to Insulin Reduction with Decreases in Ovarian P450c17a Activity and Serum Androgens*, J. CLINICAL ENDOCRINOLOGY & METABOLISM 4075, 4075, 4077 (1997).

<sup>318</sup> Cindy T. Pau, et al., *Metformin Improves Glucose Effectiveness, Not Insulin Sensitivity: Predicting Treatment Response in Women with Polycystic Ovary Syndrome in an Open-Label, Interventional Study*, 99 J. CLINICAL ENDOCRINOLOGY & METABOLISM 1870, 1871 (2014).

<sup>319</sup> *Id.*

<sup>320</sup> *Id.* at 1874.

<sup>321</sup> *Id.*

<sup>322</sup> See Richard S. Legro et al., *Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline*, 98 J. CLINICAL ENDOCRINOLOGY & METABOLISM 4565 (2013).

<sup>323</sup> *Id.* at 4580-82.



impaired glucose tolerance.<sup>324</sup> In addition, the clinical practice guidelines only suggest the use of metformin to treat infertility when treatment with clomiphene alone is not sufficient.<sup>325</sup> Metformin is likewise only suggested as a second-line treatment in adolescents; however, the clinical practice guidelines do cite some studies suggesting that metformin may be more beneficial to adolescent PCOS patients than adult patients.<sup>326</sup>

## 2. Cancer

Metformin's use in cancer therapy is associated both with its ability to reduce insulin levels and with its effect on activating anti-tumor protein production.<sup>327</sup> Beginning in the early 1990s, clinical researchers at the University of Texas discovered the relationship between insulin and insulin-like receptors in the growth of colon cancer.<sup>328</sup> The discovery prompted researchers worldwide to investigate the relationship between insulin, insulin resistance, and various forms of cancer.<sup>329</sup> The continuing results of that work have shown that many cancer cells express insulin receptors<sup>330</sup> and have increased glucose uptake.<sup>331</sup> Insulin uptake activates pathways that support mRNA translation, cell survival, and cell proliferation.<sup>332</sup> Treatment with metformin lowers insulin levels and reduces glucose production, which limits the activation of these pathways<sup>333</sup> and which may slow the reproduction of cancer cells.<sup>334</sup> Alternatively, metformin may increase cancer survival

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<sup>324</sup> *Id.* at 4580-81.

<sup>325</sup> *See id.* at 4581.

<sup>326</sup> *Id.* at 4582-83.

<sup>327</sup> Ryan J.O. Dowling, et al., *Understanding the Benefit of Metformin Use in Cancer Treatment*, 9 BMC MED. (2011), <http://bmcmmedicine.biomedcentral.com/articles/10.1186/1741-7015-9-33> [<https://perma.cc/S79D-T9DA>].

<sup>328</sup> Yan-Shi Guo et al., *Characterization of Insulinlike Growth Factor I Receptors in Human Colon Cancer*, 102 GASTROENTEROLOGY 1101 (1992); Yan-Shi Guo et al., *Insulinlike Growth Factor—Binding Protein Modulates the Growth Response to Insulinlike Growth Factor 1 by Human Gastric Cancer Cells*, 104 GASTROENTEROLOGY 1595 (1993).

<sup>329</sup> *See* Michael Pollack, *Repurposing Biguanides to Target Energy Metabolism for Cancer Treatment*, 20 NATURE MED. 591, 592 (2014).

<sup>330</sup> *Id.*

<sup>331</sup> Alessandra Leone et al., *New Perspective for an Old Diabetic Drug: Metformin as an Anticancer Agent*, 159 CANCER TREATMENT & RES. 355, 358 (2014).

<sup>332</sup> Pollack, *supra* note 329.

<sup>333</sup> *Id.*

<sup>334</sup> *See* Leone et. al., *supra* note 331, at 367.

through mTOR inhibition.<sup>335</sup> Whatever the mechanism, long-term treatment of type II diabetes with metformin correlates with a lower incidence of cancer.<sup>336</sup> In studies of diabetic and non-diabetic cancer patients, metformin treatment appears to improve overall cancer survival for both groups.<sup>337</sup>

In a 2005 paper published in the *British Medical Journal*, researchers at the University of Dundee hypothesized that metformin's mechanism of action activated the tumor suppressing protein kinase LKB1.<sup>338</sup> In other words, the association between metformin and improved cancer outcomes was not just its effect on insulin or insulin receptors, but also involved an independent effect on tumor-suppressing enzymes. The paper prompted a wave of academic research in Canada, the United States, and the United Kingdom, into not only the association between metformin use and reduced cancer risk, but also the extent and nature of its ability to suppress cancer cell growth.<sup>339</sup> Josie Evans at Dundee and her research team performed a population study using two databases, a diabetes clinical information system (DARTS) and a database of dispensed prescriptions (MEMO), to identify type II diabetes patients, their treatments, and whether they were later admitted to the hospital with a diagnosis for malignant cancer.<sup>340</sup>

Based on epidemiological studies identifying an increase in cancer incidence in patients with type II diabetes, Bowker et al. performed a subsequent population study, using the databases of Saskatchewan Health to explore the role that antidiabetic treatments may have on this relationship.<sup>341</sup> They found that patients receiving metformin, either alone or in combination with other drugs, for the treatment of type II diabetes were

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<sup>335</sup> Hua Xu et al., *Validating Drug Repurposing Signals Using Electronic Health Records: A Case Study of Metformin Associated with Reduced Cancer Mortality*, J. AM. MED. INFORMATICS ASSOC. 179 (2014).

<sup>336</sup> See Leone et. al., *supra* note 331, at 363-66.

<sup>337</sup> Xu et al., *supra* note 335, at 179.

<sup>338</sup> See Josie M.M. Evans et al., *Metformin and Reduced Risk of Cancer in Diabetic Patients*, 330 BMJ 1304 (2005).

<sup>339</sup> Pamela J. Goodwin & Vuk Stambolic, *Obesity and Insulin Resistance in Breast Cancer—Chemoprevention Strategies with a Focus on Metformin*, 20 BREAST S31, S32 (2011); see Evans et al., *supra* note 338.

<sup>340</sup> Evans et al., *supra* note 338, at 1304.

<sup>341</sup> Samantha L. Bowker et al., *Increased Cancer-Related Mortality for Patients with Type II Diabetes Who Use Sulfonylureas or Insulin*, 29 DIABETES CARE 254 (2006).

significantly less likely to die from cancer-related causes than patients being treated with sulfonylureas or insulin.<sup>342</sup>

In the United States, results from laboratory and limited cohort studies both domestically and from British and Canadian researchers have been extrapolated over larger populations using databases assembled by major medical research organizations. Sao Jiralerspong et al. at the Baylor School of Medicine performed a retrospective study of 68 diabetic breast cancer patients taking metformin during neoadjuvant (administration of chemical agents before a main treatment) chemotherapy (the metformin group), 87 diabetic patients not taking metformin during neoadjuvant chemotherapy (the nonmetformin group), and 2,374 nondiabetic breast cancer patients (the nondiabetic group) using M.D. Anderson Cancer Center's Breast Cancer Management System Database.<sup>343</sup> They found that diabetic patients being treated with metformin in addition to their other neoadjuvant therapy had significantly higher rates of response than diabetic patients who were treated with other antidiabetic therapies.<sup>344</sup>

Building on this research, Patricia Goodwin and colleagues at the University of Toronto administered metformin to non-diabetic patients with recently diagnosed breast cancer prior to tumor excision.<sup>345</sup> Participants received metformin for a mean of eighteen days, continuing until the evening before surgery.<sup>346</sup> Goodwin's study not only found a decrease in tumor proliferation following metformin treatment, but also an increase in apoptosis.<sup>347</sup> A collaboration between researchers at the University of Texas, Vanderbilt, and Mayo Clinic linked two large electronic health record databases from Vanderbilt University Medical Center and Mayo Clinic with their tumor registries, and constructed a cohort including 32,415 adults with a cancer

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<sup>342</sup> *Id.* at 255-56. Bowker et al. admit that population studies using administrative databases often fail to account for important clinical information such as glycemic control, weight, BMI, or smoking status.

<sup>343</sup> Sao Jiralerspong et al., *Metformin and Pathologic Complete Responses to Neoadjuvant Chemotherapy in Diabetic Patients with Breast Cancer*, 20 J. CLINICAL ONCOLOGY 3297, 3298 (2009).

<sup>344</sup> *Id.* at 3300.

<sup>345</sup> Saroj Niraula et al., *Metformin in Early Breast Cancer: A Prospective Window of Opportunity Neoadjuvant Study*, 135 BREAST CANCER RES. & TREATMENT 821 (2012).

<sup>346</sup> *Id.* at 824.

<sup>347</sup> Pamela J. Goodwin, *Insulin in the Adjuvant Breast Cancer Setting: A Novel Therapeutic Target for Lifestyle and Pharmacologic Interventions?*, 26 J. CLINICAL ONCOLOGY 833 (2008); Pamela J. Goodwin, *Metformin in Breast Cancer: Time for Action*, 27 J. CLINICAL ONCOLOGY 3271-3273 (2009); see Saroj Niraula et al., *supra* note 345, at 826; see also Jiralerspong et al., *supra* note 343, at 3297.

diagnosis at Vanderbilt and 79,258 cancer patients at Mayo from 1995 to 2010.<sup>348</sup> Using automated informatics methods, they identified type II diabetes patients within the cancer cohort and determined their drug exposure information, as well as other covariates such as smoking status.<sup>349</sup> They evaluated health records for all-cause mortality and patients' metformin exposure, adjusted for age at diagnosis, sex, race, body mass index, tobacco use, insulin use, and cancer type.<sup>350</sup> Among all Vanderbilt cancer patients, metformin was associated with a 22% decrease in overall mortality compared to other oral hypoglycemic medications, and with a 39% decrease compared to type II diabetes patients on insulin only.<sup>351</sup> Diabetic patients on metformin also had a 23% improved survival compared with non-diabetic patients.<sup>352</sup> The associations were replicated using Mayo Clinic's electronic health records data. Many site-specific cancers, including breast, colorectal, lung, and prostate, demonstrated reduced mortality with metformin use in at least one electronic health record. Metformin has been associated with positive outcomes or cell inhibition in colorectal, pancreatic, hepatocellular, lung,<sup>353</sup> prostate, endometrial, and ovarian cancers, as well as gliomas.<sup>354</sup>

Like other potential uses, the use of metformin to treat cancer needs more exploration to answer several questions.<sup>355</sup> First, metformin's exact mechanism of effect on cancer cells is currently unknown.<sup>356</sup> Second, research has uncovered a generalized anticancer effect, but metformin may be most effective against certain types of cancer<sup>357</sup> such as cancers of the liver and pancreas.<sup>358</sup> Finally, cancer treatment may require higher doses and different methods of delivery than those used to treat diabetes; oral use may not result in sufficient concentration of metformin to achieve a satisfactory clinical result.<sup>359</sup> It is also possible that the other biguanides, such as

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<sup>348</sup> Xu et al., *supra* note 335.

<sup>349</sup> *Id.*

<sup>350</sup> *Id.*

<sup>351</sup> *Id.*

<sup>352</sup> *Id.*

<sup>353</sup> Ana Elisa Lohmann & Pamela J. Goodwin, *Hype Versus Hope: Metformin and Vitamin D as Anticancer Agents*, AM. SOC'Y CLINICAL ONCOLOGY EDUC. BOOK e69-e74 (2014).

<sup>354</sup> Ryan J.O. Dowling et al., *Understanding the Benefit of Metformin Use in Cancer Treatment*, 9 BMC MED. 2 (2011).

<sup>355</sup> Pollack, *supra* note 329, at 593.

<sup>356</sup> See Xu et al., *supra* note 335, at 184.

<sup>357</sup> *Id.*

<sup>358</sup> Leone et al., *supra* note 331.

<sup>359</sup> Pollack, *supra* note 329, at 592.

phenformin, may be more effective for cancer treatment because they are less dependent on active transport, addressing some of the potential dosing and delivery issues.<sup>360</sup> Although other biguanides are more toxic than metformin, they still have a lower risk of serious side effects than most conventional cancer treatments.<sup>361</sup>

### 3. Non-Alcoholic Fatty Liver Disease

The use of metformin to treat non-alcoholic fatty liver disease is attributable to clinicians at Johns Hopkins, who prescribed metformin to treat the condition notwithstanding its contraindication for patients with liver disease.<sup>362</sup> Nonalcoholic fatty liver disease is a term used to describe the accumulation of fat in the liver of people who drink little or no alcohol.<sup>363</sup> Nonalcoholic fatty liver disease is common and, for most people, causes no signs and symptoms and no complications.<sup>364</sup> But in some people with nonalcoholic fatty liver disease, the fat that accumulates can cause inflammation and scarring in the liver.<sup>365</sup> At its most severe, nonalcoholic fatty liver disease can progress to liver failure.<sup>366</sup>

Non-alcoholic fatty liver disease is a common condition in patients with type II diabetes and insulin resistance.<sup>367</sup> Other than interest in using metformin to treat fatty liver disease, there is no pharmacological agent known to prevent or reverse fatty liver disease.<sup>368</sup> Because it is often associated with obesity

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<sup>360</sup> Samuel E. Weinberg & Navdeep S. Chandel, *Targeting Mitochondria Metabolism for Cancer Therapy*, 11 NATURE CHEMICAL BIOLOGY 9, 9-15 (2015).

<sup>361</sup> Pollack, *supra* note 329.

<sup>362</sup> Hui Zhi Lin et al., *Metformin Reverses Fatty Liver Disease in Obese, Leptin-deficient Mice*, 6 NATURE MED. 998, 998 (2000) (“Recently, some clinicians noted improved liver test abnormalities in a few patients with fatty liver disease that were treated with metformin. However, because lactic acidosis is a rare complication of metformin, liver disease is often considered to be a contraindication for metformin therapy . . .”).

<sup>363</sup> *Nonalcoholic Fatty Liver Disease*, MAYO CLINIC, <http://www.mayoclinic.org/diseases-conditions/nonalcoholic-fatty-liver-disease/basics/definition/con-20027761> [<https://perma.cc/27B3-MHHS>].

<sup>364</sup> Emily Carey et al., *Nonalcoholic Fatty Liver Disease*, CLEVELAND CLINIC (Mar. 2013), <http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/hepatology/nonalcoholic-fatty-liver-disease/> [<https://perma.cc/AR58-R692>].

<sup>365</sup> *Id.*

<sup>366</sup> *Id.*

<sup>367</sup> Lin et. al., *supra* note 362.

<sup>368</sup> *Treatment and Drugs: Fatty Liver Disease*, MAYO CLINIC <http://www.mayoclinic.org/diseases-conditions/nonalcoholic-fatty-liver-disease/basics/treatment/con-20027761> [<https://perma.cc/G53B-NUAZ>] (“No FDA-approved drug treatment exists for nonalcoholic fatty liver disease, but a few drugs are being studied with promising results.”).

and type II diabetes, treatment is primarily focused on weight management through diet and exercise.<sup>369</sup> However, this is not always sufficient to improve outcomes in fatty liver disease patients,<sup>370</sup> and it is not helpful for normal-weight patients.<sup>371</sup>

Based on a strong association between fatty liver disease and hyperinsulinemia and insulin resistance in patients,<sup>372</sup> Lin et al. tested metformin's effectiveness in obese, hyperinsulinemic, and insulin-resistant mice with fatty liver disease.<sup>373</sup> They found that both a combination of caloric restriction and metformin and caloric restriction alone led to improvement in liver enlargement, but the effect was greater with metformin treatment.<sup>374</sup> In addition, metformin treatment virtually eliminated fat accumulation in the liver, whereas calorie restriction alone had no effect on fat accumulation.<sup>375</sup>

Building on Lin's work, Giulio Marchesini and his team at Italy's University of Bologna completed the first human study using metformin to treat fatty liver disease.<sup>376</sup> They administered metformin to non-diabetic patients with fatty liver disease for four months.<sup>377</sup> In addition, patients were encouraged to reduce their lipid and non-complex carbohydrate intake and to increase their physical activity.<sup>378</sup> Following treatment, patients who received metformin in addition to diet and exercise demonstrated a greater decrease in alanine transaminase concentration as well as liver volume.<sup>379</sup> Participants receiving metformin also had significant increases in insulin sensitivity.<sup>380</sup> Marchesini et al. concluded that diet and exercise combined with metformin was more effective at treating fatty liver disease than diet and exercise alone.<sup>381</sup> Marchesini's study spurred a number of small adult trials as well as research into therapies for children and adolescents.

Academic physicians at the University of Colorado-Denver developed a pediatric study for metformin therapy, because rising pediatric obesity rates corresponded to increases in the

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<sup>369</sup> *Id.*

<sup>370</sup> *Id.*

<sup>371</sup> Giulio Marchesini et al., *Metformin in Non-Alcoholic Steatohepatitis*, 358 LANCET 893, 893 (2001).

<sup>372</sup> Lin et al., *supra* note 362, at 998.

<sup>373</sup> *Id.* at 1001.

<sup>374</sup> *Id.* at 998.

<sup>375</sup> *Id.* at 998-99.

<sup>376</sup> Marchesini et al., *supra* note 371, at 894.

<sup>377</sup> *Id.* at 893-94.

<sup>378</sup> *Id.* at 894.

<sup>379</sup> *Id.*

<sup>380</sup> *Id.*

<sup>381</sup> *Id.*

incidence of fatty liver disease among children and adolescents.<sup>382</sup> The shortage of effective treatments for fatty liver disease is particularly troubling in this context for two reasons: (1) fatty liver disease is more likely to progress to cirrhosis and fibrosis in youth, and (2) lifestyle changes are more difficult to sustain in adolescents.<sup>383</sup> They administered metformin to obese, non-diabetic twelve-to-eighteen-year-old participants who either exhibited existing fatty liver disease or who were at risk for fatty liver disease.<sup>384</sup> After six months of treatment, participants with fatty liver disease showed significant decreases in fasting insulin and fatty liver score, and fatty liver disease resolved completely in several subjects.<sup>385</sup> No participants without fatty liver disease at baseline developed fatty liver disease while undergoing metformin treatment.<sup>386</sup>

To date, there are no approved drugs to treat non-alcoholic fatty liver disease and, based on these studies, metformin is widely prescribed off-label to treat the condition.<sup>387</sup>

## V. THE REPURPOSING OF METFORMIN AND THE CURRENT INCENTIVE DEBATE

Metformin therefore represents exactly the kind of problem current scholars and industry advocates say occurs with drug repurposing. Bristol-Myers Squibb and Merck KGaA sit upon a trove of consumption, off-label prescription, pharmacological, toxicological, and clinical trial data related to metformin. That data may potentially support new drug applications for the wide range of indications that have a long history of successful use, like polycystic ovary syndrome, and new indications, like the cancers for which metformin appears to be a promising therapy. Moreover, these companies already have dedicated marketing and promotion staff to metformin who could, with relative ease, market it for other purposes. The reason the companies are not contributing their knowledge nor

<sup>382</sup> Kristen J. Nadeau et al., *Treatment of Non-Alcoholic Fatty Liver Disease with Metformin Versus Lifestyle Intervention in Insulin-Resistant Adolescents*, 10 PEDIATRIC DIABETES 5, 5 (2008).

<sup>383</sup> *Id.* at 6.

<sup>384</sup> *Id.*

<sup>385</sup> *Id.* at 9.

<sup>386</sup> *Id.*

<sup>387</sup> Ligong Chen et al., *OCT1 Is a High-Capacity Thiamine Transporter that Regulates Hepatic Steatosis and Is a Target of Metformin*, 111 PROC. NAT'L ACAD. SCI. 9983 (2014); Press Release, Intercept Receives Breakthrough Therapy Designation from FDA for Obeticholic Acid for Nonalcoholic Steatohepatitis (NASH) with Liver Fibrosis, INTERCEPT (Jan. 29, 2015), <http://ir.interceptpharma.com/releasedetail.cfm?releaseid=893699> [<https://perma.cc/HX46-D5F6>].

attempting to develop new indications, the argument goes, is because doing so would result in no benefit to the firms.<sup>388</sup> Physicians would simply prescribe metformin for an alternative, off-patent or off-exclusivity indication. Indeed, because so many of metformin's uses are related to patients with comorbidities—more than one illness—that seems probable.<sup>389</sup>

**A. *Metformin Ascended as a Repurposing Candidate through Governmental and Academic Investments***

Yet without industry investment (Bristol-Myers Squibb has supported studies for metformin for its primary indication—type II diabetes), metformin became a breakthrough therapy for polycystic ovary syndrome and nonalcoholic fatty liver disease, and “numerous early stage clinical trials are currently under way to investigate metformin’s potential to prevent an array of cancers”. For polycystic ovary syndrome, metformin’s promise was discovered as most repurposed drugs have been discovered: through serendipity. For nonalcoholic fatty liver disease, researchers prescribed metformin for patients that had a *contraindicated* condition—liver disease—because they understood how metformin worked in diabetes patients and why it might work for nonalcoholic fatty liver disease. Metformin’s potential for cancer prevention and treatment—including early stage clinical trials—was similarly driven by academic researchers and financial support from the National Cancer Institute and the National Institute for Diabetes and Digestive and Kidney Diseases.<sup>390</sup>

This finding is consistent with analyses undertaken over a wider range of breakthrough drugs.<sup>391</sup> In a recent study, Aaron Kesselheim, Yongtian Tina Tan, and Jerry Avorn determined that of twenty-six transformative drugs approved between 1984 and 2009, a complex set of relationships between academic researchers, industry, and governmental funders explained the emergence of breakthrough therapies; nine drugs were repurposed.<sup>392</sup> Their findings at the very least suggest caution in

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<sup>388</sup> See Graham Rena et al., *Molecular Mechanisms of Action of Metformin: Old or New Insights*, 56 *DIABETOLOGY* 1898, 1904 (2013) (“What about new drugs? At first sight, the impressive safety profile and low cost of metformin itself might discourage pharmaceutical companies from developing drugs that act in a similar manner.”).

<sup>389</sup> See *id.*

<sup>390</sup> *Metformin: Can a Diabetes Drug Help Prevent Cancer?*, NAT’L CANCER INST., <http://www.cancer.gov/about-cancer/causes-prevention/research/metformin> [<https://perma.cc/5PF4-9Y9B>].

<sup>391</sup> Arti Rai & Rebecca Eisenberg, *The Public Domain: Bayh-Dole Reform and the Process of Biomedicine*, 66 *LAW & CONTEMP. PROB.* 289 (2003).

<sup>392</sup> Kesselheim et al., *supra* note 43, at 396.



determining which actors in the health system, operating under different incentives, are best placed to promote repurposing activity.

***B. Using Currently Proposed Market Exclusivity Incentives Would Not Have Resulted in Metformin's Ascent as a Repurposed Drug***

**1. Clinical Trials for Alternative Uses May Undermine Metformin's Profitability for Its Primary Indication**

Conversely, it is not clear that extending market exclusivity incentives in the hopes of generating more repurposing activity—especially Phase II and Phase III clinical trials—would generate the kinds of investments advocates predict. First, there is a chance that additional Phase II or Phase III trials for alternative indications may expose adverse events—like cardiac events—that would negatively impact Bristol-Myers Squibb's and Merck KGaA's global market for the drug.<sup>393</sup> Because type II diabetes is associated with four times greater risk of developing cardiovascular disease compared with nondiabetic patients, extensive clinical trials for alternative indications are likely to bring greater clarity as to the relationship between metformin—alone or in combination with other drugs—with cardiac events, including the possibility of a negative relationship.<sup>394</sup>

In a meta-analysis of randomized controlled trials evaluating metformin efficacy (in studies of metformin versus diet alone, versus a placebo, and versus no treatment; metformin as an add-on therapy; and metformin withdrawal) against cardiovascular morbidity or mortality in patients with type II diabetes, researchers at the Universite de Poitiers concluded that “[a]lthough metformin is considered the gold standard, its

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<sup>393</sup> Thayer, *supra* note 24 (“Other companies shy away from repurposing efforts after approval because of what they might uncover. Merck & Co.’s experience with Vioxx is a cautionary tale, points out David P. Cavalla, founder of Cambridge, England-based Numedicus, which provides services around repurposing. After getting approval for the drug as an analgesic, Merck began testing it for treating colon polyps. Cardiovascular issues that arose had to be reported to regulators and scuttled the blockbuster entirely.”).

<sup>394</sup> Erin L. St. Onge et al., *A Review of Cardiovascular Risks Associated with Medications Used to Treat Type-2 Diabetes Mellitus*, 34 PHARMACY & THERAPEUTICS 368 (2009).

benefit/risk ratio remains uncertain. We cannot exclude a 25% reduction or a 31% increase in all-cause mortality.”<sup>395</sup>

There is therefore a strong incentive for firms to avoid additional knowledge of metformin risks given its already lucrative status.

## **2. Current Proposals Would Encourage Firms to Explore Only One (Potentially Suboptimal) Alternative Use**

Second, even if product liability hesitations were overcome, the incentives now proposed might not be enough to move metformin into clinical trials for alternative uses. Those incentives, advocated by members of Congress like Orrin Hatch and industry leaders like Don Frail, include *twelve to fifteen years of market exclusivity on the entire drug for a new use that meets an unmet medical need*. Consider a law that creates a class of drugs designated as “dormant therapies,” new drugs or new biological products made the subject of a request for designation in compliance with the legislation.<sup>396</sup> The assignment of dormant therapy would be given to a drug or new biological product that had been determined to have insufficient patent protection and that meets an unmet medical need, improves outcomes, or reduces risk compared to existing treatments. In its request for designation of dormant therapy, the manufacturer would provide a list of all patents and applications for patents to which the manufacturer has rights, and must agree to waive those rights in order to receive the designation.<sup>397</sup> The law, as it was proposed, would provide fifteen years’ data exclusivity to encourage manufacturers to investigate a dormant therapy to determine if it could prevent, slow the progression of, or cure diseases. The Secretary of Health and Human Services would be required to make its determinations available to the public, and could not approve a generic for a drug or biosimilar or a biological product that has the same active ingredient as a drug that has been designated a dormant therapy.<sup>398</sup>

Under that regime, if Bristol-Myers Squibb or Merck KGaA obtained a new use approval for metformin for polycystic ovary syndrome or cancer, it would then be able to re-impose the high

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<sup>395</sup> Rémy Boussageon et al., *Reappraisal of Metformin Efficacy in the Treatment of Type 2 Diabetes: A Meta-Analysis of Randomized Controlled Trials*, 9 PLOS MED. e1001204 (2012).

<sup>396</sup> Dormant Therapies Act, S. 3004, 113th Cong. (2014)

<sup>397</sup> *Id.*

<sup>398</sup> *Id.*

prices it charged for metformin for all uses, including type II diabetes, with severe effects on the millions of people who now take the drug because it is incredibly affordable to do so.<sup>399</sup> More importantly, why then would it undertake the costs of clinical trials for metformin's other uses if it exhausted the benefit of the law with the first dormant therapy designation that satisfied the statutory requirement? In the aggregate, such a regime would *reduce* repurposing activity.

One of the emerging lessons from the Orphan Drug Act experience is that once an exclusivity designation is authorized under law, it will tend to attract more research and investment, even when the designation results in the raised cost of previously inexpensive medications.<sup>400</sup> Indeed, as this Article and substantial medical evidence shows, the primary incentive problem is the funding of Phase II and Phase III clinical trials for new indications, for which an alternative reimbursement structure might be constructed without giving market exclusivity with unpredictable effects.<sup>401</sup>

### ***C. Creating Statutory Market Exclusivity Extensions for New Uses That Are Not Absolute Would be Vulnerable to Off-Label Prescription***

Even should more effective use patents or market exclusivity mechanisms be adopted to encourage new use approvals, there are significant practical limitations. The uses for which metformin has shown therapeutic promise could easily justify a physician's prescription as part of a relatively minor intervention. So even if changes in the law allowed Bristol-Myers Squibb to obtain market exclusivity for metformin to treat polycystic ovary syndrome, nonalcoholic fatty liver disease, or breast cancer, prescribers could still circumvent that market

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<sup>399</sup> Michael T. Eaddy et al., *How Patient Cost-Sharing Trends Affect Adherence and Outcomes*, 37 PHARMACY & THERAPEUTICS 45 (2012); Lisa M. Hess et al., *Measurement of Adherence in Pharmacy Administrative Databases: A Proposal for Standard Definitions and Preferred Measures*, 40 ANNALS PHARMACOTHERAPY 1280 (2006); Ramin Mojtatabi & Mark Olfson, *Medication Costs, Adherence, and Health Outcomes Among Medicare Beneficiaries*, 22 HEALTH AFF. 220 (2003); Rishi Sikka et al., *Estimating Medication Adherence Using Administrative Claims Data*, 11 AM. J. MANAGED CARE 449 (2005).

<sup>400</sup> Letter from Orrin Hatch, Chuck Grassley, & Tom Cotton, U.S. Senators, to Hon. Gene L. Dodaro, Comptroller Gen. of U.S. Gov't Accountability Office (Mar. 3, 2017), <https://kaiserhealthnews.files.wordpress.com/2017/03/gao-request-oda-signed1-002.pdf> [<https://perma.cc/SPG9-YRHP>].

<sup>401</sup> Paul & Lewis-Hall, *supra* note 54, at 187.

exclusivity by instructing use of metformin for short-term weight loss as part of a broader lifestyle intervention.<sup>402</sup>

#### ***D. Additional Market Exclusivities May Undermine Industry-Academic Collaboration***

Repurposing has often been accomplished through industry-university collaborations, especially when industry-based researchers encounter unusual results in the course of investigating a drug candidate for a specific purpose and then reach out to academic experts to help them explain the phenomena. It is possible that eliminating the uncertainty surrounding method-of-use patents, extending market exclusivity for drugs approved through the section 505(b)(2) process, or even off-label prescription as discussed below may facilitate more of these partnerships and therefore more repurposed candidates. In the current system, there is overwhelming consensus that substantial transaction costs stand in the way of effective partnerships between large pharmaceutical firms and smaller biotechnology players, universities, and public research institutions.<sup>403</sup> With entitlements to intellectual property clearly delineated, the argument goes, large pharmaceutical firms would be positioned to control research and development partnerships so as to protect lucrative IP assets while licensing aspects of the research and development process to the entities best suited to undertake their respective tasks.<sup>404</sup>

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<sup>402</sup> SARAH H. BEACHY ET AL., DRUG REPURPOSING AND REPOSITIONING: WORKSHOP SUMMARY 47 (2014), <http://www.ncbi.nlm.nih.gov/books/NBK202175/pdf/TOC.pdf> [<https://perma.cc/FM6L-E2Y3>].

<sup>403</sup> Ian Cockburn & Rebecca Henderson, *Public-Private Interaction in Pharmaceutical Research*, 93 PROC. NAT'L ACAD. SCI. 12725 (1996); Peter Lee, *Transcending the Tacit Dimension: Patents, Relationships, and Organizational Integration in Technology Transfer*, 100 CAL. L. REV. 1503, 1534 (2012); Michael D. Rawlins, *Cutting the Cost of Drug Development?*, 3 NATURE REVIEWS DRUG DISCOVERY 360 (2004).

<sup>404</sup> Katherine J. Strandburg, *Intellectual Property at the Boundary* (N.Y.U. Public Law & Legal Theory Working Papers, Paper No. 432, 2013), [http://lsr.nellco.org/cgi/viewcontent.cgi?article=1431&context=nyu\\_plltwp](http://lsr.nellco.org/cgi/viewcontent.cgi?article=1431&context=nyu_plltwp) [<https://perma.cc/T7XY-94YJ>] (“Of course, intellectual property rights may be more or less well-suited to different creative enterprises. If creative outputs are well-delineated, with relatively well-understood potential embodiments and relatively predictable downstream co-mingling, the legally-defined contours of patent or copyright may ‘fit’ relatively well. Unfortunately, this is rarely the case, meaning that, despite its potential to solve various incentive problems, intellectual property is a costly system for structuring creative interactions.”); COMMISSION EUR. COMMUNITIES, VOLUNTARY GUIDELINES FOR UNIVERSITIES AND OTHER RESEARCH INSTITUTIONS TO IMPROVE THEIR LINKS WITH INDUSTRY ACROSS EUROPE 10-12 (2007).

While it is an open question, there are good reasons to doubt that greater control over a drug's marketability will not encourage effective knowledge sharing.<sup>405</sup> Peter Lee has argued in the context of Myriad Genetics' BRCA1 and BRCA2 diagnostic tests that its selective control over the genes (before that control was deemed partially invalid by the U.S. Supreme Court) deterred rather than encouraged research into both the underlying genes as well as potentially improved diagnostics.<sup>406</sup> The problem of firms and their internal researchers having discrete disease portfolios and therefore limiting new use investigations to within those controlling schema would appear to be steepened rather than resolved by creating incentives to keep drugs in house.<sup>407</sup>

***E. Additional Market Exclusivities Will Unavoidably Implicate Socially Undesirable Evergreening Strategies***

Between the current Hatch-Waxman regime and the kind of market exclusivity envisioned under many recent legislative proposals is the possibility of use-by-use determinations as now undertaken by the FDA for new drug applications that cite literature (published versions of studies) or a previously

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<sup>405</sup> Liza S. Vertinsky, *Patents, Partnerships, and the Precompetitive Collaboration Myth*, 48 U.C. DAVIS L. REV. 1509, 1540 (2015) ("The incentive problems that patents create for partnerships also lead to higher transaction costs in the negotiation of partnership agreements, particularly provisions concerning intellectual property ownership and use, and increase the possibility that no agreement will be reached").

<sup>406</sup> Peter Lee, *The Supreme Court's Myriad Effects on Scientific Research: Definitional Fluidity and the Legal Construction of Nature*, 5 U.C. IRVINE L. REV. 1077, 1083-84 (2015) ("Myriad's narrow conception of 'research' use, however, created difficulties for scientists seeking to conduct BRCA research. In May 1998, Myriad Genetics accused University of Pennsylvania cancer researchers Dr. Arupa Ganguly and Dr. Haig Kazazian of infringing five of its patents. Myriad offered the researchers a license, but it was 'of very limited scope,' as it would have prevented the scientists from completing diagnostic testing services for BRCA1 or conducting comprehensive research on the gene. Ultimately, the researchers ceased 'all BRCA1 and BRCA2 testing, whether for research or clinical purposes.' In particular, the inability to share diagnostic results with test subjects made it more difficult for scientists to enlist patients in research studies. This restriction especially discouraged the most important potential research subjects—those with a family history of breast cancer—from participating in studies. Although Myriad offered to perform full-gene 'research' sequencing at its own laboratory for a discount, the fee was still substantial. Furthermore, the requirement of submitting samples to Myriad would have foreclosed researchers from utilizing their own preferred sequencing techniques. Commentators suggest that chilled research on the BRCA1 and BRCA2 genes may have delayed important discoveries, such as the role of 'big deletions' in developing breast cancer.").

<sup>407</sup> Thomas P. Stossel, *Regulating Academic-Industrial Research Relationships —Solving Problems or Stifling Progress?*, 353 NEW ENG. J. MED. 1060 (2005); see Kendall W. Artz & Thomas H. Brush, *Asset Specificity, Uncertainty and Relational Norms: An Examination of Coordination Costs in Collaborative Strategic Alliances*, 41 J. ECON. BEHAV. & ORG. 337 (2000).

approved product.<sup>408</sup> When they work, they effectively give pharmaceutical firms an incentive to evergreen their drugs through incremental improvements that may nevertheless qualify as new uses. That is what Bristol-Myers Squibb endeavored to do with the introduction of Glucophage XR and Glucovance, as well as its investments in earning an additional pediatric indication and corresponding six-month exclusivity window. A 2011 paper in *Nature Biotechnology* suggests that pharmaceutical firms' strategy is conscientiously oriented toward filing new drug applications and patents so as to maximize exclusivity windows.<sup>409</sup> While certain definitions and designations may help draw the line between a meaningful "breakthrough" therapy and a relatively minor adjustment to dose, drug combination, or method of administration, any additional categorization will open additional avenues for firms to claim market exclusivities that may not generate the social benefits those exclusivities were intended to achieve.

In short, deploying the kinds of market exclusivity incentives now being advocated may result in less repurposing activity, including reduced opportunity for serendipitous discovery and revelations made through academic practice, even if it does increase industry activity.

***F. Giving Pharmaceutical Firms Access to Physician Prescription Practices Will Generate as Much or More Off-Label Promotion Activity and Compromise the Physician-Patient Relationship***

Ben Roin argues that the problem of new uses is not an exclusivity problem, but an information problem—firms simply need to know when physicians are prescribing off-label, so that they can enforce existing exclusivities under law.<sup>410</sup> Monitoring prescribers' off-label activity, he argues, could be solved by giving pharmaceutical firms access to patient health records (with personally identifiable information redacted) so they could effectively price their products fully informed by prescription practices.<sup>411</sup> Insurers and pharmaceutical benefit management firms routinely require doctors to report a patient's diagnosis and health records before the insurance company will authorize

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<sup>408</sup> Eisenberg, *supra* note 8, at 720 (2005).

<sup>409</sup> Gaudry, *supra* note 102, at 876-78.

<sup>410</sup> Roin, *supra* note 26.

<sup>411</sup> *Id.*

payment for expensive brand name drugs.<sup>412</sup> By granting pharmaceutical companies limited access to patient records in order to check the accuracy of reported diagnoses and prescriptions, they would be able to charge payers when doctors prescribe an old drug for a new use or require pharmacists to dispense the expensive brand name drug rather than a generic when it is prescribed for patented indications.<sup>413</sup> Although this would require some expansion of the Health Information Portability and Accountability Act (“HIPAA”), Roin argues it could be a workable solution to increase the profitability of repurposed drugs.

Like market exclusivity approaches, however, giving large pharmaceutical firms access to electronic medical records for purposes of monitoring off-label activity confronts its own set of practical limitations. First, it is not clear that pharmaceutical benefit management firms—insurers’ agents—are particularly good at using “medically necessary” limitations to affect prescription behavior.<sup>414</sup> Roin cites pharmaceutical benefit management companies themselves for the proposition that they have “had great success at preventing payments for drugs not prescribed for medically accepted indications,” but academic analyses, supported by judicial decisions, have largely determined that “this tactic has met with limited success.”<sup>415</sup> Politically speaking, the off-label system largely drives down (at least direct) costs setting up a confrontation between the interests of payers and pharmaceutical firms in any effort to amend HIPAA which Roin’s proposal requires.<sup>416</sup>

Even assuming the proposal were practically and politically viable, the effect on the drug repurposing ecosystem would be inevitably profound. Pharmaceutical firms would not limit their use of the prescribing information for pricing, and there would be no effective way to make them do so. Now-unconstitutional legislative efforts by physicians to limit pharmaceutical company influence have been based on the combination of data and soft coercion that physicians both resent and worry may

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<sup>412</sup> *Id.*

<sup>413</sup> *Id.*

<sup>414</sup> Katherine T. Adams, *The Off-Label Conundrum*, 3 BIOTECHNOLOGY HEALTHCARE 27 (2006) (“In fact, Pezalla, at Prescription Solutions, estimates that at least half the pharmacy benefit manager’s total reimbursement load is for off-label usage.”).

<sup>415</sup> Abbott & Ayres, *supra* note 186, at 392.

<sup>416</sup> Mark Gaynor et al., *A Tale of Two Standards: Strengthening HIPAA Security Regulations Using the PCI-DSS*, 4 HEALTH SYSTEMS 111 (2015) (noting the general difficulty with amending HIPAA).

affect their patient care practices.<sup>417</sup> Pharmaceutical firms already capture revenues from alternative uses through their off-label marketing activity. Giving pharmaceutical firms access to physician prescription practices would just increase the revenue stream flowing from off-label marketing practices and would potentially distort the kind of clinical off-label practice that has given rise to new use breakthroughs, to say nothing of patient care generally.<sup>418</sup>

Thalidomide was initially licensed for the treatment of erythema nodosum leprosum in 1998, and it was not until 2006 that thalidomide was approved for the treatment of myeloma.<sup>419</sup> Yet, in this time period, more than 720,000 thalidomide prescriptions were written, with only 0.1% of prescriptions for the label indication of erythema nodosum leprosum.<sup>420</sup> The initial off-label use of thalidomide for the treatment of myeloma after approval for leprosy highlights a broader issue in drug repurposing related to the need to obtain a labeled indication.<sup>421</sup> The potential new use for an old drug may be quickly and widely disseminated through publications and presentations.<sup>422</sup> If the drug is currently available in an appropriate formulation, off-

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<sup>417</sup> Tamara Piety, *A Necessary Cost of Freedom?*, 64 ALA. L. REV. (2012) (“Pharmaceutical companies pay hundreds of thousands of dollars to third-party firms that gather sales data from the nation’s pharmacy chains; reps get detailed reports informing them how many prescriptions—of their own drugs, as well as those of their competitors—each doctor has written in a particular week. This allows the rep who discovers that a promise hasn’t been honored to police the promise: ‘Now, Doctor, last month you agreed to try Zithromax in your next ten otitis media patients. What stopped you from doing so?’ . . . IMS Health, Inc., the plaintiff in the *Sorrell* case, is one such prescription drug information intermediary. It gathers information from pharmacies about the prescriptions doctors write. Although the patients’ names in the data are protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPPA), prescribers’ names are not scrubbed. Thus, IMS and other PDIIIs can organize the data by physician and by drug, so it is possible to see what drugs, and how much of each, every doctor is prescribing. Companies like IMS Health then buy lists of licensed physicians from the AMA and cross-reference these records against the records obtained from the pharmacies, analyze and summarize all of this data, and then sell it back to interested parties.” (internal quotation marks omitted)).

<sup>418</sup> *Id.* (“Predictably, many doctors feel this practice is incredibly intrusive. As one witness testified, having the detailer know so much information about his prescription practices ‘puts me at a disadvantage that I’m not comfortable being at.’ Moreover, the evidence adduced in the cases litigating statutes like that of Vermont demonstrates that the purpose of data mining is to stimulate the sales of brand-name drugs. Studies suggest that ‘detailing has “a significant effect on physician prescription behavior.””).

<sup>419</sup> Sukhai et al., *supra* note 118.

<sup>420</sup> *Id.*

<sup>421</sup> *Id.*

<sup>422</sup> Abbott & Ayres, *supra* note 186, at 390 (“Off-label drug use . . . may also serve as a pathway to innovation. Off-label drug use can provide valuable data about the effects of the drug for different conditions and populations, and this data can then be used to inform future clinical practice.”).



label prescribing could lead to wide adoption of this therapy in the absence of formal regulatory approval.

## VI. CONCLUSION

This article has argued that current solutions to the drug repurposing problem focus on market exclusivity incentives without fully exploring the interruptions those incentives may cause in the drug repurposing ecosystem. That ecosystem, while certainly dependent in part on innovation driven within and by large pharmaceutical firms, is equally or more supported by serendipitous observations by treating physicians, a complex and opaquely regulated off-label prescription system and, to an extent not effectively assessed in the current literature, patients' access to affordable medicines and product liability concerns held by innovator pharmaceutical firms. This ecosystem is complex and global, but its focus of activity is not equally distributed. Even breakthroughs for metformin use initially discovered in other countries were rapidly developed and more effectively exploited in the United States. The experience with metformin suggests that new-use incentives may not be used where proponents now imagine they will do the most work, and may in fact erect additional barriers to patient access to medicines while complicating academic research efforts. Finally, industry appears to be undertaking repurposing activity *as a natural result of a changing market*; therefore, additional incentives would reward work that was going to be undertaken anyway. Before there is determined to be a drug repurposing problem, the scope and magnitude of that problem must be better understood and solutions developed that are sensitive to the successes the current system now achieves.