



DEPAUL UNIVERSITY
UNIVERSITY LIBRARIES

DePaul Journal of Art, Technology
& Intellectual Property Law

Volume 28
Issue 1 Fall 2017

Article 2

Repurposing Old Drugs for New Uses

Kathryn Brown

Follow this and additional works at: <https://via.library.depaul.edu/jatip>



Part of the [Computer Law Commons](#), [Cultural Heritage Law Commons](#), [Entertainment, Arts, and Sports Law Commons](#), [Intellectual Property Law Commons](#), [Internet Law Commons](#), and the [Science and Technology Law Commons](#)

Recommended Citation

Kathryn Brown, *Repurposing Old Drugs for New Uses*, 28 DePaul J. Art, Tech. & Intell. Prop. L. 1 (2019)
Available at: <https://via.library.depaul.edu/jatip/vol28/iss1/2>

This Seminar Articles is brought to you for free and open access by the College of Law at Via Sapientiae. It has been accepted for inclusion in DePaul Journal of Art, Technology & Intellectual Property Law by an authorized editor of Via Sapientiae. For more information, please contact digitalservices@depaul.edu.

REPURPOSING OLD DRUGS FOR NEW USES

I. INTRODUCTION

Despite recent advancements in the drug discovery and development process, it is still lengthy, expensive, and prone to failure. Developing and bringing a new drug to market costs an estimated \$2.558 billion¹ and takes, on average, twelve to sixteen years.² This lengthy and expensive process, however, does not seem to have any advantages in terms of the number of approved drugs as it is approximately twenty-seven per year.³ As Part II will explain, it is clear why the cost and time for doing so are extremely high. Drug repurposing, however, is able to more quickly and efficiently bring new drugs to market. Part II explains the usual drug development process and why so few drugs actually enter the market. Part III explores the process of drug repurposing, how it facilitates faster and more efficient drug development, as well as the advantages and disadvantages of utilizing this process. Part IV elaborates on how drug repurposing is currently being utilized. Part V examines whether drug repurposing could constitute patent infringement. Part VI analyzes the different

¹ Joseph A. DiMasi et al., *Innovation in the pharmaceutical industry: New estimates of R&D costs*, 47 J. HEALTH ECON. 31 (May 2016). Note that this number increased from \$1.2 billion in 2007. See Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 469, 475, 476-77 (2007). Some research suggests it could cost as much as \$4 billion. See Garret A. FitzGerald, *Re-engineering Drug Discovery and Development*, 17 LEONARD DAVIS INST. OF HEALTH ECON. 1, 1 (2011).

² See UNITED STATES GOVERNMENT ACCOUNTABILITY OFFICE (GAO), *NEW DRUG DEVELOPMENT: SCIENCE, BUSINESS, REGULATORY, AND INTELLECTUAL PROPERTY ISSUES CITED AS HAMPERING DRUG DEVELOPMENT EFFORTS* 1, 6 (2006) (estimating drug development takes approximately fifteen years); Joseph A. DiMasi, *New Drug Development in the United States from 1963 to 1999*, 69 CLINICAL PHARMACOLOGY & THERAPEUTICS 286, 292 fg. 6 (2001).

³ Nicola Nosengo, *New tricks for old drugs*, 534 NATURE 315 (June 16, 2016), http://lib.shsmu.edu.cn/Assets/userfiles/sys_183695/files/534314a.pdf.

routes through which repurposed drugs can achieve market exclusivity—Food and Drug Administration (FDA) exclusivity and patent exclusivity. Part VII then discusses the areas in which drug repurposing can be improved so as to allow drug developers to facilitate higher utilization. Part VIII concludes.

II. PHARMACEUTICAL DRUG DEVELOPMENT MARKET FAILURE

Part A explains the usual drug development process and why the process is so lengthy. Part B then discusses why so few drugs successfully complete the lengthy drug development process and enter the market.

A. *The Usual Drug Development Process*

Typical drug development proceeds through four phases: (1) basic research, (2) preclinical trials, (3) clinical trials, and (4) FDA New Drug Application (NDA) filing and approval.⁴ Basic research involves biological screening and pharmacologic testing,⁵ pharmaceutical dosage formulation and stability testing,⁶ and toxicology and safety testing.⁷ Preclinical trials, conducted on at least two animal species, establish the drug's toxicological and pharmacological profile. The test results determine whether it is

⁴ See *Biopharmaceutical Research & Development: The Process Behind New Medicines*, PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AM. 18 (2015), http://www.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf for a visual depiction of the drug development process.

⁵ “These are studies to explore the pharmacological activity and therapeutic potential of compounds.” *Regulatory Science*, UNIV. S. CAL., <https://regulatory.usc.edu/consulting/resources/drugs/basic-research/> (last visited Dec. 1, 2016).

⁶ This is the “process of turning an active compound into a form and strength suitable for human use.” *Id.*

⁷ These are “[t]ests to determine the potential risk a compound poses to animals, tissue cultures, and other test systems prior to their human introduction.” *Id.*

reasonably safe to proceed with human trials;⁸ if the results indicate it is reasonably safe, then drug development moves into human clinical trials. These trials consist of three phases, each with their own testing purpose.⁹ Phase I tests the safety of the drug, Phase II tests its efficacy, and Phase III involves the blind testing of the drug in one to two thousand patients.¹⁰ If all goes well during clinical trials,¹¹ the pharmaceutical company files a New Drug Application (NDA) for FDA approval. In order to receive FDA approval, “[t]he FDA requires extensive [data from the] clinical trials demonstrating a new drug’s safety and efficacy for at least one indication before that drug can enter the market.”¹²

⁸ *Preclinical Trial*, UNIV. S. CAL.,

<https://regulatory.usc.edu/consulting/resources/drugs/preclinical/> (last visited Dec. 1, 2016).

⁹ See *FAQ ClinicalTrials.gov – Clinical Trial Phases*, U.S. NAT’L LIBRARY OF MEDICINE, <https://www.nlm.nih.gov/services/ctphases.html> (last updated Apr. 18, 2008); *Clinical Trials 101*, CROHN’S & COLITIS FOUND. OF AM., <http://www.ccfa.org/resources/clinical-trials-101.html?referrer=https://www.google.com/> (last accessed Dec. 1, 2016).

Note that the FDA Modernization Act of 1997 allows the FDA to base its approval of a NDA on data from one adequate and well-controlled clinical investigation and confirmatory evidence. 21 U.S.C. § 355(d). This would allow a drug developer to complete only one phase of clinical trials; however, the “FDA has in practice implemented this provision only when the single adequate and well-controlled clinical investigation has statistical significance that is an order of magnitude greater than is normally required.” Peter Barton Hutt, *The Regulation of Drug Products by the United States Food and Drug Administration*, in *THE TEXTBOOK OF PHARMACEUTICAL MEDICINE* 585 (John P. Griffin & John O’Grady eds., 5th ed. 2006).

¹⁰ See *FAQ ClinicalTrials.gov – Clinical Trial Phases*, *supra* note 9.

¹¹ Drugs fail during clinical trials either because the drug is not safe or it is ineffective. See JP Hughes et al., *Principles of Early Drug Discovery*, 162 *BRITISH J. PHARMACOLOGY* 1239, 1239 (2011).

¹² Benjamin N. Roin, *Solving the Problem of New Uses* 21 (Oct. 18, 2016), <https://www.bu.edu/law/files/2016/10/Solving-the-Problem-of-New-Uses-Ben-N.-Roin.pdf> (draft). An indication is the particular use for which the drug is approved. *Approved Drug Uses*, PUBMED HEALTH (Aug. 20, 2015), <https://www.ncbi.nlm.nih.gov/pubmedhealth/approved-drug-uses/>.

Adding to the already lengthy process, FDA approvals take, on average, two to three years to review all of the data and issue a decision.¹³

B. A Long Process for Minimal Results

Unfortunately, most pre-clinical drug candidates do not survive human clinical trials. Of five thousand pre-clinical drug candidates, on average five will survive to human clinical trials, and only one will receive NDA approval.¹⁴ Stated another way, only approximately 0.02% of all drugs tested are approved and enter the market.¹⁵ Further exacerbating this problem, pharmaceutical companies spend billions of dollars on research and development for drugs that ultimately never make it out of clinical trials. This then translates into higher drug prices for consumers. Dov Greenbaum, intellectual property attorney and Associate Professor at Yale University, asserts “[t]he high failure rate of potential compounds is a huge component of the costs of drugs.”¹⁶

This gap between the thousands of pre-clinical candidates arising out of basic research and the few that actually enter the market is known as the “Valley of Death.”¹⁷ Drug repurposing,¹⁸ however, can potentially bridge this valley by more efficiently and successfully bringing drugs to the market.

¹³ Hutt, *supra* note 9, at 585.

¹⁴ Daniel S. Sem, Comment, *Repurposing – Finding New Uses for Old (And Patented) Drugs: Bridging the “Valley of Death,” to Translate Academic Research into New Medicines*, 18 MARQ. INTELL. PROP. L. REV. 139, 147 (2014).

¹⁵ Katherine S. Gaudry, *Evergreening: A Common Practice to Protect New Drugs 1* (May 30, 2011) (on file with Harvard University DASH system).

¹⁶ Dov Greenbaum, *Incentivizing Pharmacogenomic Drug Development: How the FDA Can Overcome Early Missteps in Regulating Personalized Medicine*, 40 RUTGERS L.J. 97, 111 (2008).

¹⁷ Sem, *supra* note 14, at 146.

¹⁸ Drug repurposing is also known as drug rediscovery, reusing, and repositioning.

III. DRUG REPURPOSING AS A SOLUTION

Drug repurposing is an alternative strategy for stimulating drug innovation, which could be part of the solution to bringing more drugs to the market and lowering the cost of both drug development and the drugs themselves. Repurposing is the process of studying existing drugs to see if they are safe and effective for treating other diseases or illnesses than the one(s) for which they were originally produced.¹⁹ Essentially, it is the process of using old drugs for new uses. Historically, repurposing has occurred by chance observation. For example, Viagra was developed for heart disease, but became a blockbuster drug²⁰ for erectile dysfunction after researchers noticed clinical trial patients maintained erections for a longer period of time while taking the drug.²¹ Consequently, repurposing is now a systematic approach to drug innovation, with pharmaceutical drug collections and libraries²² offering scientists thousands of drugs to screen and test for new uses.²³

¹⁹ Sem, *supra* note 14, at 147.

²⁰ “Blockbuster drug” refers to “medicines that bring in more than \$1 million in sales every year. . . They can make a pharmaceutical company and send them to rock-star status among investors.” Laura Lorenzetti, *7 New Blockbuster Drugs to Watch in 2016*, FORTUNE (Mar. 25, 2016), <http://fortune.com/2016/03/25/new-blockbuster-drugs-to-watch/>.

²¹ Julia Kollewe, *Why finding new uses for old drugs is a growing business*, THE GUARDIAN (Nov. 27, 2012, 1:14 PM), <https://www.theguardian.com/business/2012/nov/27/new-uses-old-drugs-business>.

²² Drug collections and libraries are collections of stored drugs which allow drug discovery via high throughput screening of the “entire compound library directly against the drug target.” Hughes, *supra* note 11, at 1242. “The screening paradigm involves the use of complex laboratory automation . . . to identify molecules that interact with the drug target.” *Id.* The drug collections and libraries can be owned by private companies, such as pharmaceutical companies, and universities. *Id.*

²³ Curtis R. Chong & David J. Sullivan Jr., *New uses for old drugs*, 448 NATURE 645 (Aug. 2007).

A. *The Repurposing Drug Development Process*

Drugs may be repurposed for new uses, such as a new indication,²⁴ dosage form, regimen or route of administration, or a new target patient population.²⁵ The drug to be repurposed can be FDA approved and currently in use (on or off patent),²⁶ approved but no longer in use (also called “shelved”), or unapproved by the FDA (“failed” drugs that did not pass clinical trials or receive FDA approval).

The process of repurposing begins when a researcher chooses a drug from a pharmaceutical library,²⁷ such as the Prestwick Chemical Library in Washington D.C.²⁸ or Harvard Medical School’s NINDS Custom Collection 2,²⁹ to study the drug for treatment of a specific indication. There are essentially two

²⁴ A drug indication is a “particular use for the drug, such as treating asthma.” *Approved drug uses*, PUBMED HEALTH (Aug. 20, 2015), <https://www.ncbi.nlm.nih.gov/pubmedhealth/approved-drug-uses/>.

²⁵ Ned Israelsen, *New Patents for Old Drugs*, PHARMA FOCUS ASIA, <https://www.pharmafocusasia.com/strategy/new-patents-old-drugs> (last accessed Nov. 28, 2016). Note that drugs can be prescribed for off-label uses (those uses of which a pharmaceutical would likely repurpose and seek approval) without violating any law. See *U.S. v. Caronia*, 703 F.3d 149, 166 (2d Cir. 2012).

²⁶ On or off patent refers to whether the drug is currently protected by a patent.

²⁷ See Dorothea Emig et al., *Drug Target Prediction and Repositioning Using an Integrated Network-Based Approach*, 8 PLOS ONE e60618 (Apr. 2013), http://images.info.science.thomsonreuters.biz/Web/ThomsonReutersScience/%7Bc9082186-f3fc-4623-8953-573a8a4cbb0f%7D_Drug_Target_Prediction.pdf.

²⁸ See *A Recognized Chemical Screening Library*, PRESTWICK CHEMICAL LIBRARY, <http://www.prestwickchemical.com/prestwick-chemical-library.html> (last accessed Dec. 1, 2016).

²⁹ See *NINDS Custom Collection 2*, HARVARD MED. SCH., <http://iccb.med.harvard.edu/ninds-custom-collection-2> (last accessed Apr. 10, 2017) (The collection was originally compiled by MicroSource Discovery Systems for the National Institute of Neurological Disorders and Stroke (NINDS), the Huntington’s Disease Society of America, the Amyotrophic Lateral Sclerosis Association, and the Hereditary Disease Foundation.)

ways to repurpose drugs: (1) the researcher can create new formulations or indications for a previously shelved active pharmaceutical ingredient (API); or (2) the researcher can create new formulations or indications for existing market drugs.³⁰ The first approach is the more attractive option, because any patents covering the old drug were likely filed many years ago and are near expiration or already expired at the time of repurposing.³¹ It is worth noting that while the industry struggles to deliver twenty-seven drugs to the market each year, as of 2012, there were approximately 25,000 drugs off-patent that could be studied for repurposing.³² Under the second approach, the drug will likely face a “patent thickets” problem³³ as the drug is probably still on patent, which requires licensure or clearing any patents on the drug before it can be studied. This option makes repurposing more expensive than it otherwise could be.

Once a drug is chosen, the researcher is able to begin studying the drug at Phase II clinical trials because the drug has already undergone basic research, preclinical trials, and (at a minimum) Phase I clinical trials testing.³⁴ Much like the process described above, if the drug survives human clinical trials, then the researcher can apply for FDA approval and may potentially receive a patent for the new indication or formulation.

³⁰ Richard B. Smith, *Repositioned drugs: integrating intellectual property and regulatory strategies*, 8 DRUG DISCOVERY TODAY: THERAPEUTIC STRATEGIES 136 (2011).

³¹ *Id.*

³² Kollewe, *supra* note 21.

³³ Patent thickets are “dense web of overlapping intellectual property rights that a company must hack its way through in order to actually commercialize new technology. With cumulative innovation and multiple blocking patents, stronger patent rights can have the perverse effect of stifling, not encouraging, innovation.” Carl Shapiro, *Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Standard Setting*, in INNOVATION POLICY AND THE ECONOMY 120 (2001).

³⁴ See *Assets & Agreements for NIH-Industry Partnerships*, U.S. DEP’T OF HEALTH & HUM. SERVS., <https://ncats.nih.gov/ntu/assets> (last updated Nov. 30, 2016). The pharmacological and toxicological data already exists and there is not much use in recreating it.

The 21st Century Cures Act,³⁵ which was signed into law in late 2016,³⁶ further facilitates drug developers' ability to speed up drug development via repurposing by allowing drug developers submitting a NDA application to rely upon data and information previously developed and submitted to the FDA³⁷ and by allowing drug developers to submit "data summaries."³⁸ These data summaries "could include previously submitted data for the same chemical compound, real world evidence, anecdotal evidence, insurance data, observational data, and in-house data, such as evidence of efficacy, safety, and quality."³⁹

³⁵ 21st Century Cures Act, H.R. 6, 114th Cong. (2016).

³⁶ *21st Century Cures Act*, CONGRESS.GOV, <https://www.congress.gov/bill/114th-congress/house-bill/34/text?q=%7B%22search%22%3A%5B%2221st+century+cures+act%22%5D%7D&r=1#toc-H0328EF4534A74A058F979A7D3481A316> (last accessed Dec. 3, 2016).

³⁷ 21st Century Cures Act, H.R. 34, 114th Cong. § 3012 (2016) (as codified in 21 U.S.C. § 529A(b)(1)–(2)).

³⁸ Sheila Kaplan, *Winners and Losers of the 21st Century Cures Act*, STAT (Dec. 5, 2016), <https://www.statnews.com/2016/12/05/21st-century-cures-act-winners-losers/>.

³⁹ Kathryn Brown, *21st Century Cures Act & Its Wide-Reaching Impact*, E-PULSE NEWSLETTER (Feb. 14, 2017), <https://law.depaul.edu/about/centers-and-institutes/health-law-institute/newsletter/Pages/2017-Jan/21st-Century-Cures-Act-and-its-Wide-Reaching-Impact.aspx>. Deborah Mazer and Gregory Curfman argue that the 21st Century Cures Act may actually lower public confidence in FDA-approved drugs. They explain that the Act's changes to the evidentiary standard for drug approval, "may have the result of weakening the traditional standards required by the FDA, with an unpredictable long-term effect on drug safety and efficacy. Bringing new medical products to market efficiently is a laudable goal, but the government must carefully walk the fine line between speed of drug approval and the rigor of the approval process." Deborah Mazer & Gregory Curfman, *21st Century Cures Act Lowers Confidence in FDA-Approved Drugs and Devices*, HEALTH AFF. (Feb. 14, 2017), <http://www.healthaffairs.org/doi/10.1377/hblog20170214.058710/full/>. They also indicate that the Act, which "gives substantial discretion to the [HHS] Secretary to accept, limit, or reject the use of ambiguous 'real-world evidence'"

B. Benefits of Drug Repurposing

Drug repurposing boasts many advantages over the usual drug discovery and development process. First, repurposed drug development takes approximately three to twelve years as opposed to the twelve to sixteen years necessary in the normal process of creating a drug from scratch. This shortened time frame is due to the existing pharmacologic and toxicological data collected during basic research, preclinical trials, and clinical trials previously performed on the drug. Given that the data already exists, researchers skip to Phase II clinical trials and therefore spend less time and money on research and development. Through repurposing, it is estimated that drug developers save forty percent on the overall cost of bringing a drug to market.⁴⁰ Additionally, the success rates of receiving FDA approval is two times higher when repurposing.⁴¹ This is, again, due to the ample pharmacological, toxicological, and formulation information already available on the drug.⁴² Researchers assess this information and, based on their knowledge and experience, determine if there is a reasonable likelihood that the drug could effectively treat a different disease or illness. The ability to examine the drug data has led to an approval rate of repurposed drugs that is nearly two times higher than that of drugs developed through the usual process.⁴³

is a “novel departure from the traditional view of the level of evidence that would be required [to approve a drug].” *Id.*

⁴⁰ Chong & Sullivan, Jr., *supra* note 23, at 645.

⁴¹ Ann M. Thayer, *Drug Repurposing*, 90 CHEM. & ENG’G NEWS 15 (2012), <http://cen.acs.org/articles/90/i40/Drug-Repurposing.html?h=-1031248274>.

⁴² *Repurposing Drugs*, U.S. DEP’T OF HEALTH & HUM. SERVS., <https://ncats.nih.gov/preclinical/repurpose#learn-more> (last updated Nov. 9, 2016),

⁴³ Simon Kremer & Rachel Jones, *Old drugs, new tricks: patent considerations in drug repurposing*, LIFE SCI. INTELL. PROP. REV. (Dec. 19, 2014) (republished at LEXOLOGY (Jan. 28, 2015),

C. Drawbacks to Drug Repurposing

Drug repurposing has many benefits, yet there are also a number of drawbacks to its implementation. Scholars have suggested that drug repurposing is itself a market failure. Professor Benjamin Roin claims that there is little to no incentive for pharmaceutical companies to repurpose once its drug is approved and even less incentive to do so once the generic version is approved.⁴⁴ Further, “[i]t is possible that a large pharmaceutical company may have known or suspected new and alternative uses for their patented drug in some cases, but decided not to explore the less financially lucrative new uses, such as treating rare or neglected diseases.”⁴⁵ It is also possible that pharmaceutical companies do not repurpose due to concerns that the repurposing research will expose adverse effects of the old drug such that it would necessitate taking the drug off the market and destroy its profitability.⁴⁶ For example, while studying Vioxx as a possible treatment for colon polyps, Merck discovered Vioxx increased the risk of heart attacks and stroke in patients taking the drug.⁴⁷ The drug was removed from the market after an estimated 20 million Americans have taken the drug, unknowingly exposing themselves to the increased risks of heart attack and stroke.⁴⁸ Significant consumer backlash resulted in response to these study findings in the form of thousands of lawsuits.⁴⁹

An additional drawback to drug repurposing is that it does comparatively little to incentivize the development of orphan

<http://www.lexology.com/library/detail.aspx?g=0e11981f-5268-4b0f-b6a6-1cb27e97e07c>.

⁴⁴ Roin, *supra* note 12, at 2.

⁴⁵ Sem, *supra* note 14, at 163–64.

⁴⁶ Thayer, *supra* note 41.

⁴⁷ See Snigdha Prakash & Vikki Valentine, *Timeline: The Rise and Fall of Vioxx*, NPR (Nov. 10, 2007),

<http://www.npr.org/templates/story/story.php?storyId=5470430>.

⁴⁸ *Id.*

⁴⁹ Associated Press, *Merck Agrees to Settlement Over Vioxx Ads*, N.Y. TIMES (May 21, 2008), <http://www.nytimes.com/2008/05/21/business/21vioxx.html>.

drugs.⁵⁰ Although repurposing can produce orphan drugs, the process is not solely directed towards the production of drugs for rare or orphan diseases. Pharmaceutical companies, given the choice, would prefer to make a blockbuster drug that will be used by millions of consumers rather than an orphan drug that reaches a much smaller segment of consumers. There is a real need to incentivize the development of orphan drugs; there are over 5,000 rare diseases (and new ones are discovered every week),⁵¹ but there are only 575 approved orphan drugs and devices.⁵² To encourage the development of orphan drugs via repurposing, the FDA created the Rare Disease Repurposing Database which compiles publicly available information not readily available to potential developers.⁵³ While drug repurposing could more effectively bring orphan drugs to market, there is no extra financial incentive to do so.

It should also be noted that although drug repurposing's shortened production cycle could help reduce the price of drugs, there are no formal industry price constraints.⁵⁴ Pharmaceutical companies that produce repurposed drugs could still charge the

⁵⁰ Orphan drugs are those that treat a condition that affects less than 200,000 people in the United States. Shannon Gibson, *Orphan drug incentives in the pharmacogenomics context: policy responses in the US and Canada*, 2 J.L. BIOSCI. 263 (July 2015).

⁵¹ Aarti Sharma et al., *Orphan drug: Development trends and strategies*, 2 J. PHARM. BIOALLIED SCI. 290 (Oct.–Dec. 2010).

⁵² *Developing Products for Rare Diseases & Conditions*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm> (last updated Nov. 17, 2016).

⁵³ Margaret Foster Riley, *An Unfulfilled Promise: Changes Needed to the Drug Approval Process to Make Personalized Medicine a Reality*, 70 FOOD DRUG L.J. 289, 310 (2015).

⁵⁴ *But see* Mark Kessel, *The problems with today's pharmaceutical business—an outsider's view*, 29 NATURE BIOTECHNOLOGY 27, 28 (Jan. 2011) (noting informal price constraints exist in the form of regulators and third party payors (or insurance companies) who “measure what benefits patients are deriving from the drugs” thus enabling them to “bear down on prices, access, utilization and prescribing patterns”).

same or inflated prices, thus reaping more profits than normal. Despite these drawbacks, drug repurposing has been utilized in several ways.

IV. DRUG REPURPOSING UTILIZATION

In recent years, increasingly more repurposing of old drugs has occurred. Better yet, many contemporary, well-known pharmaceuticals have been repurposed: Cymbalta was developed as an antidepressant but is now approved to treat fibromyalgia;⁵⁵ Evista is a birth control drug that was repurposed as an osteoporosis treatment and to prevent breast cancer;⁵⁶ and, tretinoin was originally developed to treat acne and is now also used to manage acute promyelocytic leukemia.⁵⁷

This Section reviews how drug repurposing is currently implemented both in the private and public sector. Part A discusses how pharmaceutical companies are currently utilizing repurposing to develop new drugs more quickly. Part B explains the National Institute of Health (NIH) National Center for Advancing Translational Sciences (NCATS) Program, which, through several initiatives, aims to improve the drug repurposing process. Part C describes the repurposing work of private partnerships between researchers and disease advocacy groups, such as Cures Within Reach. Lastly, Part D examines how black-box medicine facilitates drug repurposing by identifying potential connections between existing drugs and new uses.

A. *Pharmaceutical Companies Conducting Repurposing*

Despite the drawbacks mentioned above, pharmaceutical companies are no strangers to repurposing; however, in recent years, “[t]here is a greater emphasis [on repurposing] now as companies try to squeeze more revenue out of their existing

⁵⁵ Kollewe, *supra* note 21.

⁵⁶ *Id.*

⁵⁷ J.K. Aronson, *Old drugs – new uses*, 64 BRITISH J. CLINICAL PHARMACOLOGY 564 (2007).

assets.”⁵⁸ In a sense, pharmaceutical companies’ repurposing their own drugs is an obvious, financially-smart decision.⁵⁹ “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.”⁶⁰

To be sure, a considerable amount of “evergreening” occurs through marginal tweaks to brand-name drugs.⁶¹ These minor modifications allow brand-name pharmaceutical companies to patent the modified drug as new and to gain a resulting additional twenty years of patent exclusivity.⁶² Evergreening and

⁵⁸ Thayer, *supra* note 41.

⁵⁹ It should be noted that pharmaceutical companies have an additional incentive to formally repurpose and approve new treatments for approved drugs. Pharmaceutical companies cannot formally promote drugs as treatments for indications for which the drug is not FDA approved. This is called off-label promotion, and the Food Drug and Cosmetics Act (FDCA) prohibits such action by prohibiting the introduction of un-approved drugs into interstate commerce. *See* 21 U.S.C. § 331(a). The FDA, however, has been largely ineffective in preventing off-label promotion due to First Amendment protections. *See, e.g., U.S. v. Caronia*, 703 F.3d 149, 168–69 (2d Cir. 2012) (holding truthful off-label promotion of FDA-approved drugs is not prohibited by FDCA misbranding provisions). Pharmaceutical companies can avoid off-label promotion violations by utilizing its previously generated data to submit a new treatment NDA for its already approved drugs.

⁶⁰ Thayer, *supra* note 41.

⁶¹ Roger Collier, *Drug patents: the evergreening problem*, 185 CANADIAN MED. ASSOC. J. E385 (June 11, 2014), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3680578/pdf/185e385.pdf>. Evergreening is the development of new drugs by slightly tweaking old drugs. *Id.* As one scholar notes, “Because of the huge commitment of time and resources it takes to obtain FDA approval for a new drug, many pharmaceutical companies prefer to invest in a safer bet: promoting existing drugs by extending labels, changing doses, or changing drug combinations for existing treatments.” Franklin Allen & Glenn Yago, *Financing Cures*, in FINANCING THE FUTURE: MARKET BASED INNOVATIONS FOR GROWTH (2010).

⁶² Gaudry, *supra* note 15, at 3.

repurposing, though, have distinct purposes. Evergreening is largely criticized as a practice to raise drug prices, thereby protecting pharmaceutical company's market exclusivity. It rarely results in any therapeutic advantage.⁶³ Repurposing, by contrast, seeks to transform existing drugs into a new therapeutic treatment.

Much of the repurposing conducted by pharmaceutical companies tends to be performed in collaboration with academic institutions or through industry partnerships.⁶⁴ For example, AstraZeneca, which has been particularly active in partnering for drug repurposing, partnered with (1) Taiwan's National Research Program for Biopharmaceuticals to develop drug candidates for therapies targeting diseases prevalent in Asia,⁶⁵ (2) Cancer Research UK to repurpose an asthma therapy into a treatment for kidney cancer,⁶⁶ and (3) Sanofi to provide "free access to 210,000 usually closely guarded compounds . . . [to] diversify . . ." ⁶⁷ the companies' drug portfolios. Pfizer has also taken an active role in repurposing its existing drugs for rare diseases through collaborative efforts within the industry and through the NIH-

⁶³ Aaron Kesselheim et al., *Extensions of Intellectual Property Rights and Delayed Adoption of Generic Drugs: Effects on Medicaid Spending*, 25 HEALTH AFF. 1637 (Nov. 2006); Leigh Purvis & Crystal Kuntz, *Is High Prescription Drug Spending Becoming Our New Normal?*, HEALTH AFF. BLOG (May 17, 2016), <http://healthaffairs.org/blog/2016/05/17/is-high-prescription-drug-spending-becoming-our-new-normal/>.

⁶⁴ See *infra* notes 65–56, 66–77 and accompanying text.

⁶⁵ Dave Silver, *Astrazeneca Allies with Taiwan in Drug Repurposing Project*, BIOWORLD (Oct. 13, 2013), <http://www.bioworld.com/content/astrazeneca-allies-taiwan-drug-repurposing-project-1>.

⁶⁶ Emily Mullin, *Cancer Research UK will repurpose an AstraZeneca asthma drug for kidney cancer*, FIERCEBIOTECH (Jan. 3, 2014, 8:00 AM), <http://www.fiercebiotech.com/deals/cancer-research-uk-will-repurpose-an-astrazeneca-asthma-drug-for-kidney-cancer>.

⁶⁷ Denise Roland, *AstraZeneca, Sanofi Agree to Share Proprietary Compounds*, WALL STREET J. (Nov. 19, 2015, 7:03 PM), <https://www.wsj.com/articles/astrazeneca-sanofi-agree-to-share-proprietary-compounds-1447977780>.

Industry Partnership program.⁶⁸ Additionally, pharmaceutical companies have begun “licensing potential NCEs [new chemical entities] from biotechnology companies or universities” that have already conducted the basic research and pre-clinical trials.⁶⁹ These strategic partnerships allow pharmaceutical companies to combine their institutional knowledge in order to identify potential new treatments for existing drugs.

Further, although Professor Benjamin Roin claims “there is no viable business model for repurposing old drugs at present,”⁷⁰ the efforts of pharmaceutical companies dedicated to repurposing would suggest otherwise. The number of pharmaceutical companies that exclusively repurpose old drugs is growing to the tune of three to four new companies each year.⁷¹ Smaller pharmaceutical companies, such as BioVista and SOM Biotech, are solely dedicated to repurposing existing drugs. BioVista systematically studies and develops repositioned drugs for neurodegenerative diseases, epilepsy, oncology, and orphan diseases.⁷² Through its research and development efforts, BioVista has filed twelve novel use patents on repurposed drugs.⁷³ SOM Biotech only repurposes drugs to treat rare diseases.⁷⁴

⁶⁸ Kevin Lee, *Repositioning Existing Drugs for Rare Diseases*, PFIZER, INC. 3, 4, 12 (Apr. 16, 2013), <http://www.irdirc.org/wp-content/uploads/2013/06/Kevin-Lee.pdf>.

⁶⁹ Sem, *supra* note 14, at 147. New chemical entities are drugs for which the FDA has not previously approved a drug with the same chemical composition. The drug is novel, the first of its kind. See *New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products, Guidance for Industry*, FOOD & DRUG ADMIN. (Oct. 2014), <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm386685.pdf>.

⁷⁰ Roin, *supra* note 12, at 9.

⁷¹ Nosengo, *supra* note 3, at 315.

⁷² *About us*, BIOVISTA, <http://www.biovista.com/about/> (last accessed Dec. 2, 2016).

⁷³ *Id.*

⁷⁴ *SOM Biotech, The Drug Repositioning Company*, SOM BIOTECH, <http://www.sombiotech.com/> (last accessed Dec. 2, 2016).

*B. National Center for Advancing Translational Sciences
(NCATS)*

In 2012, President Obama provided funding to launch the NIH's NCATS's Discovering New Therapeutic Uses for Existing Molecules program.⁷⁵ The program's goal is to improve the process of repurposing drugs and "tackle bottlenecks in drug development."⁷⁶ In order to do so, the program collects drugs to be included in NCATS's pharmaceutical library, the NCATS Pharmaceutical Collection.⁷⁷ Similar to the pharmaceutical libraries previously mentioned, researchers are able to access the NCATS Pharmaceutical Collection to screen drugs for repurposing. Additionally, in August 2016, the program launched its Bench-to-Clinic Initiative which is directed at designing a systematic approach to identifying existing drugs that could be suitable candidates for repurposing.⁷⁸

Perhaps most influential to the progression of drug repurposing is the program's offering of non-IP incentives to pharmaceutical companies in the form of grants. In 2013, NCATS funded nine cooperative agreements between pharmaceutical companies and academic researchers to conduct repurposing studies for the discovery of novel therapies for a variety of diseases.⁷⁹ In 2015, NCATS funded another four cooperative

⁷⁵ *New Therapeutic Uses in Action*, U.S. DEP'T OF HEALTH & HUM. SERVS., <https://ncats.nih.gov/ntu/about/action> (last updated Aug. 30, 2016).

⁷⁶ Jocelyn Kaiser, *Acting Director Thomas Insel Explains New NIH Translational Center's Aims and Structure*, SCIENCE (Jan. 10, 2012, 10:53 AM), <http://www.sciencemag.org/news/2012/01/acting-director-thomas-insel-explains-new-nih-translational-centers-aims-and-structure>.

⁷⁷ *Early-Stage Repurposing*, U.S. DEP'T OF HEALTH & HUM. SERVS., <https://ncats.nih.gov/preclinical/repurpose/early> (last updated Apr. 22, 2015).

⁷⁸ *NCATS Announces Funding Opportunity for New Bench-to-Clinic Purposing Initiative*, U.S. DEP'T OF HEALTH & HUM. SERVS. (Sept. 2016), <https://ncats.nih.gov/news/releases/2016/drug-repurposing-bench-to-clinic-funding>.

⁷⁹ *New Therapeutic Uses 2013 Project Awards*, U.S. DEP'T OF HEALTH & HUM. SERVS., <https://ncats.nih.gov/ntu/projects/2013> (last updated Sept. 2, 2016).

agreements.⁸⁰ The participating companies include many pharmaceutical giants, such as GlaxoSmithKline, Pfizer, AstraZeneca, and Abbott.⁸¹ Although these studies are not solely dedicated to finding therapies for rare diseases, many of the studies are directed towards discovering therapies for tropical or orphan diseases, such as Chagas disease and glioblastoma.⁸²

The NIH-Industry Partnerships effectively unite the pharmaceutical industry, academic researchers, and the NIH, a federal agency.⁸³ Pharmaceutical companies provide the knowledge about how to make and use the drug, the previous clinical data (which is not always publicly available), and the drug itself. Researchers provide knowledge of the disease or illness to be studied, as well as the manpower to conduct the repurposing studies. Lastly, the NIH provides the funding necessary to conduct the repurposing studies. The NIH-Industry Partnerships are not without their detractors: Roy Vagelos, former Chairman and CEO of Merck, claims drug repurposing is a “fishing expedition” and “the NIH [should] not support clinical studies of marketed drugs.”⁸⁴ Instead, he believes repurposing research and drug

⁸⁰ *New Therapeutic Uses 2015 Project Awards*, U.S. DEP’T OF HEALTH & HUM. SERVS., <https://ncats.nih.gov/ntu/projects/2015> (last updated Oct. 11, 2016).

⁸¹ Minna Allarakhia, *Open-source approaches for the repurposing of existing or failed candidate drugs: learning from and applying the lessons across diseases*, 7 *DRUG DESIGN, DEV., & THERAPY* 753 (Aug. 7, 2013), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3743608/pdf/dddt-7-753.pdf>. One such NIH-Industry Partnership grant funds Steven Grant from Virginia Commonwealth University, who partnered with AstraZeneca to explore drug combinations that kill acute myeloid leukemia cells. *NACTS Matches Researchers with Pharmaceutical Industry Assets to Test Ideas for New Therapies*, U.S. DEP’T OF HEALTH & HUM. SERVS. (July 24, 2015), <https://ncats.nih.gov/news/releases/2015/ntu-awards>.

⁸² *New Therapeutic Uses 2015 Project Awards*, *supra* note 80.

⁸³ Brian F. Yagi, Note, *Triune Synergy in Biomedical Research: Uniting Pharmaceutical Companies, University Researchers, and the NIH Through the Drug Repurposing Project at NCATS*, 44 *WASH. U. J.L. & POL’Y* 179, 201 (2014).

⁸⁴ Budget Hearing of the Dep’t of Health and Human Services before the H. Subcomm. of Labor, Health, and Human Serv. Comm. on Appropriations, 112th

development should be left to the pharmaceutical companies that own the drug.⁸⁵

The studies conducted pursuant to the NIH-Industry Partnerships use partially developed drugs that the pharmaceutical company abandoned (meaning the drugs are not FDA approved). “Participating companies provide pre-clinical and clinical supplies of drugs and matched placebos to funded investigators [academic researchers] at no charge.”⁸⁶ Thus, the studies go directly into Phase II clinical trials, with the pre-clinical data for the drug already established.⁸⁷

For each the partnership contract, any future intellectual property rights will be held by the academic institution. This is legally permissible in accordance with the Bayh-Dole Act of 1980, which allows university recipients of federal grants to retain intellectual property rights arising from publicly-funded research.⁸⁸ Since the university, in all likelihood, will not have the capacity to manufacture any resulting drug, the university will give the partnering pharmaceutical company the first chance to license the drug.⁸⁹

Cong. 4 (2012) (statement of P. Roy Vagelos, M.D., President of Merck & Co., Inc.),

<http://appropriations.house.gov/calendar/eventsingle.aspx?EventID=281151>.

“Trying to find a use for a drug that has not been approved is a fishing expedition that has a very low possibility of success. As for repurposing of drugs, I would recommend that the NIH not support clinical studies of marketed drugs. Such studies that are aimed at obtaining additional claims for drugs already being sold should be funded by the company that owns the drug and will benefit financially for the additional claim.” *Id.*

⁸⁵ *Id.*

⁸⁶ *Assets & Agreements for NIH-Industry Partnerships*, *supra* note 34.

⁸⁷ *Id.*

⁸⁸ Bayh-Dole Act of 1980, P.L. 96-517, 94 Stat. 3015 (codified as amended at 35 U.S.C. § 200–212).

⁸⁹ *NIH-Industry Partnership Frequently Asked Questions*, U.S. DEP’T OF HEALTH & HUM. SERVS., <https://ncats.nih.gov/ntu/about/partnerships-faq#conclusion> (last updated Aug. 31, 2016).

*C. Partnerships Between Disease Advocacy Groups and
Researchers: Venture Philanthropy*

Historically, disease advocacy groups, such as Cures Within Reach⁹⁰ and the Alzheimer's Drug Discovery Foundation,⁹¹ supported individuals suffering from diseases through charitable contributions to fund the development of cures and therapies, educational resources, and participant recruitment for clinical trials.⁹² These groups focused their drug discovery efforts on both new and repurposed drugs.⁹³

Believing these contributions were not effectively helping afflicted individuals, disease advocacy groups began partnering with private sector bioscience and pharmaceutical companies to fund basic research and translational research, which is similar to repurposing.⁹⁴ Through these partnerships, disease advocacy groups are assuming a more active role in drug development by employing a venture capitalist structure to funding research in order to achieve their philanthropic goal—discovering a disease treatment or cure.⁹⁵ Similar to pharmaceutical libraries which enable scientists to choose which drugs to repurpose, these partnerships are facilitated by the creation of “research registries and biological repositories [that] enable research studies on

⁹⁰ *Mission and Impact*, CURES WITHIN REACH, <http://www.cureswithinreach.org/about-us> (last accessed Dec. 3, 2016).

⁹¹ *About Us*, ALZHEIMER'S DRUG DISCOVERY FOUND., <https://www.alzdiscovery.org/about-addf> (last accessed Dec. 3, 2016).

⁹² Anne M. Readel, *Finding a Cure: Incentivizing Partnerships Between Disease Advocacy Groups and Academic and Commercial Researchers*, 26 J.L. & HEALTH 285, 288 (2013).

⁹³ *Id.* at 288–89.

⁹⁴ *Id.* at 290. Similar to repurposing, translational research applies “discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans.” *Institutional Clinical and Translational Science Awards*, U.S. DEP'T OF HEALTH & HUM. SERVS., <http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-06-002.html> (last accessed Dec. 2, 2016).

⁹⁵ Readel, *supra* note 92, at 288.

particular diseases.”⁹⁶

These partnerships for basic and translational research, as well as the disease advocacy groups’ historical emphasis on repurposing research, give disease advocacy groups a strong foundation upon which they may build.

D. Black-box Medicine

Modern medicine increasingly uses personalized medicine, a rapidly advancing field of healthcare that tailors treatment to the individual patient.⁹⁷ “Black-box medicine,” which is the “use of opaque computational models to make decisions related to health care,”⁹⁸ is a growing subset of personalized medicine. Essentially, black-box medicine utilizes “‘predictive analytics,’ involving the use of real time large datasets and predictive algorithms to help inform treatment decisions, such as who should be sent first to intensive care units.”⁹⁹

One legal scholar has suggested black-box medicine could provide a systematic approach to identifying potential drug candidates for repurposing.¹⁰⁰

The wealth of data available in electronic health records of patients suffering from different ailments and responding to drugs they take for other purposes may be mined by big-data algorithms, which can suggest new uses To the extent that black-box medicine identifies

⁹⁶ *Id.* at 298 n.107.

⁹⁷ See W. Nicholas Price II, *Black-box Medicine*, 28 HARV. J.L. & TECH. 419, 421 (2015); see also *Personalized Medicine*, U.S. NEWS & WORLD REPORT, <http://health.usnews.com/health-conditions/cancer/personalized-medicine/overview> (last updated Jan. 20, 2011).

⁹⁸ Price, *Black-box Medicine*, *supra* note 97, at 421.

⁹⁹ See *id.* at 421 n.7 (citing Ruben Amarasingham et al., *Implementing Electronic Health Care Predictive Analytics: Considerations and Challenges*, 33 HEALTH AFF. 1148, 1148 (2014)).

¹⁰⁰ *Id.* at 436–37.

relationships between complex sets of variables that are largely implicit, black-box medicine suggests potential new research pathways to make those implicit connections explicit.¹⁰¹

The NIH seems to agree that black-box medicine could be the future of drug repurposing. Through NCATS's Bench-to-Clinic Initiative, the NIH is supporting pre-clinical studies to "test the utility of [a] . . . computational algorithm or big dataset from patient records to predict new uses of a drug."¹⁰² Black-box medicine, however, is a relatively new concept, and the intellectual property rights, privacy concerns, and regulation of black-box medicine currently remains unsettled.¹⁰³

V. REPURPOSING RESEARCH AND PATENT INFRINGEMENT

Drug repurposing can be performed by the developer of the original drug. For example, GlaxoSmithKline originally developed Zyban to treat depression, but later repurposed the drug to assist individuals to quit smoking.¹⁰⁴ "More often [repurposing is performed] in collaboration with academic medicine or others, and sometimes by developers that have no relationships at all with the original developer."¹⁰⁵ When the repurposing research is performed by developers without any relationship to the original developer, complicated patent scenarios arise.¹⁰⁶ A researcher

¹⁰¹ *Id.*

¹⁰² *New Therapeutic Uses Funding Information*, U.S. DEP'T OF HEALTH & HUM. SERVS., <https://ncats.nih.gov/ntu/funding> (last updated Nov. 30, 2016).

¹⁰³ See W. Nicholas Price II, *Big Data, Patents, and the Future of Medicine*, 37 *CARDOZO L. REV.* 1401 (2016) for a discussion on these issues.

¹⁰⁴ Smith, *supra* note 30, at 135.

¹⁰⁵ Foster Riley, *supra* note 53, at 309.

¹⁰⁶ This is presuming that the repurposing research done in collaboration is subject to a contract which specifies the rights of the academic or partner institution.

conducting repurposing studies on a drug must ensure that he is not infringing on any patent rights owned by the original developer of the drug to be studied.

The Drug Price Competition and Patent Term Restoration Act of 1984 (the “Hatch-Waxman Act”)¹⁰⁷ includes a safe harbor provision for the use of on-patent drugs in drug development research. The provision states:

It shall not be an act of infringement to make, use, offer to sell, or sell within the United States . . . a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs.¹⁰⁸

This statute was passed to allow generic pharmaceutical companies to more effectively compete with brand-name companies. Generic pharmaceutical companies previously could not conduct research and development on the patented drug without infringing on the patent, so the generic pharmaceutical companies were reduced to waiting until the patent expired. After the patent had expired, “the generic company still needed to do many years of research and clinical studies before they could enter the market with their generic version of the drug.”¹⁰⁹ Although the statute is intended to support generic research, the language of the statute can be expansively read to apply to repurposing research.¹¹⁰ Such broad language could protect a drug developer as the language is not limited to only generic drugs.

The United States Supreme Court has not explicitly stated

¹⁰⁷ Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended 35 U.S.C. § 271(e)(1)) (1984)

¹⁰⁸ 35 U.S.C. § 271(e)(1) (2006).

¹⁰⁹ Sem, *supra* note 14, at 152.

¹¹⁰ *Id.* (noting courts have opted for a broad, expansive reading of the safe harbor protection).

that the provision applies to both generic and repurposing research; however, it also has not limited the application to only generic drug research. Instead, the Supreme Court held in *Merck KGaA v. Integra Lifesciences I, Ltd.*,¹¹¹ that “the use of patented compounds in pre-clinical studies is protected under § 271(e)(1) as long as there is a reasonable basis for believing that the experiments will produce ‘the types of information that are relevant to an IND [investigational new drug application] or NDA.’”¹¹² The Court further held that § 271(e)(1) protection extends to “experimentation on drugs that are not ultimately the subject of an FDA submission.”¹¹³ As such, research using on-patent drugs is permissible so long as the research is “reasonably related to the development and submission of information to the FDA.”¹¹⁴ Ultimately, in order to avoid a claim of patent infringement, “[a]ll that is required is that the researcher had a ‘reasonable basis for believing that a patented compound may work’ in clinical studies.”¹¹⁵

Application of the Hatch-Waxman Act and case law to drug repurposing shows that repurposing of on-patent drugs will likely not be considered patent infringement. First, a researcher conducting a repurposing study must demonstrate that he chose the drug to be repurposed because, based on the clinical data, he reasonably believed the drug could be useful in treating a specific disease or illness.¹¹⁶ It is highly likely that the researcher will always have a scientific reason for choosing the drug to be repurposed—presumably based on the pharmacological and toxicological drug data and knowledge about the target disease or illness. Further, it would be illogical, as well as a waste of time and money, for a researcher to randomly choose a drug to study from a pharmaceutical library for a new therapeutic use without

¹¹¹ *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193 (2005).

¹¹² *Id.* at 208 (citing Brief of United States as Amicus Curiae 23).

¹¹³ *Id.* at 206.

¹¹⁴ *Id.*

¹¹⁵ *Sem, supra* note 14, at 160 (citing *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 207 (2005)).

¹¹⁶ *Id.*

any reasonable belief that a successful drug will be ultimately be developed.

Second, a researcher conducting the study must demonstrate that the information derived from the study was relevant to a FDA filing, such as a NDA. The researcher conducting the repurposing study will want to receive FDA approval for any drug that is developed, and therefore will want to file an NDA. If a NDA is filed, any information derived from the clinical trials regarding the safety and efficacy of the drug will be included in the application.¹¹⁷ Thus the study and the information derived from it will be relevant to a FDA filing. Despite the lack of explicit protection under the Hatch-Waxman Act, repurposing studies “are largely protected from patent infringement suits under the § 271(e)(1) safe harbor protections.”¹¹⁸

VI. OBTAINING MARKET EXCLUSIVITY

A major hurdle to the development of repurposed drugs is the lack of exclusivity. If pharmaceutical companies cannot obtain market exclusivity for a repurposed drug, then the company will likely not pursue repurposing. Due to the high cost of drug research and development, in order for a pharmaceutical company to bring a drug to market, it must be able to recoup research and development expenses and profit from the drug sales. To incentivize drug development, pharmaceutical companies are given market exclusivity as a reward for drug innovation. The market exclusivity prevents competitor drugs from entering the market, which enables pharmaceutical companies to recoup its losses and profit from the drug.

The high cost of drug development, however, also tends to

¹¹⁷ See *New Drug Application (NDA)*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/newdrugapplicationnda/default.htm> (last updated Mar. 29, 2016) (The goal of the NDA is to provide enough information to the FDA such that the agency can determine whether the drug is safe and effective.).

¹¹⁸ Sem, *supra* note 14, at 166.

be the rationale for charging such high prices for drugs. Companies justify their prices by explaining that “[i]t costs a lot of money to invent a medicine and bring it to the market, so the prices have to be high or the companies will be unable to continue their important research and development.”¹¹⁹ Repurposed drugs should allow pharmaceutical companies to lower drug prices because the company is spending less on research and development yet still potentially receiving twenty years of patent exclusivity in addition to FDA exclusivity.

This Section first discusses the different FDA exclusivity available for repurposed drugs and then turns to the various kinds of patents a developer could seek for a repurposed drug so as to receive patent exclusivity.

A. FDA Exclusivity

Under the current drug approval regime, there are three kinds of FDA regulatory exclusivity that a repurposed drug could receive: new use exclusivity, NCE exclusivity, and orphan drug exclusivity.¹²⁰ Under the Food, Drug, and Cosmetic’s Act § 501(b)(2),¹²¹ a new use or formulation provides three years of market exclusivity. New use exclusivity is granted for a drug that provides a new indication, dosage, strength, form, or delivery method of an existing drug.¹²² A repurposed drug may receive new use exclusivity of three years if it alters the old drug in at least one of these ways.¹²³

Under the Food, Drug, and Cosmetics Act § 501(b)(1),¹²⁴ a NCE provides the holder of an approved NDA five years of market

¹¹⁹ Sarah Boseley, *Big Pharma’s worst nightmare*, THE GUARDIAN (Jan. 26, 2016), <https://www.theguardian.com/society/2016/jan/26/big-pharmas-worst-nightmare>.

¹²⁰ Emily Michiko Morris, *The Myth of Generic Competition Under the Hatch-Waxman Act*, 22 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 245 (2012).

¹²¹ 21 U.S.C. § 355(b)(2) (2016).

¹²² Smith, *supra* note 30, at 134.

¹²³ *Id.*

¹²⁴ 21 U.S.C. § 355(b)(1) (2016).

exclusivity.¹²⁵ NCE exclusivity is granted to a drug with an active pharmaceutical ingredient (API) that is not already FDA approved.¹²⁶ In order to receive NCE exclusivity, the repurposed drug must alter the old drug's chemical composition such that the repurposed drug's API is innovative.¹²⁷

Finally, under the Orphan Drug Act,¹²⁸ an approved orphan drug provides a drug developer with seven years of market exclusivity.¹²⁹ Orphan drug exclusivity is only granted to drugs that treat orphan diseases;¹³⁰ thus, for a repurposed drug to receive orphan drug exclusivity, it must treat an orphan disease. Although developers of repurposed drugs can likely receive FDA exclusivity, three to five years, or even seven years, this exclusivity may still be insufficient to recoup developers' financial investment. Instead, development of repurposed drugs will likely hinge on the drug's patentability.¹³¹

B. Patent Exclusivity

Drug developers can also gain market exclusivity through patent protection. Patents provide twenty years of exclusivity. Developers typically receive patents eight to ten years before the drug is FDA approved, leaving approximately ten to twelve years of exclusivity remaining when the drug hits the market.¹³²

¹²⁵ Smith, *supra* note 30, at 134.

¹²⁶ *Id.*; *Small Business Assistance: Frequently Asked Questions for New Drug Product Exclusivity*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069962.htm> (last updated Feb. 11, 2016). This is similar to the novelty requirement for patent eligibility.

¹²⁷ Smith, *supra* note 30, at 134.

¹²⁸ Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049, 2051 (1983).

¹²⁹ Smith, *supra* note 30, at 134.

¹³⁰ *Patents and Exclusivity*, U.S. FOOD & DRUG ADMIN. 2 (May 19, 2015), <http://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm447307.pdf>.

¹³¹ Israelsen, *supra* note 25.

¹³² Alfred Engelburg, *How Government Policy Promotes High Drug Prices*, HEALTH AFFAIRS BLOG (Oct. 29, 2015).

Repurposing expedites the drug development process, so new drugs enter the market sooner, and they are able to use more of the market exclusivity provided by the patent.

i. Patent Eligibility

To receive a patent, an invention must meet the patent eligibility requirements of non-obviousness, novelty, and usefulness¹³³ and cannot be a law of nature, physical phenomena, or an abstract idea (the “*Chakrabarty* factors”).¹³⁴ Obviousness means that “an invention must not have been obvious to one with ordinary skill in the art to which the subject matter of the invention pertains . . . and in light of the teaching of prior art.”¹³⁵ Novelty means the invention was new at the time of discovery,¹³⁶ and useful means it somehow benefits society.¹³⁷

To patent any repurposed drug, the drug must be non-obvious, novel, and useful. Patent eligibility will differ based on the drug being analyzed;¹³⁸ however, because a repurposed drug is necessarily a physical object produced through a systematic process, a developer will not encounter any eligibility problems with respect to the *Chakrabarty* factors. Two kinds of patents typically protect pharmaceutical innovations: composition of matter and method of use patents.¹³⁹ A repurposed drug can be protected by either, or both, kinds of patents.

¹³³ 35 U.S.C. §§ 101–103 (2016).

¹³⁴ *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980).

¹³⁵ DONALD S. CHISUM, CHISUM ON PATENTS § 5.01 (2016).

¹³⁶ *Id.* § 3.01.

¹³⁷ *Id.* § 4.01.

¹³⁸ The analysis of whether a repurposed drug may be patented will be conducted on every repurposed drug that a developer wishes to patent, because no drug will (or can be) exactly the same.

¹³⁹ Tahir Amin & Aaron Kesselheim, *Secondary Patenting of Branded Pharmaceuticals: A Case Study on Two HIV Drugs Could Be Extended for Decades*, 31 HEALTH AFF. 2286 (2012).

ii. Composition of Matter Patent

Composition of matter patents protect “all compositions of two or more substances,”¹⁴⁰ also known as the API and the drug’s unique chemical formulations. In order to receive a composition of matter patent, a repurposed drug faces a major roadblock: establishing novelty. The old drug’s API already exists, so in order for a repurposed drug to receive a composition of matter patent, the repurposed drug must have a novel API. This means the developer must manipulate the old drug’s API such that new repurposed drug’s API is a new chemical compound. At the same time, the new API or chemical formulation must still be non-obvious and useful. If it is obvious or not useful, then the repurposed drug will not be patent eligible.

Composition of matter patents generally provide the strongest protection for pharmaceuticals because it prevents others from using the API for any purpose.¹⁴¹ Richard Smith, an attorney whose practice focuses on representing life science companies,¹⁴² notes, however, that “[t]he success of such composition of matter patents in protecting the repositioned drug product will depend in large part on the availability of generic products that can be substituted through off-label use to achieve the same therapeutic result as the repositioned product.”¹⁴³

The requirements for FDA NCE exclusivity are quite similar to the composition of matter patent requirements in that both exclusivity regimes require the API to be novel. Therefore, if a repurposed drug’s API is not novel, then a developer will receive neither a composition of matter patent, nor NCE exclusivity. For example, Mozobil was originally indicated as an inhibitor for HIV infection (it never launched on the market) and was repurposed to treat multiple myeloma, a cancer that forms in the white blood

¹⁴⁰ *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980).

¹⁴¹ Smith, *supra* note 30, at 131.

¹⁴² *Richard B. Smith*, MCDERMOTT WILL & EMERY,

<https://www.mwe.com/en/team/s/smith-richard-b> (last accessed Dec. 3, 2016).

¹⁴³ Smith, *supra* note 30, at 133.

cells causing cancer cells to build up in the bone marrow.¹⁴⁴ Mozobil's repurposed treatment was used in combination with G-CSF (a protein that makes white blood cells for bone marrow)¹⁴⁵ to mobilize haematopoietic stem cells (cells that can develop into blood cells)¹⁴⁶ to treat multiple myeloma.¹⁴⁷ In 2008, the FDA granted NCE exclusivity for Mozobil, which expired in 2013, and the developer received a composition of matter patent that will expire in 2023.¹⁴⁸ If Mozobil's new API was not innovative, then it could not have received protection under either type of exclusivity.

iii. Method of Use Patents

Method of use patents protect the use of the API to treat a specific disease and the method of dosing a patient.¹⁴⁹ The API itself need not be novel, just the indication for which the API is being used. A repurposed drug can receive a method of use patent when the repurposed drug treats a new indication or a new method of dosing a patient. Again, the new indication or method of dosing must still be non-obvious and useful. In the event that the new indication was obvious or not useful, a repurposed drug will not be patent eligible. In order to establish non-obviousness, drug developers filing for a method of use patent for a repurposed drug must surpass the "obvious to try doctrine." The doctrine,

¹⁴⁴ Mayo Clinic Staff, *Diseases and conditions: Multiple Myeloma*, MAYO CLINIC (Dec. 4, 2015), <http://www.mayoclinic.org/diseases-conditions/multiple-myeloma/basics/definition/con-20026607>.

¹⁴⁵ *Granulocyte colony stimulating factor (G-CSF)*, CANCER RESEARCH UK, <http://www.cancerresearchuk.org/about-cancer/cancers-in-general/treatment/cancer-drugs/gcsf> (last accessed Dec. 3, 2016).

¹⁴⁶ *NCI Dictionary of Cancer Terms*, NAT'L CANCER INST. <https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=693540> (last accessed Dec. 3, 2016).

¹⁴⁷ Smith, *supra* note 30, at 132.

¹⁴⁸ *Patent and Exclusivity for: N022311*, U.S. FOOD & DRUG ADMIN., http://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=022311&Appl_type=N (last accessed Dec. 3, 2016).

¹⁴⁹ Smith, *supra* note 30, at 133.

established in *KSR International v. Teleflex*, holds that a patent claim can be proven obvious by showing that the combination of elements used in the invention was obvious to try.¹⁵⁰ This means that if a person having ordinary skill in the art would have tried the new method of dosing or tried combining the API to treat the new indication, then the repurposed drug will be considered obvious and thus patent ineligible.

Method of use patents tend to provide less protection to drug developers because they do not prevent competitors from selling the drug for other indications (provided the drug is off-patent for those other indications).¹⁵¹ Although discovering new indications may be scientifically easier than discovering a new, safe, and effective API (for which the developer could receive a composition of matter patent), drug developers may be wary of doing this due to the less robust patent protection the developer would receive under a method of use patent. Further, in the event that a drug developer receives a method of use patent for a new indication or method of dosing, the developer may have to contend with existing patents on the original drug. This could “prevent the discoverer of a new method of treatment from marketing that treatment without a license from the owner of the patent on the drug.”¹⁵²

A drug developer conceivably could receive both composition of matter and method of use patents. For example, the developer of Mozobil received a composition of matter patent, NCE exclusivity, as well as a method of use patent for the

¹⁵⁰ *KSR Int’l v. Teleflex*, 550 U.S. 398, 421 (2007); *2141 Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 [R-07.205]*, USPTO.GOV, <https://www.uspto.gov/web/offices/pac/mpep/s2141.html> (last updated Nov. 4, 2015).

¹⁵¹ Rebecca S. Eisenberg, *Pharmaceutical Innovation and Cost: An American Dilemma: The Problem of New Uses*, 5 YALE J. HEALTH POL’Y L. & ETHICS 717, 724 (2005) (citing *Allergan Inc. v. Alcon Labs. Inc.*, 324 F.3d 1322 (Fed. Cir. 2003)).

¹⁵² James R. Whittle, Note, *Tailored Treatment, Tailored Enforcement: Protecting Innovation in Personalized Medicine from a Patent-Protection Loophole*, 84 GEO. WASH. L. REV. 480, 488 (2016); Eisenberg, *supra* note 151, at 724 (citing *In re Marshall*, 578 F.2d 301, 304 (C.C.P.A. 1978)).

mobilization of the haematopoietic stem cell, which expires in 2023.¹⁵³ With such market exclusivity, a drug developer may find it worthwhile to license the original drug to exercise the method of use patent.

VII. ROOM TO GROW

There are many areas in which the industry can be improved so as to facilitate more drug repurposing, including greater access to data, identifying alternative incentives to repurpose, and clarifying the drug repurposing regulatory regime.

A. *More Access to Data*

Currently, data sharing is not required in the pharmaceutical industry, and the pharmaceutical industry is very competitive by nature. “Pharmaceutical manufacturers, like other businesses, keep many details of their research and development (R&D) secret to gain and preserve a competitive advantage.”¹⁵⁴ The identification of potential uses of old drugs, however, can only be done by understanding the pharmacologic and toxicological drug factors.¹⁵⁵ For approved drugs, this data is held with the FDA. The data is also sometimes published in publicly available open science journals, such as PLoS.¹⁵⁶ The industry is “less forthcoming, however, when disclosing the thousands of ‘failed’ drug assets to the wider research community. . . . [F]or drug repurposing of failed compounds to truly realize its potential, additional mechanisms need to be found that incentivize both large

¹⁵³ Smith, *supra* note 30, at 132; *Patent and Exclusivity for: N022311*, *supra* note 148.

¹⁵⁴ Aaron S. Kesselheim & Michelle M. Mello, *Confidentiality Laws and Secrecy in Medical Research: Improving Public Access to Data on Drug Safety*, 26 *HEALTH AFFAIRS* 483 (Mar. 2007).

¹⁵⁵ Foster Riley, *supra* note 53, at 309.

¹⁵⁶ See *id.* at 310; see *PLoS Open for Discovery*, PLoS, <https://www.plos.org/> (last accessed Dec. 3, 2016).

and small companies to release data.”¹⁵⁷ Understandably, the idea of open source data for repurposing would receive resistance from pharmaceutical companies; however, pharmaceutical companies may be more forthcoming if they were compensated for disclosing failed drugs to a government pharmaceutical library.

Additionally, the creation of a comprehensive database containing the pharmacological and toxicological data for drugs in every pharmaceutical library would assist researchers in finding different disease targets for which a drug may be used.¹⁵⁸ Drug data is held either in the various pharmaceutical libraries (for which access can cost as much as \$5,000),¹⁵⁹ by the pharmaceutical company, by the FDA, or is publicly available in scientific literature. Collecting the data in one place would greatly ease and increase a researcher’s ability to identify target diseases. An alternative option to a comprehensive database would be to allow open access (or a minimal fee) to pharmaceutical libraries. Currently, the libraries require researchers to purchase the drug in order to acquire it.¹⁶⁰

B. Creating New and Additional Incentives

Literature focuses on intellectual property rights and FDA regulatory exclusivity as the main drivers of drug repurposing research and development; however, there is debate as to what other incentives could properly motivate the pharmaceutical industry to invest in drug repurposing.¹⁶¹ Bruce Bloom, President and Chief Science Officer of Cures Within Reach, asserts

¹⁵⁷ Editorial, *Bring Out Your Dead*, 33 NATURE BIOTECHNOLOGY 1 (Jan. 9, 2015), <http://www.nature.com/nbt/journal/v33/n1/pdf/nbt.3123.pdf>.

¹⁵⁸ Chong & Sullivan, *supra* note 23, at 646.

¹⁵⁹ *Id.*

¹⁶⁰ *Id.*

¹⁶¹ See, e.g., Smith, *supra* note 30, at 131; Sem, *supra* note 14, at 152; Stephen Naylor et al., *Therapeutic Drug Repurposing, Repositioning and Rescue Part III market exclusivity using Intellectual Property and regulatory pathways*, DDW (Summer 2015), <http://www.ddw-online.com/drug-discovery/p274232-therapeutic-drug-repurposing:-repositioning-and-rescue.html>; Kremer & Jones, *supra* note 43.

“government incentives focused on rare diseases will fuel this industry repurposing revolution.”¹⁶² Mr. Bloom, however, does not specify what those incentives should be – whether it be grants, prizes, tax incentives, or extended market exclusivity.

Some scholars argue that offering prizes¹⁶³ could prove to be an additional financial motivator for drug developers to utilize drug repurposing so as to develop new drugs.¹⁶⁴ Prizes, which are conditioned on delivering the specified invention,¹⁶⁵ would motivate drug developers to repurpose in order to receive the prize (money). These scholars claim that a prize system would encourage pharmaceutical companies to repurpose drugs because the government would offer prizes for new uses of old drugs based on the indications’ social value.¹⁶⁶ Professor Roin doubts the effectiveness of such a system. He claims prize payouts would be based on the drug’s sales volume which “would conflate sales for the old and new uses, much like monopoly rights that block generic entry.”¹⁶⁷ There is little agreement on which additional incentives will properly motivate pharmaceutical companies.

¹⁶² Bruce E. Bloom, *Recent successes and future predictions on drug repurposing for rare diseases*, 4 EXPERT OP. ON ORPHAN DRUGS 1, 3 (2016).

¹⁶³ Prizes are payments funded out of general revenue that is made to a drug developer conditional on delivering the specified invention. See Nancy Gallini & Suzanne Scotchmer, 2 *Intellectual Property: When is it the Best Incentive System?*, in INNOVATION POLICY AND THE ECONOMY 53 (2002). Prizes are frequently utilized by the federal government. See generally *Challenges*, U.S. GEN. SERV. ADMIN., <https://www.challenge.gov/list/> (last visited Apr. 16, 2017).

¹⁶⁴ AIDAN HOLLIS & THOMAS POGGE, THE HEALTH IMPACT FUND: MAKING NEW MEDICINES AVAILABLE FOR ALL 14–15, 17 (2008); William Fisher & Talha Syed, *Prizes*, 43, 46 (2012), http://cyber.law.harvard.edu/people/tfisher/Drugs_Chapter7.pdf.

¹⁶⁵ Gallini & Scotchmer, *supra* note 163, at 53.

¹⁶⁶ Roin, *supra* note 12, at 1051 (citing AIDAN HOLLIS & THOMAS POGGE, THE HEALTH IMPACT FUND: MAKING NEW MEDICINES AVAILABLE FOR ALL 14–15, 17 (2008) and William Fisher & Talha Syed, *Prizes* 43 & 46 (2012), http://cyber.law.harvard.edu/people/tfisher/Drugs_Chapter7.pdf).

¹⁶⁷ *Id.*

C. Clarification of the Regulatory Regime

As previously discussed, there is no explicit regulatory guidance regarding how drug developers may gain FDA approval for repurposed drugs or avoid patent infringement when conducting repurposing research. Instead, drug developers rely on the ambiguities of the Hatch-Waxman Act's safe harbor provision to protect their repurposing research from claims of infringement. The Hatch-Waxman Act, however, was intended to create a regulatory regime for generic drugs, not for repurposed ones.¹⁶⁸

Nonetheless, drug developers may likely receive FDA guidance on the use of real life data in drug approval applications. As previously discussed, the 21st Century Cures Act¹⁶⁹ facilitates the submission of data summaries¹⁷⁰ of real life data and data previously submitted to the FDA¹⁷¹ for NDA applications.¹⁷² The FDA's deliverable schedule for the implementation of the 21st Century Cures Act provides for the development of a plan, framework, draft guidance, and revised draft or final guidance related to the use of real world evidence. These deliverables, however, currently have no statutory deadline for completion.¹⁷³

¹⁶⁸ Sem, *supra* note 14, at 152.

¹⁶⁹ 21st Century Cures Act, H.R. 6, 114th Cong. (2016).

¹⁷⁰ Kaplan, *supra* note 38.

¹⁷¹ 21st Century Cures Act, H.R. 34, 114th Cong. § 3012 (2016) (as codified in 21 U.S.C. § 529A(b)(1)–(2)).

¹⁷² 21st Century Cures Act, H.R. 34, 114th Cong. § 3012 (2016) (as codified in 21 U.S.C. § 529A).

¹⁷³ *21st Century Cures Act Deliverables*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentsToTheFDCAct/21stCenturyCuresAct/ucm562475.htm> (last updated Nov. 5, 2017).

* J.D. 2017, DePaul University College of Law. This Article was written for DePaul University College of Law's Fall 2016 Health Innovation and Intellectual Property course.

So while the FDA intends to provide guidance, it is unknown when the industry may expect such.

VIII. CONCLUSION

Drug repurposing has the potential to bring drugs to market more quickly, inexpensively, and successfully than before. Despite the lack of a regulatory regime directed explicitly towards drug repurposing, industry players seemingly have not been deterred from engaging in the practice. To encourage increased participation in repurposing, the industry needs wider access to data, new and additional incentives, and a clear intellectual property and regulatory regime.

*Kathryn Brown**

