

SOLVING THE PROBLEM OF NEW USES BY CREATING INCENTIVES FOR PRIVATE INDUSTRY TO REPURPOSE OFF-PATENT DRUGS

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Abstract

One of the most dramatic public-policy failures affecting biomedical research is the lack of incentives for industry to develop new therapeutic uses (“indications”) for off-patent drugs—generally known as “the problem of new uses.” Recent technological advances have allowed researchers to identify hundreds of potential new indications for older drugs that could address critical unmet medical needs. And researchers are poised to discover hundreds more. Developing new uses for FDA-approved drugs (known as “drug repurposing”) is much faster, cheaper, and less risky than developing new drugs, and therefore offers what may be the single most promising avenue for delivering new medical treatments to the public. Many commentators argue that a viable business model to support drug repurposing could solve the pharmaceutical industry’s protracted “productivity crisis,” and that it would provide the NIH with a pathway across the proverbial “Valley of Death” in biomedical research. Unfortunately, that business model does not exist. Pharmaceutical companies invariably lose interest in developing new uses for drugs once generics enter the market. The prior scholarship on this problem attributes it to a gap in the patent-based incentives for drug development. But the government already offers patent rights for new uses of existing drugs, which could provide the appropriate incentives for developing those new medical treatments. On paper, these new-use patents give pharmaceutical companies the right to charge payers when physicians prescribe an off-patent drug for a new use without preventing patients from using low-cost generics for the drug’s older, unpatented uses. However, pharmaceutical companies cannot enforce these rights without knowing when physicians prescribe the drug for the patented indication as opposed to some other use. In this sense, the problem of new uses is not about the patent system, but rather about the information barriers preventing firms from separating the markets for drugs’ different indications. If the government established an infrastructure for pharmaceutical companies to monitor the prescribed indications when pharmacists fill a prescription, those firms would possess the information necessary to enforce patents on new indications, thereby solving the problem of new uses. This Article argues that the government could easily create such an infrastructure with electronic-prescribing software and electronic medical records, and that the insurance industry’s success in using prior authorization to enforce indication-based coverage restrictions is proof-of-concept for this solution’s effectiveness.

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I. INTRODUCTION

Society’s investments in pharmaceutical R&D are subject to a significant economic distortion that is likely denying the public medical treatments for critical unmet needs. The pharmaceutical industry spends tens of billions of dollars each year on clinical trials for new drugs.¹ Yet it spends almost nothing on trials to establish new therapeutic uses (“indications”) of existing drugs that are off patent.² Over the past few years, researchers have uncovered hundreds of potential new indications for older drugs, many of which would provide desperately needed medical breakthroughs if they prove effective.³ There is a growing consensus among

1. See Kenneth A. Getz, *Sizing Up the Clinical Research Market*, CENTERWATCH 3 (2010).

2. See Philip Walson, *Generic and Therapeutic Orphans*, 1 GENERICS & BIOSIMILARS INITIATIVE J. 39 (2012).

3. See *infra* notes 331-341 and accompanying text.

experts that testing old drugs for new uses (“drug repurposing”)⁴ is one of the most promising avenues for developing new medical treatments⁵—including Francis Collins, director of the National Institutes of Health (NIH), who describes it as a “key opportunity” to become “more efficient and effective at delivering therapies and diagnostics to patients.”⁶ The public foregoes these benefits unless someone tests the safety and efficacy of these potential new indications in clinical trials.⁷ Clinical trials are costly,⁸ and the government remains unwilling or unable to provide the necessary funding.⁹ The public primarily relies on private industry to finance clinical studies for investigational new medical treatments,¹⁰ particularly the expensive late-stage clinical trials necessary to complete a new treatment’s development.¹¹ But the government does not offer pharmaceutical companies any meaningful incentives to repurpose existing drugs once generics are available.¹² This well-known gap in the incentives for pharmaceutical innovation¹³—which is

4. The National Institutes of Health (NIH) defines “repurposing” as “studying a small molecule or a biologic approved by the FDA to treat one disease or condition to see if it is safe and effective for treating other diseases.” National Center for Advancing Translational Sciences, NIH, *Rescuing and Repurposing Drugs*, at <http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/rescue-repurpose.html>.

5. See Michael J. Barratt & Donald E. Frail, *Introduction*, in *DRUG REPOSITIONING: BRINGING NEW LIFE TO SHELVED ASSETS AND EXISTING DRUGS* 1 (Michael J. Barratt & Donald E. Frail, Eds. 2012); *infra* notes 343-359 and accompanying text.

6. Francis S. Collins, *Mining for Therapeutic Gold*, 10 *NATURE REVIEWS DRUG DISCOVERY* 397 (2011).

7. See JERRY AVORN, *POWERFUL MEDICINES: THE BENEFITS, RISKS, AND COSTS OF PRESCRIPTION DRUGS* 39-68 (2004) (discussing the crucial importance of evaluating new treatments in clinical trials for medical practice); *infra* notes 163-174 and accompanying text.

8. *Infra* Part II.D.

9. See Tudor I. Oprea & J. Mestres, *Drug Repurposing: Far Beyond New Targets for Old Drugs*, 14 *AAPS J.* 759, 762 (2012); 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); see *infra* Part IV.B.

10. See Getz, *supra* note 1, at 3 (reporting that in 2008, private industry spent \$35.3 billion on clinical trials for investigational drug and device treatments compared to \$3.0 billion spent by the U.S. federal government); *infra* note 287.

11. See *infra* notes 295-298, and accompanying text.

12. See *infra* Part III.

13. See Christopher P. Austin, *Systematic Drug Repurposing: Some Successes, Caveats, and Directions*, presentation at IOM Roundtable on Translating Genomic-Based Research for Health, Mar. 20, 2012, at 16; Henry Grabowski, et al., *Does Generic Entry Always Increase Consumer Welfare?*, 67 *FOOD & DRUG L.J.* 373, 382 (2012); Thomas A. Hemphill, *The NIH Promotes Drug Repurposing and Rescue*, 55 *RESEARCH TECHNOLOGY MANAGEMENT* 6, 8 (2012); INSTITUTE OF MEDICINE (IOM), *GENOME-BASED THERAPEUTICS: TARGETED DRUG DISCOVERY AND DEVELOPMENT: WORKSHOP SUMMARY* 45 (2012); PRESIDENT’S COUNCIL OF ADVISORS ON SCIENCE AND TECHNOLOGY (PCAST), *REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION* 24-25 (2012); Arti K. Rai, *Use Patents, Carve-Outs, and Incentives – a New Battle in the Drug-Patent Wars*, 367 *N. ENG. J. MED.* 491, 492 (2012); Walson, *supra* note 2, at 39; Weir et al., *supra* note 9, at 1057; Editorial, *Change of Purpose*, 465 *NATURE* 267, 267-68 (2010); Mark S. Boguski et al., *Repurposing with a Difference*, 324 *SCIENCE* 1394, 1395 (2009); Talha Syed, *Should a Prize System for Pharmaceuticals Require Patent Protection for Eligibility?*, IGH Discussion Paper No. 2, 3-5 (2009), at http://healthimpactfund.org/wp-content/uploads/2012/11/DP2_Syed.pdf; Christopher-Paul Milne & Jon B. Bruss, *The Economics of Pediatric Formulation Development for Off-Patent Drugs*, 30 *CLINICAL THERAPEUTICS* 2133, 2136 (2008); Rebecca S. Eisenberg, *The Problem of New Uses*, 5 *YALE J. HEALTH POL’Y & ETHICS* 717, 718 (2005) (hereinafter, *New Uses*); Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 *FOOD & DRUG L.J.* 187, 191 (1999); Annetine C. Gelijns et al., *Capturing the Unexpected Benefits of Medical Research*, 339 *N. ENG. J. MED.* 693 (1998).

sometimes called the “problem of new uses”¹⁴—has resulted in nearly all of these potential new medical treatments remaining untested hypotheses.¹⁵ Experts widely agree that this public-policy failure must be corrected,¹⁶ but thus far have been unable to identify a viable solution.¹⁷

The pharmaceutical industry, perhaps more than any other industry, depends on legal barriers to imitation to generate a return on its R&D investments.¹⁸ Nowhere else in our economy will firms spend in excess of \$1 billion to bring a discrete product to market that rivals can imitate for mere fractions of a cent on the dollar.¹⁹ With minimal R&D expenses, generic manufacturers sell their products for 15% to 25% of the brand-name drug’s price on average.²⁰ Not surprisingly, generics usually capture about 80% of the pharmaceutical company’s sales within four to six weeks of launching.²¹ Since pharmaceutical companies cannot compete effectively against generic manufacturers, their business model hinges on the ability to block generic entry for long enough to recoup their R&D investments.

14. Eisenberg, *New Uses*, *supra* note 13.

15. *See* Oprea & Mestres, *supra* note 9.

16. NIH officials have called for “a new funding paradigm” to support repurposing generic drugs. Austin, *supra* note 13 at 19; *see also* Weir et al., *supra* note 9, at 1057. A recent *Nature* editorial declared that “[t]he United States should protect investments used to find new uses for old drugs.” *Change of Purpose*, *supra* note 13, at 267. And a report from the President’s Council of Advisors on Science and Technology concludes that new “economic incentives may be required ... to encourage study of potential new uses of drugs that no longer have patent protection.” PCAST, *supra* note 13, at 73 (reserving judgment on specific reform proposals).

17. *See infra* notes 432-437, and accompanying text.

18. Pharmaceuticals is one of the few industries about which scholars widely agree that firms rely heavily on legal barriers to imitation to appropriate the returns from their R&D investments. *See* DAN L. BURK & MARK A. LEMLEY, *THE PATENT CRISIS AND HOW THE COURTS CAN SOLVE IT* 4, 65 (2009); Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 *TEX. L. REV.* 503, 507-15 (2009) (hereinafter *Unpatentable Drugs*); JAMES BESSEN & MICHAEL J. MEURER, *PATENT FAILURE: HOW JUDGES, BUREAUCRATS, AND LAWYERS PUT INNOVATORS AT RISK* 88-89 (2008); FEDERAL TRADE COMMISSION (FTC), *TO PROMOTE INNOVATION: THE PROPER BALANCE OF COMPETITION AND PATENT LAW AND POLICY* 14 (2003); ADAM B. JAFFE & JOSH LERNER, *INNOVATION AND ITS DISCONTENTS: HOW OUR BROKEN PATENT SYSTEM IS ENDANGERING INNOVATION AND PROGRESS, AND WHAT TO DO ABOUT IT* 39-41 (2004).

19. While pharmaceutical companies spend over \$1 billion to successfully develop a single new drug, generic manufacturers can usually imitate those products for only a few million dollars. *See Big Generic Pharma*, *ECONOMIST*, vol. 376, Jul. 30, 2005, at 58; Federal Trade Commission (FTC), *Emerging Health Care Issues: Follow-on Biologic Drug Competition* 14 (2009). And while de novo drug development takes twelve to sixteen years on average, the average development time for generic drugs (including the time needed to setup manufacturing facilities) is reported to be around two to three years. *See* Bruce N. Kuhlik, *The Assault on Pharmaceutical Intellectual Property*, 71 *U. CHI. L. REV.* 93, 96 (2004); Sandoz Biopharmaceuticals, *Biosimilar Development*, at <http://sandoz-biosimilars.com/biosimilars/development.shtml> (“For a small-molecule generic, ... development may be completed in 2-3 years, at a cost of USD 2-3 million.”).

20. *See* United States Food and Drug Administration (FDA), *Facts About Generic Drugs* (2012) at http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/understandinggenericdrugs/ucm167991.htm#_ftnref3.

21. *See* Rich Silver, *A Wall Street Perspective on Generics*, 2007 GPhA Annual Meeting, at 6 (2007) available at <http://www.gphaonline.org/AM/CM/ContentDisplay.cfm?ContentFileID=593>. Some estimates point to a slightly more gradual erosion of brand-name drug sales to generics, such as a 70 percent drop in market share within six months of generic entry. *See* Datamonitor, *US Most Susceptible to Brand Erosion Post Patent Expiry*, Jan. 13, 2011, at <http://about.datamonitor.com/media/archives/5293>.

The Drug Price Competition and Patent Term Restoration Act of 1984 (“Hatch-Waxman Act”)²² sets up the legal framework that provides temporary monopoly protection over new drugs to encourage their development.²³ Through their patents and FDA-exclusivity periods, pharmaceutical companies usually enjoy 10 to 15 years of monopoly protection over their new drugs following FDA approval (12 years on average) before generics enter and take over their market.²⁴ Despite its well-known imperfections,²⁵ most commentators agree that this system has been effective at promoting private sector drug development.²⁶ The patent system in particular can probably take credit for private industry spending tens of billions of dollars annually developing new drugs.²⁷ The available evidence indicates that those investments generated substantial gains in social welfare.²⁸

Congress designed the Hatch-Waxman framework to encourage firms to develop new drugs, but there are other important forms of pharmaceutical innovation not covered by the Act—in particular, new uses for existing drugs.²⁹ As an alternative to creating and testing a novel drug compound to treat a particular disease, pharmaceutical companies can sometimes test a drug already on the market to demonstrate its efficacy for that same indication.³⁰ Evidence from

22. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended 21 U.S.C. §355 (1994)); *see also* Mutual Pharmaceutical Co. v. Bartlett, 133 S.Ct. 2466, 2471 (2013).

23. *See* JOHN R. THOMAS, PHARMACEUTICAL PATENT LAW 4-26 (2005).

24. *See* Henry Grabowski & Margaret Kyle, *Generic Competition and Market Exclusivity Periods in Pharmaceuticals*, 27 MANAGERIAL & DECISION ECON. 491, 497 fig. 4 (2007); C. Scott Hemphill & Baven N. Sampat, *Evergreening, Patent Challenges, and Effective Market Life in Pharmaceuticals*, 31 J. HEALTH ECON. 327, 330 (2012).

25. *See infra* notes 438-443, and accompanying text (discussing flaws in the current drug-patent system).

26. *See* Edwin Mansfield et al., *Imitation Costs and Patents: An Empirical Study*, 91 ECON. J. 907, 915 (1981); Edwin Mansfield, *Patents and Innovation: An Empirical Study*, 32 MGMT SCI. 173, 175 n.8 (1986); C.T. TAYLOR & Z. A. SILBERSTON, THE ECONOMIC IMPACT OF THE PATENT SYSTEM 199 (1973); Knut Blind et al., *Motives to Patent: Empirical Evidence from Germany*, 35 RES. POL. 655 (2006); Wesley M. Cohen et al., *Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (or Not)* 9, NBER Working Paper 7552 (2000); Stuart J.H. Graham et al., *High Technology Entrepreneurship and the Patent System: Results of the 2008 Berkeley Patent Survey*, 24 BERKELEY TECH. L.J. 1255, 1290-93 & fig.1 (2010); Richard C. Levin et al., *Appropriating the Returns from Industrial Research and Development*, 1987 BROOKINGS PAPERS ON ECONOMIC ACTIVITY 783, 796-98 (1987).

27. Devising reliable empirical tests of the patent system’s role in promoting pharmaceutical innovation is difficult. But there is compelling qualitative evidence that pharmaceutical companies are generally unwilling to develop new drugs without strong patent protection, which suggests that patents are a necessary incentive for most drug development. *See* Roin, *Unpatentable Drugs*, *supra* note 18, at 545-47; Alexander Masters, *Is It Time for the Public to Start Funding Cancer Research*, THE TELEGRAPH, Jun 15, 2013; ROBERT M. RYDZEWSKI, REAL WORLD DRUG DISCOVERY: A CHEMIST’S GUIDE BIOTECH AND PHARMACEUTICAL RESEARCH 117 (2010); William T. Comer, *Introduction*, in 8 COMPREHENSIVE MEDICINAL CHEMISTRY 4 (John B. Taylor & David J. Triggle eds. 2007); R.D. Connell, *In-House or Out-Source*, in 2 COMPREHENSIVE MEDICINAL CHEMISTRY 219 (John B. Taylor & David J. Triggle eds. 2006); Charles G. Smith, *Defining the Actual Research Approach to the New Drug Substance*, in THE PROCESS OF NEW DRUG DISCOVERY AND DEVELOPMENT 332 (Charles G. Smith & James T. O’Donnell eds. 2006).

28. *See* David M. Cutler & Mark McClellan, *Is Technological Change in Medicine Worth It?: When Costs and Benefits Are Weighed Together, Advantages Have Proved to Be Worth Far More than Their Costs*, 20 HEALTH AFF. 11, 23 (2001); Frank R. Lichtenberg, *The Benefits to Society of New Drugs: A Survey of the Econometric Evidence*, in ENGAGING THE NEW WORLD: RESPONSES TO THE KNOWLEDGE ECONOMY 204, 205–19 (Bhajan S. Grewal & Margarita Kumnick eds., 2006).

29. *See* Mossinghoff, *supra* note 13, at 191.

30. *Infra* Part II.A.

case studies suggests that the social returns from these investments may be equal (or perhaps greater) than the returns from developing a new drug.³¹

Drug repurposing was once an obscure topic in the medical literature, but no longer. Recent technological advances now permit researchers to rapidly screen known drugs for potential new indications.³² The new screening tools uncovered a wealth of potential treatments for unmet medical needs hidden within our existing arsenal of FDA-approved drugs.³³ These findings generated an explosion of interest within the biomedical research community about the possibility of repurposing existing drugs for new indications.³⁴ Researchers express hope that developing new uses for existing drugs would help “convert cancer into a treatable chronic disease.”³⁵ There is also a growing “expectation that a substantial percentage of rare diseases if not all 8000 rare diseases[, which together afflict 15% to 20% of the global population,] might be treatable with drugs in the current pharmacopeia.”³⁶ Furthermore, many experts now believe

31. See R.N. Spivey, et al., *New Indications for Already-Approved Drugs: Time Trends for the New Drug Application Review Phase*, 41 CLINICAL PHARMACOLOGY & THERAPEUTICS 368, 368-69 (1987) (citing various examples of new indications for FDA-approved drugs resulting in large public health benefits); Ernst R. Berndt, et al., *The Impact of Incremental Innovation in Biopharmaceuticals: Drug Utilisation in Original and Supplemental Indication*, 24 Suppl. 2 PHARMACOECONOMICS 69, 81-82 (2005); Joshua Cohen et al., *Role of Follow-On Drugs and Indications on the WHO Essential Drug List*, 31 J. CLINICAL PHARMACY & THERAPEUTICS 585 (2006) (finding that among drugs listed on the World Health Organization’s (WHO) Essential Drug List, 15% were included for supplemental indications).

32. See *infra* notes 326-327, and accompanying text; Francesco Iorio, *Genome-Based Drug Discovery and Repurposing: A New Golden Age for DNA Microarrays?*, REVIEWS IN COMPUTATIONAL BIOLOGY (2012) at http://christophe.dessimoz.org/revcompbiol/_media/2012/t3-drug-repurposing.pdf; Paul A. Novick et al., *SWEETLEAD: an In Silico Database of Approved Drugs, Regulated Chemicals, and Herbal Isolates for Computer-Aided Drug Discovery*, 8 PLOS ONE e79586, 1 (2013); Ruili Huang et al., *The NCGC Pharmaceutical Collection: A Comprehensive Resource of Clinically Approved Drugs Enabling Repurposing and Chemical Genomics*, 3 SCI TRANSL MED. 80ps16 (2011).

33. See *infra* notes 331-341, and accompanying text; Oprea & Mestres, *supra* note 9 (“Recent academic enthusiasm in this field has resulted in the publication of relatively long lists of drugs that could potentially be repurposed for a variety of indications, including tuberculosis, breast and prostate cancer, and myelogenous leukemia.”); Sean Ekins et al., *In Silico Repositioning of Approved Drugs for Rare and Neglected Diseases*, 16 DRUG DISCOVERY TODAY 298 (2011); Sean Ekins & Antony J. Williams, *Finding Promiscuous Old Drugs for New Uses*, 28 PHARM RES. 1785 (2011); Michael J. Keiser et al., *Predicting New Molecular Targets for Known Drugs*, 462 NATURE 175 (2009); Huang et al. *supra* note 32.

34. See Seth Lederman, *Drug Repurposing Rekindles Promise*, GENETIC ENGINEERING & BIOTECHNOLOGY NEWS, Jan. 30, 2013 (“Reflecting the appeal of drug repurposing, 2012 witnessed several conferences for researchers [on the subject] A few years ago, no such conferences existed.”); *infra* Part V.A.

35. Carlos M. Telleria, *Drug Repurposing for Cancer Therapy*, 4 J. CANCER SCI. THER. ix (2012); see also Subash C. Gupta et al., *Cancer Drug Discovery by Repurposing: Teaching New Tricks to Old Dogs*, 34 TRENDS IN PHARMACOLOGICAL SCIENCES 508, 515 (2013) (noting that because “starting with an existing old drug with a known clinical history can significantly reduce the time and cost associated with the development of new drugs for the prevention and treatment of cancer,” “[w]e hope that drug repurposing will play a high-impact role in developing new cancer drug therapies and bringing these therapies rapidly to patients who are in great need of medicine to cure this deadly disease.”); *infra* note 332.

36. See Ramaiah Muthyala, *Orphan/Rare Drug Discovery Through Drug Repositioning*, 8 DRUG DISCOV TODAY THER STRATEG. 71 (2011). The overall health burden of most rare diseases is relatively small, but the health burden associated with rare diseases collectively is massive. See INSTITUTE OF MEDICINE (IOM), RARE DISEASES AND ORPHAN PRODUCTS: ACCELERATING RESEARCH AND DEVELOPMENT xi (2010) (“Rare diseases are not rare, at least in aggregate. Approximately 7,000 rare diseases afflict millions of individuals in the United States and are responsible for untold losses in terms of physical health, behavioral health, and socioeconomic condition.”).

that drug repurposing offers the best—and perhaps only—chance in the near-term to discover effective treatments for Alzheimer’s disease and many other central nervous system disorders.³⁷

Developing new uses for existing drugs offers significant economic advantages over the standard practice of developing new drugs (a process referred to as “de novo drug development”).³⁸ Developing a new drug is a massive financial undertaking, costing an estimated \$1.2 billion³⁹ and taking 12 to 16 years on average.⁴⁰ Roughly one-third to one-half of the total costs are attributable to the drug-discovery and preclinical-development stages, with the remainder attributable to clinical development and FDA approval.⁴¹ When firms test an FDA-approved drug for a new indication instead of developing a new drug, they skip most of the de novo drug development process, including the work involved in drug discovery, preclinical development, and often early clinical trials.⁴² Consequently, drug repurposing reportedly costs

37. See Anne Corbett et al., *Drug Repositioning for Alzheimer’s Disease*, 11 NAT REV DRUG DISCOV. 833 (2012); Nancy Butcher, *Old Drugs and New Tricks: Repurposing Drugs to Treat Psychiatric Disorders*, 1 IMS MAGAZINE 21, 21 (2013) (“As industry retreats from psychiatric drug development,” drug repurposing “could provide an unprecedented opportunity to rapidly identify, evaluate, and bring new psychiatric drugs to market and to the patients who need them.”); cf. Lederman, *supra* note 34 (“Repurposing drugs is particularly important in the treatment of CNS disorders, CVD, metabolic disorders, and cancer.”).

38. See Boguski et al., *supra* note 13; Barratt & Frail, *supra* note 5, at 1; Sivanesan Dakshanamurthy et al., *Predicting New Indications for Approved Drugs Using Proteochemometric Method*, 55 J. MED. CHEM. 6832 (2012) (“The most effective way to move from target identification to the clinic is to identify already approved drugs with the potential for activating or inhibiting unintended targets.”); Asher Mullard, *Could Pharma Open Its Drug Freezers?*, 10 NAT. REV. DRUG DISCOVERY 399, 400 (2011).

39. Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 469, 469 & 475 (2007); see also Christopher P. Adams & Van V. Brantner, *Spending on New Drug Development*, 19 HEALTH ECON. 130, 138 (2010); Ben Hirschler, *Drug Industry Treading Water on R&D Productivity*, REUTERS, Dec. 3, 2012. More recent studies estimate that the average capitalized cost of developing a new drug has risen to between \$1.5 and \$1.8 billion. See Jorge Mestre-Ferrandiz et al., *The R&D Cost of a New Medicine*, Office of Health Economics (2012); Steven M. Paul et al., *How to Improve R&D Productivity: the Pharmaceutical Industry’s Grant Challenge*, 9 NAT. REV. DRUG DISCOV. 203, 203 (2010). A few commentators remain adamant that the published studies of pharmaceutical R&D costs grossly overestimate the true costs of drug development. See MARCIA ANGELL, *THE TRUTH ABOUT DRUG COMPANIES AND HOW THEY DECEIVE US* 37-51 (2004); Donald W. Light & Rebecca Warburton, *Demythologizing the High Costs of Pharmaceutical Research*, 6 BIOSOCIETIES 34 (2011); Public Citizen, *Rx R&D Myths: The Case Against the Drug Industry’s R&D ‘Scare Card’* (2001). However, many of the criticisms leveled against these studies are difficult to reconcile with basic financial principles. For example, these critics argue that it is inappropriate to consider the costs of capital when calculating the total costs of drug development for private investors. See ANGELL, *supra* at 45; Light & Warburton, *supra* at 8.

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

41. See DiMasi & Grabowski, *supra* note 39, at 469; Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 180-83 (2003); Paul et al., *supra* note 39, at 206; cf. THOMSON REUTERS, 2012 CMR INTERNATIONAL PHARMACEUTICAL R&D FACTBOOK: EXECUTIVE SUMMARY fig. 5 (2012) (reporting that the distribution of R&D costs between preclinical research (including drug discovery) and clinical research varies by therapeutic class).

42. See Corbett et al., *supra* note 37 (“The time and cost required to advance a [repurposing] candidate treatment into clinical trials can be substantially reduced because in vitro and in vivo screening, chemical optimization, toxicology studies, bulk manufacturing and formulation development have, in many cases, already been completed and can therefore be bypassed.”); *infra* notes 347-349, and accompanying text.

only \$300 million on average and takes between 3 and 12 years.⁴³ Drug repurposing also has a significantly higher success rate because of the greater information available to firms about the pharmacological properties of FDA-approved drugs.⁴⁴ Given these advantages, drug repurposing could allow pharmaceutical companies to invest in more innovative drugs that have a higher risk of failure but, if successful, are more likely to be a medical breakthrough.⁴⁵ Firms could also pursue treatments for smaller markets that would otherwise be unprofitable,⁴⁶ and they could rapidly deliver these new medical treatments to patients in need.⁴⁷

In addition to its economic advantages, drug repurposing also bypasses a critical technological impediment within de novo drug development—the difficulty of finding new compounds suitable for use in medicine.⁴⁸ Designing a compound to be both safe and effective in humans is challenging because making a drug more potent to increase its efficacy also increases its toxicity (among other reasons).⁴⁹ Pharmaceutical companies rely on their medicinal

43. See *infra* notes 177 & 354.

44. INSTITUTE OF MEDICINE (IOM), GENOMICS-ENABLED DRUG REPURPOSING AND REPOSITIONING: A WORKSHOP, Apr. 10, 2013, at <http://iom.edu/Activities/Research/GenomicBasedResearch/2013-JUN-24.aspx> (“While approximately 10% of new drug applications gain market approval, repurposed drugs approach approval rates near 30%, presenting a significant market-driven incentive for companies that also aligns with patient desires for new therapeutics.”); Patricia Fitzpatrick Diamond, *Drug Repositioning Gains in Popularity*, 30 GENETIC ENGINEERING & BIOTECHNOLOGY NEWS (2010); Zhichao Liu et al., *In Silico Drug Repositioning – What We Need To Know*, 18 DRUG DISCOVERY TODAY 110 (2013) (“Because the safety profiles of these drugs are known, clinical trials for alternative indications ... carry less risk than de novo drug development.”); Spyros N. Deftereos et al., *Drug Repositioning and Adverse Event Prediction Using High-Throughput Literature Analysis*, 3 WIRES SYSTEM BIOLOGY & MED. 323 (2011); Xiaoyan A. Qu et al., *Inferring Novel Disease Indications for Known Drugs by Semantically Linking Drug Action and Disease Mechanism Relationships*, 10(Suppl. 5) BMC BIOINFORMATICS S4 (2009); *infra* notes 355-359, and accompanying text.

45. See Francis Collins, *We Need Better Drugs—Now*, TED Talks, Apr. 2012, at http://www.ted.com/talks/francis_collins_we_need_better_drugs_now.html (hereinafter, *Better Drugs*) (“Now [that] we’re learning about all these new molecular pathways” underlying human diseases, existing drugs “could be repositioned or repurposed ... for new applications, basically teaching old drugs new tricks. That could be a phenomenal, valuable activity.”).

46. See John C. Reed, et al., *The NIH’s Role in Accelerating Translational Sciences*, 30 NATURE BIOTECHNOLOGY 16, 18 (2012) (“A more robust drug repurposing effort is particularly needed for rare and neglected diseases, where the return on investment doesn’t warrant billion-dollar investments in development.”); Kovi Bessoff et al., *Drug Repurposing Screen Reveals FDA-Approved Inhibitors of Human HMG-CoA Reductase and Isoprenoid Synthesis That Block Cryptosporidium parvum Growth*, 58 ANTIMICROBIAL AGENTS AND CHEMOTHERAPY 1804, 1805 (2013) (“[D]rug repurposing ... provides an attractive alternative to de novo drug development” because “the prohibitive cost ... poses a barrier to drug development for pathogens ... that disproportionately affect residents in poor countries.”).

47. See Huang et al., *supra* note 32 (“[R]epurposing will not only provide the possibility of rapid therapeutic advances, but also obviate the need for NME [New Molecular Entity] development, a long and expensive process.”).

48. Youssef L. Bennani, *Drug Discovery in the Next Decade: Innovation Needed ASAP*, 17S DRUG DISCOVERY TODAY S31, S36 (2012) (“Currently, the greatest contributors to preclinical and clinical NME failures remain toxicology and translational biology for efficacy.”); Kenneth I. Kaitin, *Deconstructing the Drug Development Process: the New Face of Innovation*, 87 CLINICAL PHARMACOLOGY & THERAPEUTICS 356 (2010) (explaining that “the greatest challenges confronting the research-based industry involve bringing promising new drug candidates out of discovery and into development ...”).

49. See Bennani, *supra* note 48, at S36 (“Striking the right therapeutic window, with a safe profile is often a challenge in discovery settings.”); Michael M. Hann & György M. Keserü, *Finding the Sweet Spot: the Role of Nature and Nurture in Medicinal Chemistry*, 11 NAT REV DRUG DISCOV. 355, 355 (2012) (stating with respect to “analyses comparing compounds that have become marketed drugs with those that failed during development ... it is apparent

chemists to create compounds that can be safely administered to humans at a therapeutically effective dose.⁵⁰ But medicinal chemists acknowledge that it “is an extremely difficult task” to determine whether a compound strikes the right balance between safety and efficacy before it enters clinical trials.⁵¹ Researchers synthesize and evaluate thousands of novel drug compounds to find a handful worthy of testing in clinical trials.⁵² And even with these elaborate and costly screening procedures, the success rate for new drugs entering clinical trials remains a dismal 10 to 20 percent.⁵³ Many of these failures trace back to problems with drugs’ chemical structures.⁵⁴ Repurposing an old drug for a new use allows firms to avoid this technological bottleneck by using one of the select few drug compounds known to be suitable for use in medicine.⁵⁵

Given the economic and scientific advantages to drug repurposing, many commentators argue that a viable business model to support developing new uses for existing drugs would help

that a key challenge for successful drug discovery is finding a balance (or ‘sweet spot’) between two aspects: acknowledging the constraints on the physicochemical properties of drug candidates imposed by the higher risks of compound-related attrition outside the ‘drug-like space’; and maintaining sufficient potency to provide an efficacious dose”); *Overcoming Bottlenecks in Drug Discovery*, MEDNOUS, Feb. 2009, at 8 (“Lack of efficacy and safety are to some extent interrelated because if you select the low dose you very often fail because of lack of efficacy. If you go higher with the dose you obtain efficacy, but also serious side effects.”).

50. See generally EDWARD KERNS & LI DI, *DRUG-LIKE PROPERTIES: CONCEPTS, STRUCTURE DESIGN AND METHODS: FROM ADME TO TOXICITY OPTIMIZATION* (2008).

51. *Overcoming Bottlenecks in Drug Discovery*, *supra* note 49, at 8; see also Bennani, *supra* note 48, at S36 (“[T]he field is still plagued by clinical idiosyncratic toxicities.”); Kaitin, *supra* note 48, at 356 (“In the area of drug discovery, new technologies ... were supposed to usher in a new era of innovative drug discovery,” but “in the absence of appropriate validation tools that would allow researchers to identify molecules having the greatest likelihood of successful development, these discovery technologies merely added time and cost to the R&D process without providing any appreciable benefits.”); Raymond J. Winquist et al., *The Fall and Rise of Pharmacology—(Re-)defining the Discipline?*, 87 CLINICAL PHARMACOLOGY 4 (2014).

52. See GAO, *supra* note 40, at 6 (“Most compounds fail during these first two stages [of drug discovery and preclinical testing], according to PhRMA, only 5 in every 10,000 compounds, on average, successfully completes these two stages.”); Janet Woodcock, *Today’s Biomedical Innovation: ‘Lost in Translation’?*, Apr. 26, 2012, at 4, available at <http://www.qb3.org/sites/qb3.org/files/pictures/docs/Woodcock%202012%200426%20UCSF%20Innovation%20Lost%20in%20Translation.ppt> (noting that pharmaceutical companies typically screen and evaluate between 5,000 and 10,000 distinct compounds during the drug-discovery phase, and 250 compounds during preclinical development, for each novel drug compound that reaches the market).

53. See Joseph A. DiMasi et al., *Trends in Risks Associated with New Drug Development: Success Rates for Investigational Drugs*, 87 CLINICAL PHARMACOLOGY & THERAPEUTICS 272 (2010); Navjot Singh et al., *The Anatomy of Attrition*, in *INVENTION REINVENTED: MCKINSEY PERSPECTIVES ON PHARMACEUTICAL R&D* 58 (Rodney Zimmel & Mubasher Sheikh, eds. 2010).

54. See Matteo Colombo & Ilaria Peretto, *Chemistry Strategies in Early Drug Discovery: An Overview of Recent Trends*, 13 DRUG DISCOVERY TODAY 677, 677 (2008).

55. See Oprea & Mestres, *supra* note 9, at (“The large body of clinical data and experience accumulated in phase III (efficacy) and phase IV (post-marketing) trials for the drug in question offer a good understanding of its profile in terms of adverse events, long-term and chronic toxicity, as well as on—and off—label effects.”); Kui Xu & Timothy R. Coté, *Database Identifies FDA-Approved Drugs with Potential to be Repurposed for Treatment of Orphan Diseases*, 12 BRIEFINGS IN BIOINFORMATICS 341 (2011) (“Repurposing FDA-approved products has practical advantages over novel compounds” because “safety data are far better developed” and they “have demonstrated their pharmacological activity, have known toxicity profiles both in animals and in humans and have well-studied pharmacokinetics and pharmacodynamics.”).

the pharmaceutical industry overcome its decades-long productivity crisis.⁵⁶ Advances in biomedical research over the past half century were thought to promise a new “golden age of drug discovery,”⁵⁷ and the pharmaceutical industry invested heavily in R&D to capitalize on these new scientific opportunities.⁵⁸ But the number of new drugs reaching the market has remained stagnant despite the dramatic increase in R&D spending.⁵⁹ Indeed, the cost of developing new drugs has escalated to unsustainable levels,⁶⁰ causing investors to flee the industry.⁶¹ Venture capital funding for biotechnology fell by over 25% between 2007 and

56. See *Change of Purpose*, *supra* note 13, at 267-68 (“[A]s observers have lamented the declining productivity of the pharmaceutical industry, there have been many calls to speed up the process by ‘repurposing’ or ‘repositioning’ existing drugs.”); Andrew G. Reaume, *Drug Repurposing Through Nonhypothesis Driven Phenotypic Screening*, 8 *DRUG DISCOVERY TODAY THERAPEUTIC STRATEGIES* 85, 85 (2011) (“With the productivity crisis as a backdrop, drug repositioning is increasingly being recognized as a key strategy to surmount the innovation gap.”); Ted T. Ashburn & Karl B. Thor, *Drug Repositioning: Identifying and Developing New Uses for Existing Drugs*, 3 *NATURE REVIEWS DRUG DISCOVERY* 673, 673 (2004) (“Repositioning existing drugs for new indications could deliver the productivity increases that the industry needs”); Prashant Nair, *Drug Repurposing Gets a Boost as Academic Researchers Join the Search for Novel Uses of Existing Drugs*, 110 *PNAS* 2430, 2431 (2013) (“The benefits of drug repurposing to pharmaceutical companies facing drying pipelines and expiring patents, to nonprofit organizations seeking cures for rare and neglected diseases, and to patients battling intractable conditions need no overstatement.”); Boguski et al., *supra* note 13, at 1394 (noting that there is “a widening productivity gap” in pharmaceutical R&D, and that “[o]ne response to the productivity gap is drug ‘repurposing’”); Barratt & Frail, *supra* note 5, at 20; Michael Ringel, *Drug Repurposing in the Context of Drug Development*, Institute of Medicine (IOM) Workshop Jun. 24, 2013, at <http://iom.edu/~media/Files/Activity%20Files/Research/GenomicBasedResearch/2013-JUN-24/9%20-%20Michael%20Ringel.pdf>.

57. David Brown & Giulio Superti-Furga, *Rediscovering the Sweet Spot in Drug Discovery*, 8 *DRUG DISCOVERY TODAY* 1067, 1067 (2003); see also Karol Sikora, *Cancer Drug Development in the Post-Genomic Age*, 81 *CURRENT SCIENCE* 549, 551 (2001) (“The next decade is likely to be a new golden age for cancer drug discovery, with many novel targeted molecules coming into the clinic.”).

58. See Jack W. Scannell et al., *Diagnosing the Decline in Pharmaceutical R&D Efficiency*, 11 *NAT. REV. DRUG DISCOVERY* 191 (2012).

59. See *id.*, at 197; GAO, *supra* note 40, at 2 (“Significant scientific advances have raised new hope for the prevention, treatment, and cure of serious illnesses,” but it is “widely recognized” that “innovation in the pharmaceutical industry had become stagnant”); Michael Williams, *Productivity Shortfalls in Drug Discovery: Contributions from the Preclinical Sciences?*, 336 *J. PHARMACOLOGY & EXPERIMENTAL THERAPEUTICS* 3, 3 (2011) (“In the second decade of the 21st century, rarely a week has passed without a review or an article in the popular press lamenting the inverse relationship between the investment in the drug research and development process and the continued shortfall in productivity, the latter being assessed in the lack of robustness of clinical pipelines and the reduced number of new drug approvals.”); C.M. Colvis et al., *Partnering for Therapeutics Discovery*, 93 *CLINICAL PHARMACOLOGY & THERAPEUTICS* 24, 25 (2013) (“[D]espite the recent technology and knowledge advances in biomedical research, the number of drugs that make it to the market every year remains roughly the same.”).

60. See Francis S. Collins, *Reengineering Translational Science: the Time is Right*, 3 *SCI. TRANSLATIONAL MED.* 90cm17, at 2 (2011) (hereinafter, *Translational Science*) (describing current trends in drug discovery and development as “disturbing,” and noting that “[d]iverse commentators have expressed serious concerns about the sustainability of the current translational process”); Catherine Arnst, *Why Drug Development is Failing—And How to Fix it*, *TECHONOMY*, Sept. 6, 2012 (“[S]ince 2005 the value generated by a dollar invested in pharmaceutical R&D has plunged more than 70 percent.”); Michael D. Rawlins, *Cutting the Cost of Drug Development*, 3 *NAT. REV. DRUG DISCOVERY* 360, 360 (2004).

61. See Jose-Maria Fernandez et al., *Commercializing Biomedical Research through Securitization Techniques*, 30 *NATURE BIOTECHNOLOGY* 964, 964 (2012); Andrew Pollack, *Despite Billions for Discoveries, Pipeline of Drugs Is Far From Full*, *NEW YORK TIMES*, Apr. 19, 2002. Indeed, total market capitalization of large pharmaceutical companies fell by over half a trillion dollars between 2000 and 2010. See AJAY DHANKHAR ET AL., *ESCAPING THE SWORD OF DAMOCLES: TOWARD A NEW FUTURE FOR PHARMACEUTICAL R&D* 3 (2012).

2012,⁶² and most large pharmaceutical companies have scaled back or eliminated their R&D programs in several important areas,⁶³ including neurological diseases.⁶⁴ The industry's financial troubles largely stem from the stubbornly high failure rate and lengthy R&D times in de novo drug development.⁶⁵ But while the pharmaceutical industry struggles to deliver 27 new drugs to the market in the average year,⁶⁶ there are approximately 2,000 off-patent drugs already on the market⁶⁷ that may provide safe and effective treatments for those same indications.⁶⁸ Because developing new uses for existing drugs dramatically shortens R&D times and reduces the risk of failure, many believe drug repurposing would allow pharmaceutical companies to revitalize their dwindling pipelines,⁶⁹ win back their investors, and produce a wide range of valuable new medical treatments.⁷⁰

A viable business model for drug repurposing would also provide a crucial boost to the NIH's efforts to translate discoveries in basic research into new medical treatments.⁷¹ Advances in molecular biology and genomics now permit researchers to identify the distinct molecular causes for human diseases.⁷² These discoveries offer extraordinary opportunities to develop new treatments for unmet medical needs by identifying new molecular targets for therapeutic

62. See Laura Kusisto, *New York City to Start Venture Fund for Biotech*, WALL STREET J., Dec. 13, 2013 (reporting that venture capital cut its biotech investments from \$5.8 billion in 2007 to \$4.2 billion in 2012).

63. See Williams, *supra* note 59, at 3 (“Despite optimistic declarations that a “golden age” in drug discovery now exists, there is little to objectively support such claims, especially when approximately 35,000 jobs have been eliminated in the pharmaceutical industry in the first half of 2010.”); Christopher M. Holman, *Unpredictability in Patent Law and Its Effect on Pharmaceutical Innovation*, 76 MISSOURI L. REV. 645, 646-47 (2011); Sten Stovall, *R&D Cuts Curb Brain-Drug Pipeline*, Wall St. J., Mar. 27, 2011.

64. See INSTITUTE OF MEDICINE (IOM), IMPROVING AND ACCELERATING THERAPEUTIC DEVELOPMENT FOR NERVOUS SYSTEM DISORDERS: WORKSHOP SUMMARY 1 (2013).

65. See Peter Csermely, et al., *Structure and Dynamics of Molecular Networks: A Novel Paradigm of Drug Discovery: A Comprehensive Review*, 138 PHARMACOLOGY & THERAPEUTICS 333, 334 (2013) (noting that the productivity crisis is largely driven by “the high percentage of projects that fail in clinical trials,” “the recent focus on chronic diseases requiring longer and more expensive clinical trials,” and “the financial costs of tying up investment capital in multiyear drug development projects”); Scannell et al., *supra* note 58, at 199 (“R&D costs are dominated by the cost of failure. Most molecules fail. Most research scientists spend most of their time on products that fail.”).

66. B. Munos, *A Forensic Analysis of Drug Targets from 2000 through 2012*, 94 CLINICAL PHARMACOLOGY & THERAPEUTICS 407, 407 (2013) (finding that between 2000 and 2012, the FDA approved 27 new molecular entities (NMEs) each year on average (excluding imaging agents)).

67. As of 2012, there were 2,356 distinct FDA-approved drug compounds (NMEs). See Huang et al., *supra* note 32, at 80ps16. Since the FDA approves has approved 27 NMEs on average each year since 2000, see Munos, *supra* note 66, and the average effective patent life for a new drug is 11 to 12 years, see *infra* note 24, approximately 300 of those NMEs are probably still under patent protection.

68. See *supra* notes 33-37, and accompanying text; *infra* notes 331-341, and accompanying text.

69. See *supra* note 56; *infra* notes 370-395; Eftychia Lekka et al., *Literature Analysis for Systematic Drug Repurposing: a Case Study from Biovista*, 8 DRUG DISCOVERY TODAY: THERAPEUTIC STRATEGIES 103, 103 (2011).

70. See, e.g., Butcher, *supra* note 37 (noting that “[a]fter decades of research and advances in the biology underlying mental illnesses, better drugs are still desperately needed for essentially all psychiatric disorders,” but “[w]ith the potential of drug repurposing in identifying novel treatments for serious mental illnesses emerging, hope is on the horizon.”); Lederman, *supra* note 34.

71. See *infra* Part V.D.

72. See Winquist et al., *supra* note 51, at 10-17; Collins, *Translational Science*, *supra* note 60, at 1-2.

intervention.⁷³ Since the public sector generally lacks the resources and capacity to engineer novel drug compounds and complete their preclinical development,⁷⁴ the public relies on private industry to carry out this research.⁷⁵ But unvalidated therapeutic targets have a higher risk of failure, and pharmaceutical companies are increasingly reluctant to take on this risk when investing in the discovery and development of a new drug.⁷⁶ Consequently, preclinical R&D has become known as the “valley of death” in pharmaceutical innovation⁷⁷—“the gap in drug development between where NIH-funded research typically leaves off and industry development begins.”⁷⁸ A recent Institute of Medicine report notes that this breakdown in the traditional pathway from academic to commercial research has created an “ever-widening gap between scientific discoveries and the translation of those discoveries into life-changing medications.”⁷⁹ Indeed, of the approximately 4000 medical conditions with defined molecular causes, only 200 currently have drugs available to treat them.⁸⁰ Many commentators believe that testing old drugs

73. See Collins, *Translational Science*, *supra* note 60, at 2.

74. See John C. Reed, *NCATS Could Mitigate Pharma Valley of Death: National Center for Advancing Translational Science Essential to Capitalize on Basic Research*, 31 GENETIC ENG. BIOTECHNOL. NEWS 6 (2011) (noting that universities and the NIH are usually unable to carry out “many steps in the drug discovery and development process, including assay development, high-throughput screening, medicinal chemistry, exploratory pharmacology, and rigorous preclinical testing of drug efficacy and safety in animal models of disease”); Woodcock, *supra* note 52, at 19-20; Stu Borman, *Improving Efficiency*, 84 CHEMICAL & ENGINEERING NEWS 56, 78 (2006) (noting that academic groups typically lack the expertise in medicinal chemistry necessary to optimize novel drug compounds); Muthyala, *supra* note 36; Declan Butler, *Lost In Translation*, 449 NATURE 158, 158-159 (2007) (“[F]ew universities are willing to support the medicinal chemistry research needed to verify from the outset that a compound will not be a dead end in terms of drug development.”); Stephen Frye et al., *US Academic Drug Discovery*, 10 NAT REV DRUG DISCOV. 409 (2011); George J. Brewer, *Drug Development for Orphan Diseases in the Context of Personalized Medicine*, 154 TRANSLATIONAL RES. 314 (2009); Hann & Keserü, *supra* note 49.

75. See Department of Health & Human Services (DHHS) and National Institute of Health (NIH), *NIH Blueprint for Neuroscience Research Grand Challenge: Developing Novel Drugs for Disorders of the Nervous System* (U01), RFA-NS-12-002 (2011) (“[M]ost promising compounds identified through basic research are not sufficiently drug-like for human testing. Before a new chemical entity can be tested in a clinical setting, it must undergo ... activities [that] are largely the domain of the pharmaceutical industry and contract research organizations, and the necessary expertise and resources are not commonly available to academic researchers.”).

76. See Collins, *Translational Science*, *supra* note 60, at 2 (noting that “the potential utility of most of the newly discovered molecular targets will not be easy to validate” because of “the serious [economic] challenges that currently confront the private sector”); Arti K. Rai et al., *Pathways Across the Valley of Death: Novel Intellectual Property Strategies for Accelerated Drug Discovery*, 8 YALE J. HEALTH POL. L. & ETHICS 1, 7-10 (2008).

77. Barry S. Collier & Robert M. Califf, *Traversing the Valley of Death: A Guide to Assessing Prospects for Translational Success*, SCI. TRANSLATIONAL MED. 1(10) 3 (2009); see also Declan Butler, *Translational Research: Crossing the Valley of Death*, 453 NATURE 840, 841 (2008).

78. Blueprint Neurotherapeutics Scope, at http://neuroscienceblueprint.nih.gov/bpdrugs/project_pipeline_fig.pdf.

79. INSTITUTE OF MEDICINE (IOM), ACCELERATING THE DEVELOPMENT OF NEW DRUGS AND DIAGNOSTICS: MAXIMIZING THE IMPACT OF THE CURES ACCELERATION NETWORK: WORKSHOP SUMMARY 1 (2012); see also FASTER CURES, CROSSING OVER THE VALLEY OF DEATH 3 (2009) at www.fastercures.org (“[M]any basic discoveries barely get to start the journey down the therapeutic development pipeline” and instead “get stuck in an ever-widening gap in funding and support for the kind of research that moves basic science down the path toward treatments.”).

80. See David Levine, *Is the NIH's New Translational Center a Misguided Treasure Hunt?*, BIOTECHNIQUES, Feb. 29, 2012, at <http://www.biotechniques.com/news/Is-the-NIHs-New-Translational-Center-a-Misguided-Treasure>

against these new therapeutic targets is the best way to overcome this problem.⁸¹ Public-sector researchers are already using the new screening technologies discussed above to find existing drugs that may be effective against a new target.⁸² The NIH generally cannot afford the expensive late-stage clinical trials needed to establish a new treatment's safety and efficacy.⁸³ But if industry had a viable business model for drug repurposing, the NIH could move those potential new treatments through the early stages of clinical trials (which are within the NIH's resources),⁸⁴ and then attract an industry sponsor to finance the more expensive late stage trials.⁸⁵

Nearly all of these potential benefits from drug repurposing remain unrealized because the existing incentives for investing in pharmaceutical R&D fail to provide firms a viable business model for repurposing off-patent drugs.⁸⁶ Once generics enter the market, it is nearly impossible for pharmaceutical companies to maintain an exclusive marketing position to recoup investments in clinical trials.⁸⁷ Pharmaceutical companies therefore have little incentive to establish new uses for off-patent drugs.⁸⁸ Since the clinical trials for a new indication take years to complete and firms need time on the market to recoup their R&D investment, pharmaceutical companies usually stop testing their drugs for new indications five or more years before generics enter.⁸⁹

Hunt--Translational-Research-Feature/biotechniques-327542.html; cf. Collins, *Translational Science*, *supra* note 60, at 2.

81. See, e.g., Hemphill, *supra* note 13, at 6-7 ("This innovative approach to developing cost-effective, timely new pharmaceutical therapies is necessary to eliminate the backlog of untreated diseases."); Francis S. Collins, *Mining for Therapeutic Gold*, 10 NATURE REVIEWS DRUG DISCOVERY 397, 397 (2011) (hereinafter, *Therapeutic Gold*); Colvis et al., *supra* note 59, at 25.

82. See *supra* note 32-33 and accompanying text.

83. See *infra* notes 286-301, and accompanying text; Colvis et al., *supra* note 59, at 24 (2013) (describing how the available NIH funding for drug-repurposing trials "would end with the completion of proof-of-concept clinical trials that may ultimately lead to therapeutic uses for these agents").

84. See Muthyala, *supra* note 36; Curtis R. Chong & David J. Sullivan, *New Uses for Old Drugs*, 448 NATURE 645 (2007); Kerry A. O'Connor & Bryan L. Roth, *Finding New Tricks for Old Drugs: An Efficient Route for Public-Sector Drug Discovery*, 4 NATURE REVIEWS DRUG DISCOVERY 1005, 1013 (2005).

85. See John C. McKew, *Drug Repurposing at NCATS*, presentation at IOM Genomics-Enabled Drug Repurposing and Repositioning, 18, Jun. 24, 2013, at <http://iom.edu/~media/Files/Activity%20Files/Research/GenomicBasedResearch/2013-JUN-24/7%20-%20John%20McKew.pdf>; Weir et al., *supra* note 9, at 1056 (explaining that academic drug development still relies on the for-profit sector to take drugs through the more expensive later-stage clinical trials, giving the example of auranofin for chronic lymphocytic leukemia); Collins, *Better Drugs*, *supra* note 45.

86. See, e.g., Weir et al., *supra* note 9, at 1057 (discussing the importance of public-private partnerships for repurposing known drugs for new indications, but noting that "[a] particular development challenge exists in repurposing off-patent drugs" because "regulatory 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."); Boguski et al., *supra* note 13, at 1395 ("Definitive clinical trials for novel uses of existing drugs will remain costly, and pharmaceutical companies are reluctant to invest in such efforts without patent protection.").

87. See Austin, *supra* note 13, at 16 ("Difficulties in establishing exclusivity for approved drugs has deterred industry from drug repurposing.").

88. See *supra* note 13.

89. See PCAST, *supra* note 13, at 24-25 (noting that firms "may have insufficient incentives to initiate clinical trials to generate ... additional indications" for their drugs "where the end of the exclusivity period is in sight (for example, within six years)"); TONY ELLERY & NEAL HANSEN, PHARMACEUTICAL LIFECYCLE MANAGEMENT:

The existing literature on the problem of new uses generally frames it as a gap in the patent system for pharmaceutical innovation.⁹⁰ Pharmaceutical companies rely on temporary monopoly rights to block generics from the market for long enough to recoup their R&D investments.⁹¹ But the government only offers monopoly protection capable of blocking generic entry as an incentive to develop new drugs.⁹² Those rights typically expire from ten to fifteen years after the new drug launched.⁹³ Consequently, “[p]atent protection on drugs typically begins and ends too early to permit firms to capture the full value of subsequently developed information about drug effects,” notes Rebecca Eisenberg, and “therefore does a better job of motivating the initial R&D ... to bring new products to market than it does of motivating the development of new information about old drugs.”⁹⁴ With few exceptions, firms cannot extend their original monopoly term and continue to block generic entry for an FDA-approved drug by developing a new use for it.⁹⁵ Once pharmaceutical companies lose this monopoly protection and generics enter, patients can—and usually will—use the low-cost generics regardless of whether they are taking the drug for an old or new indication.⁹⁶

This standard framing for the problem of new uses—which focuses on firms’ inability to extend their monopoly protection over new drugs by developing new indications—is technically accurate, but it does not identify the problem’s source. Legislators have good reason to withhold this type of monopoly protection as a reward for drug repurposing.⁹⁷ They fear that if firms could delay generic entry by developing new uses for their drugs, they might hold off generic competition indefinitely by continually developing minor new indications with little therapeutic value.⁹⁸ Ultimately, monopoly rights that block generic entry are poorly suited for encouraging firms to develop new uses of existing drugs. They give firms a monopoly over all of a drug’s indications, which would break the link between a new use’s social value and the incentives for its development.⁹⁹ Since monopoly rights that block generic entry are not the appropriate

MAKING THE MOST OF EACH AND EVERY BRAND 123-30 (2012); ALISON SAHOO, INDICATION EXPANSION: OPPORTUNITIES FOR SUCCESSFUL LIFECYCLE MANAGEMENT 48-65 (2007); *infra* notes and text accompanying notes 262-266.

90. See Boguski et al., *supra* note 13, at 1395 (arguing that drug repurposing “focused on beneficial new uses will need to be based on new business models [such as open-sourcing] ... [or] patent reform by Congress or new doctrinal interpretations of current law by the FDA and the courts”); Hemphill, *supra* note 13 (explaining “that off-patent or near patent expired drugs will remain unattractive to the pharmaceutical industry ... [because] once a patent has expired, that technology cannot be patented again simply because a new application, or in this case a drug indication, has been discovered”); Eisenberg, *New Uses*, *supra* note 13, at 720-35; Mossinghoff, *supra* note 13, at 191 (noting that the Hatch-Waxman Act offers no “incentives for pioneers to develop second uses for patented products”); Gelijns et al., *supra* note 13, at 697 (advocating “[a]n extension of the patent for a limited period (e.g., 12 months) [to] strengthen the incentive to conduct clinical research [on new uses]”).

91. See *infra* notes 18-21, and accompanying text.

92. See *infra* notes 200-245, and accompanying text.

93. See *supra* note 24, and accompanying text.

94. Eisenberg, *New Uses*, *supra* note 13, at 720.

95. See *infra* notes 227-245, and accompanying text.

96. See Eisenberg, *New Uses*, *supra* note 13, at 729.

97. See *infra* Part III.B.

98. See *infra* note 230, and accompanying text.

99. See *infra* notes 228-229, and accompanying text.

mechanisms to promote drug repurposing, Congress' decision to withhold those incentives is not the underlying policy failure responsible for the problem of new uses.

Encouraging private sector investment in drug repurposing warrants a different type of monopoly protection—a monopoly that only covers one particular use for a drug.¹⁰⁰ These narrower monopoly rights would limit innovators' profits to sales revenue from the new use, thereby preserving the link between the incentives to develop new uses and their social value. Firms would have an incentive to invest in drug repurposing and the public would still have access to low-cost generics for drugs' older indications.

The patent system already offers this type of monopoly right for new uses of existing drugs, but the government does not provide firms with the means to enforce them.¹⁰¹ The government routinely grants method-of-use patents over newly discovered indications for FDA-approved drugs ("new use patents").¹⁰² These rights ostensibly provide the patentee with a monopoly over the act of taking or administering the existing drug for the new indication.¹⁰³ But that legal monopoly has little meaning once generics are on the market if pharmaceutical companies cannot detect when physicians prescribe drugs for patented indications.¹⁰⁴ Since physicians do not disclose the indications for their prescriptions to pharmaceutical companies,¹⁰⁵ they rarely have access to the information needed to enforce new use patents if generics are available.¹⁰⁶

Given that firms can already patent newly discovered indications for old drugs, the problem of new uses is better understood as the result of information barriers than a gap in the patent system (as currently assumed¹⁰⁷). The government now provides firms with temporary monopoly rights over new indications that would be suitable for incentivizing drug repurposing. However, since pharmaceutical companies do not know when physicians prescribe a drug for a patented indication, they cannot enforce monopoly rights specific to a new use. In the prior literature on drug-repurposing incentives, scholars sometimes mention these new-use patents, but then quickly dismiss them as economically irrelevant because of the enforcement problem.¹⁰⁸ The literature

100. See *infra* Part III.C.

101. See *infra* notes 249-254, and accompanying text.

102. See *infra* notes 210-217, and accompanying text.

103. See THOMAS, *supra* note 23, at 44-46, 235-37.

104. See Grabowski et al., *supra* note 13, at 382.

105. See *id.*

106. See *infra* notes 252-254, and accompanying text.

107. See *supra* note 90.

108. Scholars who address the issue usually devote no more than one or two sentences to the enforcement problem for new-use patents. See Rai, *supra* note 13, at 492 (noting that "the pervasive distribution of generic drugs for patented uses substantially undermines the efficacy of such [new use] patents and hence the incentives for finding other uses"); *Change of Purpose*, *supra* note 13, at 268 ("Although it is possible to file a new 'method of use' patent to cover a repurposed drug, such patents are difficult, if not impossible, to enforce if a generic copy of the drug is already on the market."); Thomas A. Hemphill, *Repurposing Pharmaceuticals: Does United States Intellectual Property Law and Regulatory Policy Assign Sufficient Value to New Use Patents?*, 16 INT'L J. INNOVATION MANAGEMENT 1250016-1, 1250016-4 n.7 (2012) ("Although it is a legal possibility to file with the USPTO a new use patent application on a off patent drug, such patents (if granted) are difficult, if not impossible to enforce if there is a generic copy of the drug in the marketplace."); Grabowski et al., *supra* note 13, at 382 ("Even though the FDA can grant new use or indication exclusivity and manufacturers can obtain method of use patents for new indications, the realities of the drug distribution system make any such exclusivity provisions impossible to enforce."); ELLERY & HANSEN, *supra* note 89,

takes for granted that the only form of monopoly protection capable of motivating private sector drug development is the right to exclude generics from the market. Discussions about the inadequate incentives for drug repurposing therefore focus on the legal rules that prevent firms from delaying generic entry by developing new uses for FDA-approved drugs.¹⁰⁹ The literature pays little attention to the information barriers preventing pharmaceutical companies from enforcing new-use patents once generics enter, even though these rights are much better suited to encouraging drug repurposing than the standard monopoly protection for new drugs.

Ascribing the problem of new uses to information barriers—as opposed to a gap in the patent system—represents a shift in focus from the previous scholarship that explains why other commentators struggled to find solutions. At present, neither the government nor pharmaceutical companies can observe and tally the instances in which physicians prescribe—and patients benefit from—a new indication for an older drug.¹¹⁰ Since a new indication’s utilization rate is a critical component of its social value, the government would almost certainly need this information to link the incentives to develop new indications to their social value.¹¹¹ The problem of new uses therefore transcends the patent system. It will impede efforts to design a socially beneficial incentive system for drug repurposing regardless of whether those incentives take the form of patents, FDA-exclusivity periods, prizes, consumer subsidies, or any other financial inducement for private sector investment in R&D.¹¹² The existing literature overlooks this underlying information problem, focusing instead on potential fixes to the legal protection for new indications.¹¹³ Not surprisingly, scholars have had trouble coming up with solutions, and usually end up portraying the problem of new uses as intractable.¹¹⁴

at 126 (“Even if the new indication is patented ... there is no mechanism to stop physicians prescribing the generic or pharmacies dispensing it off-label to patients with the protected indication.”); Eisenberg, *supra* note 13, at 724-25 (“It is more difficult to detect and prove infringing uses than it is to detect and prove infringing products, and it is less efficient to sue numerous patients and physicians than it is to sue a single manufacturer. Moreover, few industries prosper by suing customers, and the marketing interests of the pharmaceutical industry are probably better served by soliciting physicians to write prescriptions than by suing them for contributory infringement of their patents.”).

109. See Eisenberg, *supra* note 13, at 720-30; Rai, *supra* note 13, at 491-92; Hemphill, *Repurposing Pharmaceuticals*, *supra* note 108; SAHOO, *supra* note 89, at 63; ELLERY & HANSEN, *supra* note 89, at 126.

110. See Donald M. Berwick, Office of Inspector General’s (OIG), *Memorandum Report: Ensuring that Medicare Part D Reimbursement Is Limited to Drugs Provided for Medically Accepted Indications*, OEI-07-08-00152, Department of Health & Human Services, at 1-2 (2011).

111. See Benjamin N. Roin, Intellectual Property versus Prizes: Reframing the Debate, 81 U. CHI. L. REV. 101, _ (2014) (hereinafter Intellectual Property versus Prizes); Steven Shavell & Tanquy van Ypersele, Rewards Versus Intellectual Property Rights, 44 J.L. & ECON. 525, 541-42 (2001) (noting the importance of sales figures and frequency of use in calculating inventions’ social value).

112. See *infra* Part VI.

113. See, e.g., Arti K. Rai, *Repurposing and Repositioning: Policy and Legal Issues*, presentation at IOM Genomics-Enabled Drug Repurposing and Repositioning, Jun. 24, 2013, at <http://iom.edu/~media/Files/Activity%20Files/Research/GenomicBasedResearch/2013-JUN-24/14%20-%20Arti%20Rai.pdf> (discussing “IP alternatives” to provide incentives for developing new uses of known (but not yet FDA-approved) drug compounds); Eisenberg, *supra* note 13, at 720-30; Gelijns et al., *supra* note 13 (“[I]t may still be difficult to find private-sector support [for drug repurposing] if the patent on a product is about to expire. An extension of the patent for a limited period (e.g., 12 months) would strengthen the incentive to conduct clinical research. This would involve a cost to society, at least in the short term, with consumers having to pay higher prices than would be the case if the generic drug were introduced earlier, but at the same time, it might drastically reduce the high social costs of delays in the widespread application of new indications for use.”); *Change of Purpose*, *supra* note

Reframing the problem of new uses as the product of information barriers also reveals that it extends beyond R&D incentives for off-patent drugs, also affecting the market for patented drugs.¹¹⁵ Ultimately, the problem of new uses is about pharmaceutical companies' inability to separate the markets for a drug's different indications. Firms cannot selectively charge payers when physicians prescribe off-patent drugs for patented new uses because they do not observe the prescribed indication. That same information barrier also prevents pharmaceutical companies from setting separate prices for their drugs' different indications during their monopoly term. A drug's different indications require separate R&D investments to create and have distinct therapeutic values that usually warrant different prices.¹¹⁶ But pharmaceutical companies lack the information necessary to price discriminate based on indication. This impediment to differential pricing probably causes at least two (previously unnoticed) distortions in the prescription drug market. First, because setting a single price for a drug with multiple indications prevents firms from charging the profit-maximizing price for each different use, it reduces incentives to develop new uses for patented drugs.¹¹⁷ Second, because insurers cannot negotiate price discounts for indications that are experimental or of lower therapeutic value, they impose coverage restrictions instead to discourage those uses, thereby reducing patients' access to new drugs.¹¹⁸

Fortunately, the information barriers underlying the problem of new uses (and broader price-discrimination problem) are eminently solvable. Indeed, the pharmacy benefit managers (PBMs) that administer prescription-drug plans for insurers already possess a proven infrastructure for observing prescribed indications—their “prior authorization” systems.¹¹⁹ Most insurers limit their coverage for individual prescription drugs to a specified set of indications.¹²⁰ PBMs use their prior-authorization systems to enforce these coverage restrictions, requiring physicians to report the indication for their prescriptions as a condition for insurers covering the prescribed drug's cost.¹²¹ Since PBMs have access to patients' medical records, they can discourage physicians from fraudulently reporting indications by occasionally reviewing those records to verify reported diagnoses.¹²² Although this system is not foolproof,¹²³ PBMs claim that prior authorization “is the best tool they currently have to compare the diagnosis provided by the prescriber to the medically accepted indications [covered by the patient's plan],” and that they

13, at 268 (suggesting that the government might want to extend “patent exclusivity if new uses are found for an approved drug,” but recognizing that this policy would be problematic because “the drugs will remain free from generic competition, and therefore more expensive, for longer”); PCAST, *supra* note 13, at 24-25 (listing various “economic tools” that might incentivize drug repurposing, including “the length of the exclusivity period” and “a range of other tools that have been used or proposed to encourage investment, such as advanced market commitments ... , vouchers for priority FDA review of drugs ... , R&D tax credits ... , and insurance guarantees”).

114. *See infra* notes 432-437, and accompanying text.

115. *See infra* Part VII.

116. *See infra* note 459.

117. *See infra* notes 463-467, and accompanying text.

118. *See infra* notes 468-475, and accompanying text.

119. *See infra* notes 480-485, and accompanying text.

120. *See infra* notes 167 & 468, and accompanying text.

121. *Id.*

122. *See infra* note 515, and accompanying text.

123. *See infra* note 514, and accompanying text.

have “had great success at preventing payments for drugs not provided for medically accepted indications by using prior authorization when permitted.”¹²⁴ If pharmaceutical companies also had access to patients’ (de-identified) health records and received the reported indication for prescriptions, presumably they could monitor prescribed indications just as well as PBMs and insurers, allowing them to enforce their new-use patents.

Prior-authorization systems offer a clear roadmap for solving the problem of new uses. First, physicians must report indications when they prescribe a patented drug with multiple uses or an off-patent drug with one or more protected new uses. Second, the relevant pharmacies, PBMs and pharmaceutical companies must have (limited) access to that information, such that they can link prices for prescribed drugs to the reported indication. Third, the PBMs and pharmaceutical companies must have (limited) access to patients’ health records so they can verify reported indications.¹²⁵

The government could easily implement such a system through the nation’s growing infrastructure of electronic prescribing (“e-prescribing”) and electronic health (“e-health”) records.¹²⁶ E-prescribing software can allow physicians to record and transmit the indication for a drug when they write their prescriptions. That information could then be sent to the relevant pharmacist, PBM and pharmaceutical company. If PBMs and pharmaceutical companies both have limited access to patients’ e-health records (perhaps de-identified to protect patient privacy), they can police the accuracy of reported indications in most cases.¹²⁷ Consequently, with a few simple regulatory (or perhaps legislative) changes,¹²⁸ the government could take advantage of e-prescribing software and e-health records to create the necessary infrastructure to encourage private sector investment in drug repurposing.

124. Stuart Wright, *Memorandum Report: Ensuring that Medicare Part D Reimbursement is Limited to Drugs Provided for Medically Accepted Indications*, OEI-07-08-00152, Department of Health & Humans Services, at 5 (2011); see also Elizabeth Hargrave et al., *Medicare Prescription Drug Plans in 2009 and Key Changes Since 2006: Summary of Findings* 6 (2009) at <http://kaiserfamilyfoundation.files.wordpress.com/2013/01/7917.pdf> 6 (“Even if a drug is listed on a plan’s formulary, utilization management (UM) restrictions may restrict a beneficiary’s access to the drug. Part D plans may require step therapy or prior authorization before covering a drug, or may limit the quantity covered.”); Joette Gdovin Bergeson et al., *Retrospective Database Analysis of the Impact of Prior Authorization for Type 2 Diabetes Medications on Health Care Costs in a Medicare Advantage Prescription Drug Plan Population*, 19 J. MANAGED CARE PHARMACY 374, 382 (2013); P.A. Glassman et al., *Physician Perceptions of a National Formulary*, 7 AM. J. MANAGED CARE 241 (2001); W.H. Shrank et al., *A Bitter Pill: Formulary Variability and the Challenge to Prescribing Physicians*, 17 J. AM. BOARD FAMILY PRACTICE 401 (2004); Sarah J. Shoemaker et al., *Effect of 6 Managed Care Pharmacy Tools: A Review of the Literature*, 16 J. MANAGED CARE PHARMACY S1, S5 & S6 (2010).

125. To this author’s knowledge, this Article is the first to discuss how the government could create incentives for repurposing off-patent drugs through a system modeled on prior authorization (i.e., indication reporting and verification). See Benjamin N. Roin, *Solving the Problem of New Uses* 59-65 (October 1, 2013), available at SSRN: <http://ssrn.com/abstract=2337821>; Benjamin N. Roin, *Solving the Problem of New Uses* 59-65 (October 1, 2013), available at <http://nrs.harvard.edu/urn-3:HUL.InstRepos:11189865>. A working group organized by the Kauffman Foundation recently arrived at a similar conclusion, probably independent of this Article. See Dominique Pahud et al., *A New Market Access Path for Repurposed Drugs* 3-4 (May 14, 2014), available at <http://www.kauffman.org/what-we-do/research/2014/05/a-new-market-access-path-for-repurposed-drugs>. Their short (4-page) report proposes that “[a]ll prescriptions for the repurposed drug would go through a prior authorization process, in which diagnosis is confirmed, to enable differential reimbursement.” *Id.* at 4.

126. See *infra* notes 491-496, and accompanying text.

127. See *infra* notes 514-515, and accompanying text.

128. See *infra* Part VIII (outlining the regulatory and legislative changes necessary to implement this solution).

Part II of this Article discusses the need for government intervention to support investment in drug repurposing. Part III examines how existing patent rights and FDA-exclusivity periods fail to provide enforceable monopoly protection over new indications once generics are on the market, leaving private industry with little or no incentive to develop those new uses. Part IV describes the government's unwillingness to step in for private industry with adequate public funding for drug-repurposing trials. Part V reviews the recent medical literature on drug repurposing to show that the social costs of this gap in the incentives for pharmaceutical innovation are probably far greater than previously assumed and are getting worse. Part VI argues that the problem of new uses ultimately stems from information barriers that prevent pharmaceutical companies from observing prescribed indications. Part VII builds on this insight to recast the problem of new uses as a price-discrimination problem, and argues that this broader problem also likely affects the market for patented drugs. Part VIII outlines a solution to the information problem underlying the problem of new uses, which—if implemented—would allow pharmaceutical companies to enforce their new-use patents (and possibly their FDA-exclusivity periods) on off-patent drugs. Part IX examines some potential problems that might arise with new-use patents and FDA-exclusivity periods for new uses if those rights become enforceable, and possible corrective measures. Part X concludes.

II. CREATING NEW MEDICAL TREATMENTS BY DEVELOPING NEW USES FOR EXISTING DRUGS

Most of the academic and policy literature on pharmaceutical innovation focuses on de novo drug development.¹²⁹ Scholars often explicitly assume that the discovery and development of novel drug compounds (i.e., NMEs) is the only important form of pharmaceutical innovation.¹³⁰ That assumption is wrong. This Part describes how the FDA's initial approval of a new drug is often only the first milestone in that drug's development. New drugs invariably have other potential therapeutic uses besides the one for which they were first tested and approved.¹³¹ Studies suggest that the public receives substantial benefits from the efforts to develop new indications for existing drugs.¹³² However, many of these potential new indications are discovered long after pharmaceutical companies first developed the drugs.¹³³ The FDA does

129. See generally Dana Goldman & Darius Lakdawalla, *Intellectual Property, Information Technology, Biomedical Research, and Marketing of Patented Products*, in 2 HANDBOOK OF HEALTH ECONOMICS 825 (Mark V. Pauly et al., eds. 2011) (surveying the economic literature).

130. See Berndt, et al., *Impact of Incremental Innovation*, *supra* note 31, at 70 (noting that “Many analysts implicitly or explicitly exclude such supplemental or secondary approvals when measuring research output, presumably on the grounds that they are perceived as constituting trivial forms of innovation”). For example, Michelle Boldrin and David Levine cite the “54 percent of FDA-approved drug applications involved drugs that contained active ingredients already in the market” as “evidence of redundant research on pharmaceuticals,” reflecting the assumption that new indications for the same drug are not valuable. MICHELE BOLDRIN & DAVID K. LEVINE, *AGAINST INTELLECTUAL MONOPOLY* 231 (2007); cf. Michael Kremer, *Patent Buyouts: A Mechanism for Encouraging Innovation*, 113 Q.J. ECON. 1137, 1152-53 (1998) (“[P]harmaceuticals typically need little new development after they have been approved by the FDA.”).

131. See *infra* Part II.A.

132. See *supra* note 31.

133. See *infra* Part II.B.

not prohibit physicians from prescribing older drugs off-label for new indications,¹³⁴ but without clinical-trial evidence to support those new uses, physicians and payers are much less likely to accept them as appropriate medical treatments.¹³⁵ Successfully repurposing an FDA-approved drug as a treatment for a different disease therefore generally requires clinical trials establishing the drug's safety and efficacy for that new indication. The clinical trials needed to generate this evidence are expensive,¹³⁶ and those investments are highly vulnerable to free riding by generics.¹³⁷ Unless the government intervenes, pharmaceutical companies are unlikely to develop new indications for drugs once generics are on the market.

A. Most FDA-Approved Drugs Have Multiple Potential Uses

The drug-development process does not end when the FDA first approves a new drug. That initial approval generally covers only one specific therapeutic use. New drugs inevitably have other potential indications for which they might be safe and effective beyond the one initially listed on their label.¹³⁸ Although some of these potential new indications are closely related to the original FDA-approved use,¹³⁹ others involve the treatment of unrelated diseases.¹⁴⁰ For example, the drug Tarceva (erlotinib) was originally developed to treat non-small-cell lung cancer¹⁴¹ but subsequently approved for pancreatic cancer,¹⁴² and is currently being tested for breast and ovarian cancers.¹⁴³ There is also growing interest in the potential to use Tarceva as treatment for psoriasis, type-1 diabetes, Hepatitis C, and several other non-cancer diseases.¹⁴⁴

134. See *infra* note 163, and accompanying text.

135. See *infra* Part II.C.

136. See *infra* Part II.D.

137. See *infra* Part II.E.

138. See Joshua Cohen et al., *Off-Label Use Reimbursement*, 64 FOOD & DRUG L.J. 391, 393 (2009) (explaining that “[s]ponsors may focus their initial clinical development on narrowly defined subgroups within a given disease population that is expected to accrue the greatest benefit from the drug,” but “[o]nce the drug is approved for the narrow indication, its real-world use is typically much broader than the clinical trial population”); Mark Ratner & Trisha Gura, *Off-Label or Off-Limits?*, 26 NATURE BIOTECHNOLOGY 867, 870 (2008) (“‘You develop every drug knowing that medicine will advance and physicians may then use it for many other things.’”) (quoting Sara Radcliffe, vice president of Science & Regulatory Affairs for the Biotechnology Industry Organization).

139. See ELLERY & HANSEN, *supra* note 89, at 123-30; SAHOO, *supra* note 89, at 48-65. Closely related indications typically involve treatments for the same disease at a different stage, in a different subset of patients, or at a different dosage. They may also involve treatments for close variants of the disease.

140. See SAHOO, *supra* note 89, at 66-85.

141. See CDER, NDA 21-743, Nov. 18, 2004, available at www.fda.gov.

142. See CDER, NDA 21-743/S-003, Nov. 2, 2005, available at www.fda.gov.

143. See Umang Swami, et al., *Eribulin—A Review of Preclinical and Clinical Studies*, 81 CRITICAL REV. ONCOLOGY/HEMATOLOGY 163 (2012).

144. See Marvin B. Brooks, *New Uses for Old Drugs?*, *Erlotinib and Gefitinib, Small-Molecule EGFR Inhibitors*, 12 BRITISH J. DIABETES & VASCULAR DISEASE 195 (2012); Tobias R. Overbeck & Frank Griesinger, *Two Cases of Psoriasis Responding to Erlotinib: Time to Revisiting Inhibition of Epidermal Growth Factor Receptor in Psoriasis Therapy?*, 225 DERMATOLOGY 179 (2012).

Tarceva is not unusual in this regard.¹⁴⁵ Although pharmaceutical companies specifically engineer and test new drugs to treat a particular condition, their biological effects are complex and multidimensional.¹⁴⁶ The vast majority of drug compounds operate by targeting biological pathways that affect the progress or symptoms of a range of diseases,¹⁴⁷ and almost all drugs have “off-target” activity on other biological pathways that may affect a different set of diseases.¹⁴⁸

Consequently, drugs designed to treat one disease commonly have potential new indications for treating one or more entirely different conditions.¹⁴⁹ According to some estimates, approximately 90 percent of FDA-approved drugs have secondary indications.¹⁵⁰

B. New Uses for Existing Drugs Are Often Discovered Long After the Drug First Reached the Market

Since pharmaceutical companies can increase their drugs’ sales by marketing them for multiple indications, they often test their drugs for more than one therapeutic use.¹⁵¹ However,

145. See THOMSON REUTERS, WHITE PAPER: KNOWLEDGE-BASED DRUG REPOSITIONING TO DRIVE R&D PRODUCTIVITY 1, tbl.1 (2012) (listing various examples of successfully repurposed drugs).

146. See Fabrice Moriaud et al., *Identify Drug Repurposing Candidates by Mining the Protein Data Bank*, 12 BRIEFINGS IN BIOINFORMATICS 336 (2011) (“[A]single drug often interacts with multiple targets.”); Keiser et al., *supra* note 33, at 175 (reporting that “several lines of evidence suggest that drugs may have many physiological targets.”).

147. See Peter Csermely, et al., *Structure and Dynamics of Molecular Networks: A Novel Paradigm of Drug Discovery: A Comprehensive Review*, 138 PHARMACOLOGY & THERAPEUTICS 333, 337-43 (2013); Joseph Loscalzo & Albert-Laszlo Barabasi, *Systems Biology and the Future of Medicine*, 3 WIREs SYSTEMS BIOLOGY MEDICINE 619, 620 (2011) (noting that many diseases are treated through the “same intermediate pathophenotypes (e.g., anti-inflammatory or antithrombotic therapies for acute myocardial infarction.”); Silpa Suthram, et al., *Network-Based Elucidation of Human Disease Similarities Reveals Common Functional Modules Enriched for Pluripotent Drug Targets*, 6 PLOS COMPUTATIONAL BIOLOGY e1000662, 6 (2010) (finding that the average drug target is associated with treating 42 diseases).

148. See Asher Mullard, *Drug Repurposing Programmes Get Lift Off*, 11 NAT. REV. DRUG DISCOVERY 1, 2 (2012) (“It is essentially impossible to develop a drug with such extreme specificity that it will not have some kind of off-target activity.”); Camille G. Wermuth, *Selective Optimization of Side Activities: the SOSA Approach*, 11 DRUG DISCOVERY TODAY 160, 160-61 (2006) (noting that “almost all drugs used in human therapy show one or several pharmacological side effects,” which indicates that “if [drugs] are able to exert a strong interaction with the main target they can, in addition, interact with other biological targets,” and that “[m]ost of these targets are unrelated to the primary therapeutic activity of the compound.”).

149. See Joseph A. DiMasi, *Innovating by Developing New Uses of Already-Approved Drugs: Trends in the Marketing Approval of Supplemental Indications*, 35 CLINICAL THERAPEUTICS 808, 811 (2013) (finding that between 1998 and 2011 the FDA approved 982 applications for new uses of already-approved drugs, and that approximately 73% of those approvals were for new indications (as opposed to new patient populations)); Nair, *supra* note 56, at 2431 (“While the involvement of government institutions in the effort to find new uses for known drug compounds has generated a drumbeat of publicity for the initiatives, the idea of repurposing is old hat in the drug industry.”). A 2009 study found that the average drug has 18 separate indications for which physicians sometimes prescribe it. See Surrey M. Walton, et al., *Developing Evidence-Based Research Priorities for Off-Label Drug Use*, Effective Health Care Research Report No. 12, at 5 (2009), available at effectivehealthcare.ahrq.gov/reports/final.cfm.

150. See Gupta et al., *supra* note 35, at 508; Louis A. Tartaglia & Lee E. Babiss, *Repositionings Role in Drug Discovery and Development*, DRUG DISCOVERY WORLD, Winter 2006. This commonly cited figure that 90% of drugs have secondary indications comes from a NEJM study that looked only at blockbuster drugs, and thus may not be representative of all drugs. See Gelijns et al., *supra* note 13.

151. See ELLERY & HANSEN, *supra* note 89, at 123 (2012).

at the time pharmaceutical companies are initially developing their new drugs, they may recognize only a small fraction of the drugs' possible indications.¹⁵²

Some potential new indications only come to light once drugs reach the market and physicians begin prescribing them. User-generated innovation is common phenomenon in many industries,¹⁵³ including medical practice, where clinicians frequently identify potential new uses for drugs as they prescribe them.¹⁵⁴ Clinicians sometimes stumble upon these indications inadvertently, such as when patients report that a drug helped resolve an entirely unrelated condition.¹⁵⁵ In other cases, clinicians discover the new indications through deliberate experimentation, most often while attempting to treat patients for conditions without established therapies.¹⁵⁶

Researchers have also become increasingly adept at finding potential new indications for drugs, often by using scientific knowledge or technologies unavailable to pharmaceutical companies at the time they developed those products.¹⁵⁷ As science advances and researchers learn more about a drug's clinical effects, they usually gain a much better understanding of its precise mechanism(s) of action.¹⁵⁸ These insights often reveal a drug's propensity to hit distinct biological targets that may affect other diseases.¹⁵⁹ Scientific advances are continually revealing

152. See Gelijns et al., *supra* note 13 (“Unanticipated uses of diagnostic and therapeutic interventions are often identified many years after their introduction. Indeed, widespread use is often an essential precondition for the identification of new applications, and clinical practice itself is thus a particularly important source of medical innovation.”); cf. Scannell et al., *supra* note 58, at 197 (noting that it is easy for pharmaceutical companies to miss potentially promising new indications for drugs in their pipeline because “most of the drug industry [uses] a narrow clinical search strategy,” and “[o]pportunities for serendipity are actively engineered out of the system”).

153. See generally ERIC VON HIPPEL, *DEMOCRATIZING INNOVATION* 19-43 (2005); ERIC VON HIPPEL, *THE SOURCES OF INNOVATION* (1988).

154. See Harold J. Demonaco, et al., *The Major Role of Clinicians in the Discovery of Off-Label Drug Therapies*, 26 *PHARMACOTHERAPY* 323 (2006); Gelijns et al., *supra* note 13; Scannell et al., *supra* note 58, at 197 (“Even recently, it appears that many—perhaps most—new therapeutic uses of drugs have been discovered by motivated and observant clinicians working with patients in the real world.”).

155. See Joel T. Dudley, et al., *Exploiting Drug-Disease Relationships for Computational Drug Repositioning*, 12 *BRIEFINGS IN BIOINFORMATICS* 303 (2011) (“Accidental discovery, unintended side effects or obvious follow on indications have led to new uses of such drugs.”); Tohru Mizushima, *Drug Discovery and Development Focusing on Existing Medicines: Drug Re-Profiling Strategy*, 149 *J. BIOCHEM.* 499 (2011); Qu et al., *supra* note 44, at S4 (“Despite impressive successes shown by repositioned drugs, most of these are the result of ‘serendipity’, i.e. based on unexpected findings made during or after late phases of clinical study.”).

156. See, e.g., Demonaco et al., *supra* note 154; Scannell et al., *supra* note 58; Tewodros Eguale et al., *Drug, Patient, and Physician Characteristics Associated with Off-Label Prescribing in Primary Care*, 172 *ARCH. INTERNAL MED.* 781 (2012).

157. See David Bradley, *Why Big Pharma Needs to Learn the Three ‘R’s*, 4 *NATURE REVIEWS DRUG DISCOVERY* 446 (2005) (citing numerous examples of “[p]otential new disease indications for, or improved versions of, existing drugs are cropping up in unlikely situations” through laboratory research); Ekins et al., *supra* note 33 (“Analysis of the literature suggests that, by using HTS, there are many examples of FDA-approved drugs that are active against additional targets that can be used to therapeutic advantage for repositioning.”).

158. Cf. Oprea & Mestres, *supra* note 9 (“Overall, the lack of data completeness during the preclinical phases together with the accumulation of safety and efficacy data during the various clinical phases offers a wealth of opportunities for drug repurposing.”).

159. See Sarah L. Kinnings et al., *Drug Discovery Using Chemical Systems Biology: Repositioning the Safe Medicine Comtan to Treat Multi-Drug and Extensively Drug Resistant Tuberculosis*, 5 *PLOS COMPUTATIONAL BIOLOGY* e1000423

previously unknown commonalities in the underlying pathways for seemingly unrelated diseases, suggesting that treatments effective for one might work for the other.¹⁶⁰ Moreover, advances in drug-screening technologies and other drug-discovery tools frequently allow researchers to identify potential new indications for drugs that the older technologies missed.¹⁶¹

C. The Need for Clinical Trials to Test the Safety and Efficacy of New Uses for Existing Drugs

The mere discovery of a potential new indication for a drug is not enough for the public to benefit fully (or at all) from that new medical treatment. Without clinical data showing that drug's therapeutic value for the new indication, physicians are much less likely to prescribe the drug for that new use, particularly if it involves an entirely different disease.¹⁶² Although the FDA does not prohibit physicians from prescribing drugs for unapproved indications,¹⁶³ it does prohibit pharmaceutical companies from marketing their drugs for any such "off-label" uses.¹⁶⁴ If there is no pharmaceutical company to promote a new indication, and no published clinical studies reporting findings on its safety and efficacy, many physicians might never learn about it.¹⁶⁵ Assuming physicians are aware of the new indication, many of them may be unwilling to

(2009); Mizushima, *supra* note 155, at 499; Oprea & Mestres, *supra* note 9, at 759 ("[T]he lack of completeness in the knowledge of drug-target interaction profiles, in particular for older drugs, creates opportunities for repurposing of already-approved drugs for novel therapeutic indications through the discovery of biologically and clinically relevant affinities for new targets, which play a determinant role in those indications.").

160. See, e.g., Csermely et al., *supra* note 147, at 341 ("Human disease networks are expected to reveal more on the inter-relationships of diseases using both additional data-associations and novel network analysis tools," and "[t]hese advances will not only enrich our integrated view on human diseases, but will also lead to the ... identification of drug target candidates (including multi-target drugs, drug repositioning, etc.).").

161. See *infra* notes 326-330, and accompanying text (describing how researchers have recently identified hundreds of potential new indications for drugs through in silico screening technologies).

162. See Gelijns et al., *supra* note 13; cf. GUNTER UMBACH, SUCCESSFULLY MARKETING CLINICAL TRIAL RESULTS: WINNING IN THE HEALTHCARE BUSINESS (2006) (describing the importance of clinical-trial results in the pharmaceutical industry's promotional activities directed toward physicians). The threat of tort liability can also discourage physicians from prescribing drugs for indications that have not been adequately tested in clinical trials. See P.G. Casali, *Executive Committee of ESMO: the Off-Label Use of Drugs in Oncology*, 18 ANNALS ONCOLOGY 1923, 1923-24 (2007); Christopher M. Wittich, et al., *Ten Common Questions (and Their Answers) About Off-label Drug Use*, 87 MAYO CLINICAL PRACTICE 982, 986-87 (2012).

163. See 37 Fed. Reg. 16503 (Aug. 15, 1972). The FDA regulates the distribution and promotion of drugs, but not the practice of medicine. Once it approves a new drug for a particular indication, physicians are free to prescribe it for other indications not listed on the label. *Id.*

164. See 21 C.F.R. §202.1(e)(4)(i)(a); C. Lee Ventola, *Off-Label Drug Information, Regulation, Distribution, Evaluation, and Related Controversies*, 34 PHARMACY & THERAPEUTICS 428 (2009) (reviewing the history of FDA regulations on off-label promotion and some of the current changes that have been made to those rules in response to repeated legal challenges under the first amendment).

165. See Grabowski, et al., *supra* note 13, at 375-77 (reviewing the empirical literature on the effects of industry drug promotion). Even when there is strong scientific evidence to support the particular use of a drug, physician uptake can be slow and limited without planned promotional efforts or other policies to incentivize proper prescribing practices. See Roin, *Unpatentable Drugs*, *supra* note 18, at 563-64; cf. Randall S. Stafford et al., *Long-Term and Short-Term Changes in Antihypertensive Prescribing by Office-Based Physicians in the United States*, 48 HYPERTENSION 213, 216 (2006) ("The recorded trends in the prescribing of thiazide diuretics after the release of ALLHAT results suggest that the impact of evidence alone can be short-lived unless augmented by efforts that encourage widespread adoption of evidence-based medicine.").

prescribe that treatment to their patients without any clinical-trial evidence supporting its use.¹⁶⁶ Moreover, almost all insurers now limit their coverage of prescription drugs to indications that are either approved by the FDA or listed in one of the pharmaceutical compendium.¹⁶⁷ Insurers use a number of highly effective tools to enforce their indication-based restrictions on prescribing.¹⁶⁸

Some new indications work their way into medical practice without any supporting evidence from clinical trials,¹⁶⁹ although this type of prescribing is generally thought to be problematic.¹⁷⁰ Off-label prescribing for untested indications is most worrisome when the indication is for an entirely different disease, since there may be little or no sound clinical evidence supporting that use of the drug.¹⁷¹ Some of these untested indications are probably beneficial to patients, but others are probably ineffective and even harmful.¹⁷² This type of off-label prescribing might even cause more harm than good,¹⁷³ and there are constant calls for investments in clinical trials to test these indications.¹⁷⁴

166. Cf. Bradley F. Marple, *Evidence-Based Medicine: Adjusting to a Culture Shift in Health Care*, ENT TODAY, Oct. 2008 (noting that physicians increasingly accept the principles of evidence-based medicine).

167. See Cohen, et al., *supra* note 138, at 393-97;

168. See *supra* note 124; Murray Aitken et al., *Prescription Drug Spending Trends in the United States: Looking Beyond the Turning Point*, 28 HEALTH AFFAIRS w151 (2008); Casali, *supra* note 162, at 1924 (“At the very least, physicians may be facing more red tape in order to prescribe off-label drugs. ... More simply, third party payers ... might just refuse to reimburse some off-label drugs, at their discretion.”). In certain fields, such as psychiatry, insurers are sometimes prohibited from using some of these tools for discouraging off-label prescribing. See Stuart Wright, *Memorandum Report: Ensuring that Medicare Part D Reimbursement is Limited to Drugs Provided for Medically Accepted Indications*, OEI-07-08-00152, Department of Health & Humans Services, at 2-3 & 5 (2011).

169. In a 2006 study looking at prescriptions for the 500 most commonly prescribed drugs, the authors found that approximately 21 percent of prescriptions were for off-label indications, and that three-fourths of these off-label prescriptions (*i.e.*, 15 percent of total prescriptions) were not “scientifically supported.” See David C. Radley, et al., *Off-label Prescribing Among Office-based Physicians*, 166 ARCHIVES INTERNAL MED. 1021 (2006).

170. See AVORN, *supra* note 7, at _; Casali, *supra* note 167; David C. Radley et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1025 (2006); Philip M. Rosoff & Doraine Lambelet Coleman, *The Case for Legal Regulation of Physicians’ Off-Label Prescribing*, 86 NOTRE DAME L. REV. 649, 653 (2011); Gordon D. Schiff, et al., *Principles of Conservative Prescribing*, 171 ARCHIVES OF INTERNAL MED. 1433 (2011); Walton et al., *supra* note 149, at 8 (“It is not at all clear, however, that evidence of efficacy in a clinically proximate indication is sufficient to support common use for the other indication.”).

171. See Schiff et al., *supra* note 170, at 1436.

172. See Rosoff & Coleman, *supra* note 170, at 653.

173. See, *e.g.*, Adriane Fugh-Berman & Douglas Melnick, *Off-Label Promotion, On-Target Sales*, 5 PLOS MED (2008) doi:10.1371/journal.pmed.0050210.

174. See Casali, *supra* note 167; CENTER FOR MEDICAL TECHNOLOGY PROGRESS, PROPOSED RECOMMENDATIONS FOR DESIGNING CLINICAL TRIALS FOR ‘NEW INDICATIONS’ OF APPROVED ONCOLOGY DRUGS FOR TREATMENT OF LATE STAGE DISEASE 6-7 (2010); C. Daniel Mullins, *Recommendations for Clinical Trials of Off-Label Drugs Used to Treat Advanced-Stage Cancer*, 30 J. CLINICAL ONCOLOGY 661 (2012); Walton et al., *supra* note 149. A more common form of off-label prescribing for untested indications involves uses that are closely related to drugs’ FDA-approved indication. *Id.* at 8. These treatment choices are less controversial, although experts are uncertain about whether (or how often) the inference of efficacy in clinically proximate indications is justified. *Id.*; see also Schiff et al., *supra* note 170, at 1436.

D. Clinical Trials Are Expensive

Establishing the safety and efficacy of new indications for FDA-approved drugs in clinical trials requires a substantial investment of both time and resources, especially when seeking FDA approval for the new indication.¹⁷⁵ At the very least, these development programs involve running phase III studies on the new indication.¹⁷⁶ Completing these clinical trials usually takes several years or longer and, depending on their size, can cost tens or even hundreds of millions of dollars.¹⁷⁷ In some cases, firms may also be required to complete phase I and II trials.¹⁷⁸ Although developing a new use for an existing drug is much less expensive and risky than developing a new drug,¹⁷⁹ total costs often still run in the hundreds of millions of dollars.¹⁸⁰

The cost of clinical trials for new indications depends in part on whether the sponsor is planning to seek FDA approval for that new use. FDA regulations for clinical trials significantly increase the administrative costs of those studies with requirements for additional testing, recordkeeping, and reporting.¹⁸¹ Putting together an application for FDA approval of a new indication is also very costly.¹⁸² The filing fee alone for these applications is over \$1 million.¹⁸³ Sponsors can avoid these additional costs and still run a successful trial that might be published in a well-respected, peer-review journal. However, these clinical trials are generally thought to be

175. See Tudor I. Oprea et al., *Drug Repurposing from an Academic Perspective*, 8 DRUG DISCOVERY TODAY THERAPEUTIC STRATEGY 61, 61 (2011).

176. See Oprea & Mestres, *supra* note 9, at 762 (explaining that firms can often skip phase I and IIa clinical trials when repurposing an FDA-approved drug for a new indication). In most cases, new indications that are closely related to the drug's established uses are the least expensive to develop because physicians and regulators also weigh the earlier clinical trials for the original indication. See John King, *Can a Drug Live Forever?*, 9 R&D DIRECTIONS _ (2003).

177. See ELLERY & HANSEN, *supra* note 89, at 124; SAHOO, *supra* note 89, at 28 (estimating a total cost of approximately \$300 million for establishing a new disease indication for an already-approved drug); cf. *NCI Will No Longer Accept R01 and P01 Applications for Phase III Clinical Trials of Medical Interventions and Cancer Imaging Modalities*, THE ASCO POST, Jun. 17, 2013, at <http://www.ascopost.com/ViewNews.aspx?nid=5242> ("In general, medical intervention phase III clinical trials require more time than allowed by a single 5-year funding cycle associated with R01 and P01 awards.").

178. See Chong & Sullivan, *supra* note 84, at 646.

179. See *supra* notes 38-47 and accompanying text.

180. See *supra* note 177; SAHOO, *supra* note 89, at 59 ("Because of the relatively greater resources required to demonstrate efficacy in an entirely new therapeutic area compared with expanded usage of the drug for its original indication or a closely-related variant of the originally approved indication (indication extension), care must be taken to select new therapeutic applications that will provide an acceptable return on investment.").

181. See IOM, CANCER CLINICAL TRIALS, *supra* note 185, at 68-69 ("[O]ur estimate from working with those sites is that about 35 percent of the costs that accrue for a clinical trial relate to regulatory issues and regulatory compliance."); Jeanne Erdmann, *Researchers Facing Increasing Costs for Clinical Research, With Few Solutions*, 97 J. NAT. CANCER INST. 1492, 1492 (2005) (commenting on the "tremendous regulatory requirements" associated with conducting clinical trials that hopefully will be submitted to the FDA to support the approval of a new indication for an FDA-approved drug).

182. See Mark Hovde, *Management of Clinical Development Costs*, in CLINICAL TRIALS OF DRUGS AND BIOPHARMACEUTICALS 90 (Chi-Jen Lee et al. eds. 2006).

183. Department of Health and Human Services, Prescription Drug User Fee Rates for Fiscal Year 2014, 78 Fed. Reg. 46980, 46981 (proposed Aug. 2, 2013) (setting the FDA application fees for new drug approvals at \$2,169,100 for applications requiring clinical data, and \$1,084,550 for supplemental applications requiring clinical data or applications not requiring clinical data).

much less reliable than the ones used to support FDA approval for a new indication.¹⁸⁴ The FDA forces sponsors to conduct more rigorous trials.¹⁸⁵ It also closely scrutinizes the studies and demands full disclosure to prevent sponsors from distorting their study results with biased trial designs or selective reporting—both of which are thought to be a serious problems for studies published in the peer-review medical literature.¹⁸⁶ Consequently, many medical experts express a strong preference for sponsors to complete the FDA-approval process for new indications of drugs,¹⁸⁷ although the costs can make it impractical for indications with small markets.¹⁸⁸

E. The Need for Government Intervention to Support Clinical Trials for New Uses of Existing Drugs

As noted above, the clinical trials needed to establish a drug's safety and efficacy for a new indication can cost tens or even hundreds of millions of dollars.¹⁸⁹ To recover that investment through the market, pharmaceutical companies must sell the drug for its new indication at a price far above their marginal production costs.¹⁹⁰ This pricing strategy is impractical when other firms can sell the exact same drug to patients for the identical indication at a price near marginal cost, especially when those low-cost substitutes are already on the market.¹⁹¹ Consequently, without government intervention in the market, firms will have little incentive to invest in developing new indications for drugs once generics are available.

Indeed, the case for government intervention to promote the development of new indications may be even stronger than the case for intervening to promote the development of new drugs. As noted earlier, pharmaceutical companies generally lose about 80% of the market for their drugs within two months of generic entry.¹⁹² However, before entering the market for a new drug, generic manufacturers usually need two to three years to set up their production facilities.¹⁹³ Pharmaceutical companies would normally enjoy a two to three-year lead-time advantage with their new drug even without legal barriers to imitation. This short lead-time is

184. See Harold C. Sox, *Evaluating Off-Label Uses of Anticancer Drugs: Time for a Change*, 150 ANNALS INTERNAL MED. 353, 354 (2009).

185. See INSTITUTE OF MEDICINE (IOM), IMPROVING THE QUALITY OF CANCER CLINICAL TRIALS: WORKSHOP SUMMARY 78-79 (2008) (hereinafter “CANCER CLINICAL TRIALS”).

186. See Gisela Schott et al., *The Financing of Drug Trials by Pharmaceutical Companies and Its Consequences*, 107 DTSCH ARZTEBL INT'L 279 (2010); Lenard I. Lesser et al., *Relationship Between Funding Source and Conclusion Among Nutrition-Related Scientific Articles*, 4 PLOS MED. e.5 (2007).

187. See Ratner & Gura, *supra* note 138.

188. See Ratner & Gura, *supra* note 138, at 869 (noting that in the field of oncology, “it simply costs too much to obtain full FDA approval in multiple cancers,” since “[e]ach would cost \$700 million and would take 3–5 years”).

189. See *supra* text accompanying notes 175-180.

190. See F.M. Scherer, *The Pharmaceutical Industry*, in 1 HANDBOOK OF HEALTH ECONOMICS 1301-02 & 1317-18 (A.J. Culyer & J.P. Newhouse, eds. 2000).

191. See Eisenberg, *New Uses*, *supra* note 13, at 717; Grabowski et al., *supra* note 13, at ; PEDRO BARROS & XAVIER MARTINEZ-GIRALT, HEALTH ECONOMICS: AN INDUSTRIAL ORGANIZATION PERSPECTIVE § 17.1 (2012); BESSEN & MEURER, *supra* note 18, at 88-89 (2008); BOLDRIN & LEVINE, *supra* note 130, at 237; JAFFE & LERNER, *supra* note 18, at 39-41.

192. See *supra* note 21, and accompanying text.

193. See *supra* note 19, and accompanying text.

probably insufficient to incentivize the development of most new drugs,¹⁹⁴ but it might sustain at least a modicum of industry-funded drug development. When pharmaceutical companies develop a new indication for a drug with generics already on the market, their potential financial returns are much bleaker. Innovators would not enjoy any lead-time advantage at all, and likely lose their market to generics immediately.

The government could correct this market failure in one of two ways. It could offer financial incentives for firms to develop new indications for existing drugs, just as it offers for new drugs. Alternatively, it could finance the clinical development of new indications directly, relying on the NIH or some other agency to decide which new indications to test in clinical trials and carry out that research. As explained in Parts III and IV below, the government has failed to implement either strategy for promoting drug repurposing, leaving a critical gap in the incentives for pharmaceutical innovation.

III. THE FAILURE TO MOTIVATE INDUSTRY TO DEVELOP NEW USES FOR EXISTING DRUGS

The public primarily relies on private industry to finance the clinical development of new pharmacological therapies, be they new drugs or new uses for existing drugs.¹⁹⁵ Pharmaceutical companies are unlikely to invest in developing a new indication without some form of monopoly protection,¹⁹⁶ and the government does not provide effective monopoly protection for drugs' new indications once generics are on the market. Accordingly, when researchers identify a potential new use for an off-patent drug, pharmaceutical companies rarely (if ever) finance the clinical trials necessary to establish the drug's safety and efficacy for that new indication.¹⁹⁷

This Part explains both how and why the existing legal infrastructure of drug patents and FDA-exclusivity periods gives rise to this problem of new uses. Pharmaceutical companies currently rely on temporary monopoly rights that block generic manufacturers from making and selling imitations of their drugs (the "standard monopoly protection" for new drugs) to recoup

194. Several published academic studies estimate that for the average small-molecule NME, firms need 13 to 16 years of sales revenue (without generic competition) to reach the break-even point on their R&D investment. See Henry Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NAT. REV. DRUG DISCOVERY 479, 484 (2008); Henry Grabowski et al., *Data Exclusivity for Biologics*, 10 NAT. REV. DRUG DISCOVERY 15 (2010). These studies were supported in part through grants from the pharmaceutical industry. An unpublished academic study supported by Teva Pharmaceuticals, the world's large generic manufacturer, found that firms reach break-even point on the average drug after nine years. See ALEX M. BRILL, PROPER DURATION OF DATA EXCLUSIVITY FOR GENERIC BIOLOGICS: A CRITIQUE 8-10 (2008), at http://www.tevadco.com/Brill_Exclusivity_in_Biogenics.pdf (estimating that a seven-year exclusivity period would be sufficient for biologic drugs under the assumption of limited price competition in those markets following patent expiration). Qualitative evidence—including reports from industry insiders and the trade literature—suggest that pharmaceutical companies normally must anticipate ten or more years of market exclusivity over a new drug to invest in its development. See Roin, *Unpatentable Drugs*, *supra* note 18, at 552 n.259, 557 & n.290, 566 & n.335 (discussing how pharmaceutical companies are generally unwilling to develop new drugs without strong patent protection).

195. See Getz, *supra* note 1, at 3.

196. See SAHOO, *supra* note 89, at 41-42.

197. See *infra* notes 260-266, and accompanying text.

their R&D investments.¹⁹⁸ This type of monopoly protection is poorly suited to encouraging drug repurposing because they give pharmaceutical companies effective control over the entire market for a drug, not just the new indications they develop. Instead of using the standard monopoly protection to incentivize firms to develop new indications for existing drugs, the government offers firms monopoly rights that only cover the act of taking or administering the drug for the new indication. Although these rights could provide firms with a suitable incentive for developing new indications, pharmaceutical companies generally cannot enforce them because they do not know which patients are using the drug for the patented indication as opposed to some other use. As a result, pharmaceutical companies only invest in developing new indications for drugs over which they have sufficient monopoly life remaining to recoup their investment in the new use.¹⁹⁹ In this sense, the problem of new uses stems from an information problem—the inability to observe the utilization rate for a drug’s new indication distinct from the drug’s other potential uses. This Part argues that if the government were to solve that information problem, it could rely on the existing patent system—or implement some other incentive system—to encourage firms to repurpose off-patent drugs.

A. The Standard Monopoly Protection for Promoting Drug Development Gives Firms the Power to Block Generic Entry

In the pharmaceutical industry, the standard form of monopoly protection for promoting the development of new drugs is the power to exclude generic manufacturers from making or selling those new drug compounds. As discussed in the Introduction, drug development is extraordinarily expensive and involves a high risk of failure.²⁰⁰ Since firms quickly lose their market position to generics soon after they enter,²⁰¹ pharmaceutical companies depend on temporary monopoly rights to delay generic entry long enough to earn a profit from their R&D investments. The government provides this standard monopoly protection through three different types of exclusionary rights: product patents, process patents, and FDA-exclusivity periods. Although each one offers a different set of legal rights, pharmaceutical companies use them for the same purpose: to block generic drugs from entering the market entirely.

Pharmaceutical companies typically rely on product patents, which cover their drug’s active ingredient or formulation, as their primary means of protection against generic competition.²⁰² The patent system will protect any newly discovered drug that is novel, nonobvious, and useful,²⁰³ giving firms a monopoly over the drug that expires twenty years after they file the patent application.²⁰⁴ Product patents on the active ingredient in a drug are usually the strongest

198. See *supra* note 28 and accompanying text.

199. See *supra* note 89.

200. See *supra* notes 39 & 52-53 and accompanying text.

201. See *supra* notes 20-21 and accompanying text.

202. See Roin, *Unpatentable Drugs*, *supra* note 18, at 545-56; Comer, *supra* note 27, at 4 (“[T]he composition of matter patents, plus synthetic process and formulation patents, [are] king of intellectual property and sole protector of a [drug] product in the market place.”).

203. See 35 U.S.C. §§ 101-103 & 112.

204. See 35 U.S.C. § 154(a)(2).

form of patent protection for blocking generic entry.²⁰⁵ FDA regulations effectively prevent generic manufacturers from designing around these patents, since they cannot modify the brand-name drug's active ingredient without undermining their product's regulatory status as a generic, thereby subjecting themselves to the FDA's extensive clinical-trial requirements for new drugs.²⁰⁶ Pharmaceutical companies can also use product patents on their drug's formulation to block generics from the market.²⁰⁷ Formulation patents are effective as long as they are broad enough to prevent generic manufacturers from designing around the patented formulation without undermining their generic drug's status as "bioequivalent" to the brand-name drug.²⁰⁸ Both types of product patents are easy to enforce because the FDA requires generic manufacturers to disclose their drug's chemical composition to the brand-name company, allowing for automatic detection of infringement.²⁰⁹

In addition to their product patents, pharmaceutical companies sometimes rely on process patents that cover a method of using their drug, although these patent will only block generic entry under certain circumstances.²¹⁰ Federal law expressly allows for the patenting of "any new and useful process" that involves "a new use of a known . . . composition of matter."²¹¹ Patents on new uses for drugs—known as "new use" patents—give firms a legal monopoly over the act of taking or administering a particular drug for a particular indication.²¹² Generic manufacturers do not directly infringe these patents, since they only make and sell drugs, and do not take or administer them to patients.²¹³ But generic manufacturers can be held liable for indirectly infringing a new-use patent if they "actively induce infringement" by patients, pharmacists, or

205. See MARTIN A. VOET, *THE GENERIC CHALLENGE: UNDERSTANDING PATENTS, FDA & PHARMACEUTICAL LIFECYCLE MANAGEMENT* 35 (2005) ("The best pharmaceutical patent is a compound patent."). A patent on the active ingredient in a drug covers "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt ... responsible for the physiological or pharmacological action of the drug substance." *Pfizer Inc., v. Dr. Reddy's Labs. Ltd.*, 359 F.3d 1361, 1366 (Fed. Cir. 2004) (quoting 21 C.F.R. § 314.108(a)).

206. See 21 C.F.R. 314.127(a)(3) ("FDA will refuse to approve an abbreviated application for a new drug [if] ... information submitted with the abbreviated new drug application is insufficient to show that the active ingredient is the same as that of the reference listed drug."); FTC, *supra* note 18, ch. 3, page 7 ("[D]rug substance patents are typically the most valuable for the brand-name company, because they are much more difficult for potential competitors (including generic companies) to design around than formulation or method of use patents.").

207. See THOMAS, *supra* note 23, at 39. A patent on the formulation of a drug covers the combination of the drug's active ingredient and its inactive ingredients (or "excipients") that affect the delivery of the active ingredient. See Michael Enzo Furrow, *Pharmaceutical Patent Life-Cycle Management after KSR v. Teleflex*, 63 FOOD & DRUG L.J. 275, 294-295 (2008).

208. See Rasma Chereson, *Bioavailability, Bioequivalence, and Drug Selection*, in BASIC PHARMACOKINETICS 8-2 (Michael C. Makoid ed. 1996) (describing efforts by generic manufacturers to design around formulation patents on brand-name drugs).

209. See 21 C.F.R. § 314.95 (2013).

210. See Eisenberg, *New Uses*, *supra* note 13, at 720-25.

211. Congress set the boundaries of patentable subject matter to encompass "any new and useful process, machine, manufacture, or composition of matter," and defined "process" as including "a new use of a known ... composition of matter, or material." 35 U.S.C. §§ 100(b) & 101 (2012).

212. See THOMAS, *supra* note 23, at 44-46, 235-37.

213. *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363 n.7 (Fed. Cir. 2003).

physicians.²¹⁴ The FDA requires generic manufacturers to list on their label at least one FDA-approved indication for the drug.²¹⁵ Since the label instructs physicians and patients in how to use the drug, courts will hold the generic manufacturer liable for inducing infringement if their label covers a patented indication.²¹⁶ Consequently, if pharmaceutical companies have protection over every FDA-approved indication for their drug, they can effectively exclude generics from the market.²¹⁷

Congress also grants firms FDA-exclusivity periods that run concurrently with their patent rights (if any) over their new drugs. These FDA-exclusivity periods operate as a guaranteed minimum term of protection against generics that runs from the date of FDA approval,²¹⁸ but different types of drugs receive different lengths of FDA-exclusivity. When Congress established the abbreviated drug-approval pathway for generics of small-molecule drugs in 1984, it made that pathway unavailable to generic manufacturers for the first five years after the FDA approves a new drug.²¹⁹ This five-year term of “data exclusivity” prevents generic manufacturers from entering the market unless they can produce all of the necessary preclinical and clinical data to support a new drug application, effectively defeating the purpose of being a generic.²²⁰ New indications for FDA-approved drugs receive three years of data exclusivity.²²¹ Drugs approved for treating so-called “orphan” diseases—a legal designation that is usually reserved for diseases with small markets—automatically receive a seven-year term of market exclusivity.²²² When Congress created the regulatory pathway for biosimilars in 2010, pharmaceutical companies negotiated for—and received—an automatic twelve years of data exclusivity over their biologics.²²³

One or more of these exclusionary rights for blocking generic entry will almost always be available to protect new drugs. In the end, pharmaceutical companies usually manage to keep

214. See 35 U.S.C. § 271(b) (2012).

215. See 21 C.F.R. 314.127(a)(7).

216. See *AstraZeneca LP v. Apotex Corp.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010) (finding that a generic manufacturer “had the requisite specific intent to induce infringement because [it] included instructions in its proposed label that will cause at least some users to infringe the asserted method claims”); *Wyeth v. Sandoz, Inc.*, 703 F.Supp. 2d 508, 522 (E.D.N.C. 2010).

217. See Anna Volftsun & Sandra Lee, *The Future Of Skinny Labels*, INTELLECTUAL PROPERTY REPORT, vol. 8 (2011); Richard B. Smith, *Repositioned Drugs: Integrating Intellectual Property and Regulatory Strategies*, 8 DRUG DISCOVERY TODAY STRATEG. 131, 131-32 (2011).

218. See Rebecca S. Eisenberg, *Patents, Product Exclusivity, and Information Dissemination: How Law Directs Biopharmaceutical Research and Development*, 72 FORDHAM L. REV. 477, 481-86 (2003).

219. See 21 U.S.C. § 355(c)(3)(E)(ii). To qualify for this protection, new drugs cannot contain any active ingredients already approved by the FDA for use in humans. *Id.* Drugs containing one or more active ingredients previously approved by the FDA receive a three-year term of data exclusivity. See 21 U.S.C. § 355(c)(3)(E)(iii).

220. See THOMAS, *supra* note 23, at 349-52.

221. 21 U.S.C. § 355(c)(3)(E)(iii).

222. See 21 U.S.C. § 360cc(a). An orphan indication is one that “affects fewer than 200,000 people in the United States,” or for which “there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States.” See 21 C.F.R. § 316.20(b)(8) (interpreting 21 U.S.C. § 360bb(a)(2)).

223. See Patient Protection and Affordable Care Act of 2010, Pub. L. No. 111-148, § 7002(a)(2)(k)(7)(A), 124 Stat. 119, 807 (2010).

generics off the market for somewhere between ten and fifteen years following the initial FDA approval of their drug.²²⁴ The average effective patent life for new drugs—the time from FDA approval to generic entry—has remained unchanged at around twelve years for much of the past three decades.²²⁵ Once that protection expires, generics quickly enter and take over the market in most cases.²²⁶

B. The Standard Monopoly Protection is Unavailable (and Unsuitable) for New Uses of Existing Drugs

The exclusionary rights that temporarily bar generics from the market are poorly suited for encouraging the development of new indications. They block generic entry entirely, and thus give pharmaceutical companies control over the whole market for a drug, including its previously established FDA-approved uses. Since this broad monopoly protection would deny the public access to low-cost generics for the drug's older uses as well as the new use, legislators opted not to offer the standard monopoly protection to firms as an incentive for developing new indications of existing drugs.²²⁷

The primary economic justification for promoting innovation with monopoly rights is to link the incentives for investing in R&D to the social value of the resulting inventions.²²⁸ As John Stuart Mill explained, the chief virtue of the patent system is that “the reward conferred by it depends entirely upon the invention's being found useful, and the greater the usefulness the greater the reward.”²²⁹ When a firm develops a new indication for a drug, the social value of its R&D investment is the value of that new indication, not the drug's previously established uses. Since the standard monopoly protection bars generic manufacturers from the market entirely, it would allow pharmaceutical companies to charge supra-competitive prices for the drugs' old uses as well as the new. Granting that protection to encourage the development of new indications would break the link between the incentives for those R&D investments and their social value.

When legislators drafted the Hatch-Waxman Act, they feared that if pharmaceutical companies could delay generic entry by developing new indications for their drugs, they could keep generics off the market for much longer than the Act intends, perhaps indefinitely in some cases.²³⁰ The public would benefit from the development of these new indications, but it would

224. See *supra* note 24.

225. See Grabowski & Kyle, *supra* note 24, at 497 fig. 4; Hemphill & Sampat, *supra* note 24, at 328.

226. See *supra* note 21, and accompanying text.

227. See Mossinghoff, *supra* note 13, at 191; Warner-Lambert, 316 F.3d at 1362 (“As our analysis of the legislative history indicates, Congress contemplated the possibility that there could be more than one approved indication for a given drug, and that [a generic manufacturer] can seek approval to label and market the drug for fewer than all of those indications.”); Bristol-Myers Squibb Co. v. Shalala, 91 F.3d 1493, 1500 (C.A.D.C. 1996).

228. See Anup Malani & Jonathan S. Masur, *Raising the Stakes in Patent Cases*, 101 GEO. L.J. 637, 638-39 (2013); Peter S. Menell & Suzanne Scotchmer, *Intellectual Property*, in 2 HANDBOOK OF LAW AND ECONOMICS 1477 (A. Mitchell Polinsky & Steven Shavell eds. 2007); Shavell & van Ypersele, *supra* note 111, at 530.

229. John Stuart Mill, *Principles of Political Economy: With Some of Their Applications to Social Philosophy* 933 (W.J. Ashley ed., 1909).

230. See Warner-Lambert, 316 F.3d at 1359 (noting that if a pharmaceutical company could exclude generics from the market for a drug with patents on a new use for that product, it “would be able to maintain its exclusivity merely by regularly filing a new patent application claiming a narrow method of use not covered by its NDA. It would then be able to use § 271(e)(2)(A) as a sword against any competitor's ANDA seeking approval to market an

also have less access to lower-cost generics, which generate significant value for society.²³¹ Over the last decade alone, generic drugs reportedly saved the U.S. health care system more than a \$1 trillion.²³² According to one estimate, generics currently produce about \$1 billion in savings every two days.²³³ The lower prices for generics may also increase consumers' access to valuable medical treatments.²³⁴ Given these social benefits from generic drugs, legislators chose not to protect new indications within the Hatch-Waxman framework, which promotes pharmaceutical innovation through temporary monopoly rights that block generic entry.²³⁵

The system mostly operates as Congress intended. Except under unusual circumstances, pharmaceutical companies cannot delay generic entry with the monopoly rights available for new indications discovered or developed after the drug's initial FDA approval.²³⁶ Pharmaceutical companies can only patent a drug's active ingredient and formulation once, and they invariably file these patents while developing the drug for its first indication.²³⁷ As noted

off-patent drug for an approved use not covered by the patent. Generic manufacturers would effectively be barred altogether from entering the market. That would certainly not advance the purpose of making available 'more low cost generic drugs,' and was not what Congress intended.").

231. See Steven K. Dobscha et al., *Reducing Drug Costs at a Veterans Affairs Hospital by Increasing Market-share of Generic Fluoxetine*, 43 COMMUNITY MENTAL HEALTH J. 75 (2007); Amy B. Scott et al., *Effects of a Physician Office Generic Drug Sampling System on Generic Dispensing Ratios and Drug Costs in a Large Managed Care Organization*, 13 J. MANAGED CARE PHARMACY 412 (2007); William H. Shrank et al., *State Generic Substitution Laws Can Lower Drug Outlays Under Medicaid*, 29 HEALTH AFFAIRS 1383, 1387 (2010).

232. See GENERIC PHARMACEUTICAL ASSOCIATION (GPHA), SAVINGS \$1 TRILLION OVER 10 YEARS: GENERIC DRUG SAVINGS IN THE U.S. 1 (4th Ed. 2012).

233. See *id.* at 1.

234. The widespread use of prescription-drug insurance likely avoids much of the deadweight loss that might otherwise result from drug patents. See Roin, *Intellectual Property versus Prizes*, *supra* note 111, at ; Darius Lakdawalla & Neeraj Sood, *The Welfare Effects of Public Drug Insurance* 93 J. PUBLIC ECON. 541 (2007). But high drug prices can restrict access to valuable treatments even for insured patients, since insurers use cost-sharing requirements and coverage restrictions to reduce prescribing of costly medications. See *supra* note 124. On the other hand, several studies suggest that any social-welfare gains from lower generic prices are partially or entirely offset by reduced patient access due to the end of promotional activities and clinical research following a drug's patent expiration. See Gautier Duflos & Frank R. Lichtenberg, *Does Competition Stimulate Drug Utilization? The Impact of Changes in Market Structure on US Drug Prices, Marketing and Utilization*, 32 INT'L REV. L. & ECON. 95, 107-08 (2012); Grabowski et al., *supra* note 13; Darius Lakdawalla & Tomas Philipson, *Does Intellectual Property Restrict Output? An Analysis of Pharmaceutical Markets*, 55 J.L. & ECON. 151, 178-79 (2012).

235. See *supra* note 227. In the United States, there is at least one exception to this policy against extending a drug's monopoly term for expanding its label. The government offers pharmaceutical companies six-month patent-term extensions for testing their drugs in pediatric populations. 21 U.S.C. § 355a. These pediatric exclusivity periods have proven remarkably effective at encouraging firms to run pediatric trials. See Carissa M. Baker-Smith et al., *The Economic Returns of Pediatric Clinical Trials of Antihypertensive Drugs*, 156 AM. HEART J. 682, 682 (2008); U.S. Government Accountability Office (GAO), GAO-07-557, *Pediatric Drug Research: Studies Conducted Under Best Pharmaceuticals for Children Act* 4-5 (2007). However, commentators often criticize the system for providing excessive rewards that unnecessarily delay patients' access to generic drugs. See Kate Greenwood, *The Mysteries of Pregnancy: the Role of Law in Solving the Problem of Unknown but Knowable Maternal-Fetal Medication Risk*, 79 U. CIN. L. REV. 267, 313 (2010); Barbara A. Noah, *Just a Spoonful of Sugar: Drug Safety for Pediatric Populations*, 37 J.L. MED. & ETHICS 280, 282 (2009).

236. See Terry G. Mahn, *Generics Behaving Badly: Carve Outs, Off-Label Uses*, Law360, May 4, 2009, at <http://www.fr.com/Files/Uploads/attachments/Generics%20Behaving%20Badly%20by%20Terry%20Mahn%205%204%2009.pdf>.

237. See Bruno Galli & Bernard Faller, *Discover A Drug Substance, Formulate and Develop It To A Product*, in THE PRACTICE OF MEDICINAL CHEMISTRY 688 (Camille Georges Wermuth ed., 2d. 2003); Stephen T. Schreiner &

above, pharmaceutical companies can usually obtain process patents on newly discovered indications for drugs.²³⁸ However, as long as a drug has at least one FDA-approved indication that is off-patent, generic manufacturers can easily design around these new-use patents by excluding the patented indications from their label²³⁹—a practice known as “skinny labeling.”²⁴⁰ Generic manufacturers use this same tactic to design around any FDA-exclusivity periods awarded for new indications.²⁴¹ Pharmaceutical companies receive a three-year data exclusivity period for any newly approved indication of a drug²⁴² and a seven-year data exclusivity period for any new orphan indications.²⁴³ However, generic manufacturers can still enter the market if they only list the off-patent indications on their label.²⁴⁴ Much like the process patents available for additional indications, these FDA-exclusivity periods for new uses generally fail to block generic competition.²⁴⁵

C. Monopoly Rights over New Uses for Off-Patent Drug Are Difficult to Enforce

As an alternative to the standard monopoly protection that blocks generic entry, the government could encourage firms to develop new indications for drugs with monopoly protection covering the new indications only. This narrower form of monopoly protection would encourage firms to develop new indications for existing drugs without denying the public access to low-cost generics for the drugs’ older uses. The patent system ostensibly provides this protection already by allowing firms to patent newly discovered indications for known drugs.²⁴⁶ However, as explained below, pharmaceutical companies usually have no way to enforce these monopoly rights because they do not know when physicians have prescribed a drug for the patented use.

Researchers who discover a new indication can often patent it, giving them a monopoly right over the act of taking or administering a drug for that specific indication. As noted earlier, these new-use patents cannot keep generics off the market if there are any other off-patent FDA-

Patrick A. Doody, *Patent Continuation Applications: How the PTO’s Proposed New Rules Undermine an Important Part of the U.S. Patent System with Hundreds of Years of History*, 88 J. PAT. & TRADEMARK OFF. SOC’Y 556, 557 (2006); Harold C. Wegner & Stephen Macbius, *The Global Biotech Patent Application*, in BIOTECHNOLOGY LAW: BIOTECHNOLOGY PATENTS & BUSINESS STRATEGIES IN THE NEW MILLENNIUM, at 129-30 (PLI Pats., Copyrights, Trademarks, and Literary Prop. Course, Handbook Series No. G0-00R6, 2001).

238. See *supra* notes 211-212, and accompanying text.

239. In general, generic manufacturers are supposed to use the same label for their drugs as used on the brand name product they imitate. See *Mutual Pharmaceutical Co. v. Bartlett*, 133 S.Ct. 2466, 2471 (2013) (citing 21 U.S.C. § 355(j)(2)(A)(v)). However, FDA regulations explicitly allow for generic manufactures to exclude patented indications from their label to avoid infringing any new-use patents. See 21 C.F.R. 314.127(a)(7).

240. See Terry G. Mahn, *Skinny Labeling and the Inducement of Patent Infringement*, UPDATE: FOOD & DRUG LAW INSTITUTE 39, Nov/Dec 2010; Kimberly Weinreich & Jeffrey A. Wolfson, *Pharmaceuticals, Medical Devices & Biologics: Labeling*, 3 BLOOMBERG LAW REPORTS: HEALTH LAW 10, 11-12 (2010).

241. See Eisenberg, *New Uses*, *supra* note 13, at 728-30.

242. See 35 U.S.C. § 355(j)(5)(F)(iii).

243. See 21 U.S.C. § 360cc.

244. See *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1500 (C.A.D.C. 1996).

245. See SAHOO, *supra* note 89, at 42.

246. See ROBERT MERGES & JOHN DUFFY, *PATENT LAW & POLICY: CASES AND MATERIALS* 398-403 (5th Ed. 2011) (discussing the history of new-use patents, their current legal status, and limitations on their effectiveness).

approved uses for the drug.²⁴⁷ Nonetheless, they do give firms a legal right to charge patients—or their insurer—when the patients use that drug for the patented indication.²⁴⁸ If pharmaceutical companies could enforce these monopoly rights, they could require pharmacists to dispense their own, higher-priced brand-name drug instead of a low-cost generic when filling a prescription written for the patented indication. Alternatively, the pharmaceutical companies might require insurers to compensate them directly when pharmacists fill a prescription for a patented indication with a low-cost generic.

Monopoly rights over new indications require an entirely different enforcement mechanism than firms currently use to protect their new drugs. The standard form of monopoly protection for new drugs attaches to the act of manufacturing and selling those products. Pharmaceutical companies enforce these standard rights directly against generic manufacturers, which are limited in number and easily monitored. In contrast, monopoly protection over new uses must attach to the act of taking or administering a drug for a new indication. These acts of infringement are diffuse and much harder to detect than manufacturers, since they typically occur inside doctors' offices, hospitals, pharmacies, or patients' homes.²⁴⁹

Enforcing a new-use patent against pharmacists or insurers is only possible if the relevant parties know when physicians prescribe an off-patent drug for a patented indication.²⁵⁰ Pharmaceutical companies cannot charge payers for these infringing acts unless they can detect those violations. They must know when pharmacists dispense a generic drug to fill a prescription written for a patented indication. Additionally, the pharmacists and insurers cannot be held liable for indirectly infringing a new-use patent unless they know the prescription is for a patented indication.²⁵¹

247. See *supra* notes 210-217 and accompanying text.

248. Patients and physicians could be held directly liable for infringing a new-use patent if they take or administer a low-cost generic for the patented indication. See Eisenberg, *New Uses*, *supra* note 13, at 724. However, as Rebecca Eisenberg notes, pharmaceutical companies would be reluctant to file patent infringement suits against patients and physicians, since suing your customers is often bad for business. See *id.* at 724-25. Moreover, enforcing a new-use patent might be too costly if it requires filing a separate patent-infringement suit against each patient or physician who violates the patent. *Id.* at 724; see also ROBERT MERGES & JOHN DUFFY, *PATENT LAW & POLICY: CASES AND MATERIALS* 400 (5th Ed. 2011). Insurance companies, pharmacy chains and generic manufacturers would be a much more sensible target for these suits. Under current law, pharmacists could probably be held liable for indirect infringement if they knowingly dispense a generic drug for a patented indication. See Mahn, *supra* note 240. Health insurers arguably would be liable for indirect infringement when they agree to reimburse the pharmacy for dispensing a generic drug if they know the physician prescribed that drug for a patented indication, particularly if they use tiered formularies with lower co-payments for generics to encourage their use. Cf. Mark A. Lemley, *Inducing Patent Infringement*, 39 UC DAVIS L. REV. 225, 228-40 (2005) (discussing the “scope of inducement” for liability under § 271(b)). If the indirect infringement rules will reach pharmacists but not insurers, pharmacists might reasonably require insurers to indemnify them from this potential liability as part of their reimbursement agreements. Establishing liability against generic manufacturers might be more difficult, since they usually remain uninvolved in pharmacists' decisions about which product to dispense.

249. See Eisenberg, *New Uses*, *supra* note 13.

250. See 35 U.S.C. §§ 271(b)-(c); *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 377 U.S. 476 (1964).

251. See *Global-Tech Appliances, Inc. v. SEB S.A.*, 131 S.Ct. 2060, 2068 (2011) (“hold[ing] that induced infringement under § 271(b) requires that the induced acts constitute patent infringement,” which “requires knowledge of the existence of the patent that is infringed” or “willful blindness” of the patent).

Pharmaceutical companies rarely have access to the information they need to enforce a new-use patent against pharmacists or insurers. When physicians prescribe a drug to a patient to treat a particular indication, the patient's medical condition is confidential information.²⁵² Physicians will often disclose the prescribed indication to pharmacists and insurers because the insurer may require that information as a condition for coverage.²⁵³ Under these circumstances, if the pharmacist and insurer know the prescribed indication is patented and dispense the low-cost generic anyway, they could be liable for patent infringement. However, physicians almost never disclose the prescribed indication for a drug to pharmaceutical companies.²⁵⁴ Without access to this patient-level information, pharmaceutical companies cannot charge insurers when physicians prescribe an off-patent drug for a patented indication. As a result, new-use patents typically have little or no economic value for pharmaceutical companies after generics enter.

D. The Resulting Problem of New Uses

Without a viable enforcement mechanism for new-use patents, the current system fails to provide firms an incentive to develop new indications separate from the standard monopoly protection awarded to new drugs. Because that standard monopoly protection is temporary, pharmaceutical companies' incentive to test their drugs for new indications is also temporary. Firms become increasingly unwilling to invest in developing new uses for their drugs as their remaining monopoly life over those drugs runs down.

Immediately following a drug's initial FDA approval, the sponsoring pharmaceutical company usually has a strong interest in expanding that drug's indications, since these "line extensions" can boost the drug's sales.²⁵⁵ Consequently, firms often continue testing their drugs

252. See 67 Fed. Reg. 53182.

253. See *infra* note 482 and accompanying text.

254. Although physicians do not disclose the indications for their prescriptions to pharmaceutical companies, those firms can sometimes purchase patients' de-identified prescribing records from pharmacists and patients' de-identified medical records from health insurers. See Adriane Fugh-Berman, *Prescription Tracking and Public Health*, 23 J. GEN. INTERNAL MED. 1277 (2008) (noting that federal law allows pharmacists and insurers to sell patients' de-identified prescribing and medical records, and that pharmacists and insurers often sell that information to health information organizations (such as IMS Health), which use it to track individual physicians' prescribing patterns and then sell that information to pharmaceutical companies). By pairing the records from pharmacists and health insurers, pharmaceutical companies may be able to infer that pharmacists dispensed a generic drug for a patented indication to a particular de-identified patient. However, this information alone is insufficient to enforce a new-use patent. Liability for inducing infringement requires that pharmacists and insurers know the drug was prescribed for the new use at the time of dispensing and know (or be willfully blind to the fact) that the new use is patented. See *supra* note 251, and accompanying text. Even if the physician disclosed the prescribed indication to the pharmacist and insurer in a prior authorization form, pharmaceutical companies would have trouble showing that the pharmacists and insurers knew the prescribed indication was patented. See Mahn, *supra* note 240. If pharmaceutical companies could overcome this problem, the information gleaned from patient's de-identified prescribing and medical records might allow them to recover against pharmacists or insurers for indirectly infringing their new-use patents. But pharmaceutical companies would still need to acquire those de-identified records by purchasing them—either directly or indirectly—from the pharmacists and insurers they plan to sue. If the pharmacists and insurers anticipate the risk of liability, they will either build those costs into the price for their patients' de-identified records, insulate themselves from liability with contractual provisions, or refuse to sell the information.

255. See ELLERY & HANSEN, *supra* note 89, at 123; STEVEN GIPSTEIN ET AL., OPTIMIZING CLINICAL STRATEGY TO DRIVE LIFETIME BRAND VALUE 2 (2011) (arguing that "the majority of value creation arguably depends on lifecycle initiatives that build and expand the clinical profile of the brand. A strategic and sustained

for new indications, at least for a short while.²⁵⁶ These investments are treated as part of the broader lifecycle management of their drugs.²⁵⁷ Indication expansion increasingly provides a critical source of revenue for the industry²⁵⁸ as well as important treatments for unmet medical needs.²⁵⁹

However, because of the all-or-nothing system of monopoly protection for drugs, the incentives for developing each of the various indications for a drug tend to rise and fall together. The only monopoly rights that effectively encourage firms to invest in a drug's development are ones that can keep generic manufacturers off the market entirely.²⁶⁰ Although this form of protection can provide a powerful incentive for developing a new drug, it bundles together the incentives for developing all the possible indications for each drug into a single, finite term of monopoly protection. Once the core patents and FDA-exclusivity periods for a drug expire and it "goes generic," firms lose control over that drug's sales for any of its possible indications—including ones that have yet to be discovered or tested in clinical trials. Unless the new indication requires a different formulation, such that patients would be unable to use generics for the patented new use, pharmaceutical companies will lack enforceable monopoly rights.²⁶¹

release of clinical data (e.g., to support broader use, new indications, pharmacoeconomic benefit) can significantly enhance and extend lifetime brand value, and payors are increasingly demanding such evidence of healthcare value to justify reimbursement").

256. See GIPSTEIN ET AL., *supra* note 255, at 3 ("Most clinical strategies include plans to invest in new indications, phase 4 studies, and other trials.").

257. ELLERY & HANSEN, *supra* note 89, at xx (defining "lifecycle management" in the pharmaceutical industry as "the measures taken to grow, maintain, and defend the sales and profits of a pharmaceutical brand following its development in its first formulation and its first indication").

258. GIPSTEIN ET AL., *supra* note 255, at 2 (reporting that expanding drug indications "has become critical to [the] commercial success" of new drugs).

259. See *supra* note 31.

260. See VOET, *supra* note 205, at 35-39.

261. See AM Thayer, *Drug Repurposing*, 90 CHEMICAL & ENGINEERING NEWS 15 (2012) ("Many firms avoid repurposing generic drugs, even if they can find novel and patentable uses. If the repurposed drug works using available formulations and doses, it will likely compete with low-cost generics prescribed off-label. 'You would never be able to commercialize it and make any money.'"); Smith, *supra* note 217, at 131 (explaining that drug repurposing is only profitable when firms have "an effective generic substitution barrier to prevent off-label use of the existing generic products. As long as inexpensively available generics can be prescribed in a manner that achieves the same clinical result as the more expensive repositioned product, the repositioned product will probably fail. The best barriers include those repositioned products having a formulation required for treatment of a new indication, and where existing generics cannot be substituted for the new formulation."). In some cases, pharmaceutical companies must reformulate the existing drug to provide an effective treatment for the new indication, or produce the drug at a much higher dose than currently available for the drug's original indication, or produce it at a lower dose that cannot be replicated by subdividing the generic version of the drug. Under these circumstances, pharmaceutical companies may be able to control the market for the new indication with patents or FDA-exclusivity over the new formulation or dosage, while remaining insulated from price competition from generics sold for the old indication. See Susan Elvidge, *Getting the Drug Repositioning Genie Out of the Bottle*, 14 LIFE SCI LEADER 8 (2010) ("Drug repositioning can be based on marketed drugs that are off patent. This means that the active ingredients are easily available. However, if the dose required is similar to the dose used for an existing indication, physicians may simply choose to use the generic form, which is likely to be cheaper than the newly available, and possibly higher cost, branded repositioned drug. 'Because of this, it is important for a repositioned drug to have a difference in presentation. This may be a difference in delivery system or formulation, or a significant difference in dose'").

Given the limited term of protection, pharmaceutical companies' willingness to develop new indications for a drug quickly fades following the drug's initial approval. The clinical trials necessary to establish the safety and efficacy of a new indication usually take at least a few years to complete, and often longer.²⁶² Firms need time on the market to earn enough sales revenue from a new indication to recoup the costs of its development. But their patent clock started ticking years earlier when they filed their applications, and their FDA-exclusivity periods began running when the FDA first approved the drug for its original indication.²⁶³ In most cases, developing a new indication for a drug is not profitable unless the firm initiates the clinical trials relatively early in the drug's lifecycle.²⁶⁴ After a drug has been on the market for four or five years, pharmaceutical companies usually become reluctant to invest in further clinical trials for new indications.²⁶⁵ Except in rare cases, they will have stopped running any clinical trials on their drugs at least a few years before the anticipated date of generic entry.²⁶⁶

IV. THE GOVERNMENT'S FAILURE TO ADEQUATELY FUND CLINICAL TRIALS FOR NEW USES

The lack of private sector investment in developing new uses for off-patent drugs is perhaps the single most glaring failure in the existing incentive system for pharmaceutical innovation. An obvious solution to this problem would be for the government to finance those R&D projects directly.²⁶⁷ The NIH already funds much of the laboratory work that identifies potential new uses for FDA-approved drugs.²⁶⁸ In theory, it could also finance the clinical trials needed to evaluate the safety and efficacy of those treatments.²⁶⁹ Opinions differ as to whether the NIH's competency relative to private industry at identifying the most promising drugs to test in clinical trials and carrying out that research.²⁷⁰ But the public-private comparison is moot when firms

262. See *supra* note 177.

263. See ELLERY & HANSEN, *supra* note 89, at 49 (explaining that when firms are weighing whether to invest in clinical trials for a new indication, they invariably ask themselves, "How much time will we have to recover our investment in the line extensions before the primary patent expires?"); SAHOO, *supra* note 89, at 59.

264. See ELLERY & HANSEN, *supra* note 89, at 120 & 124.

265. See *id.* at 126 ("[I]t must be remembered that developing a new indication takes a long time, and that trials must therefore be started early on in the brand life cycle even if the new indication is [to reach the market] as a late-stage lifecycle management (LLCM) strategy."); cf. GIPSTEIN ET AL., *supra* note 255, at 4 ("[W]e have found that postponing the clinical development plan for a new indication by just 1 year would cost a company more value than could be obtained through hefty increases in launch price, reduction of R&D costs, or increases of peak share points.").

266. See Grabowski, et al., *supra* note 13, at 382; cf. Haiden A. Huskamp, et al., *Generic Entry, Reformulations, and Promotion of SSRIs*, 26 PHARMACOECONOMICS 603 (2008) (finding that pharmaceutical companies' promotional activities for their drugs decrease as patent expiration nears, and usually cease several years before generic entry).

267. Many commentators have called on the NIH to take on a greater role in repurposing off-patent drugs. See, e.g., Reed et al., *supra* note 46, at 18-19; Rai, *supra* note 13.

268. See Collins, *Translational Science*, *supra* note 60.

269. See Reed et al., *supra* note 46, at 18-19.

270. Compare John LaMattina, *The NIH Is Going to Discover Drugs ... Really?*, FORBES, May 15, 2012, at <http://www.forbes.com/sites/johnlamattina/2012/05/15/the-nih-is-going-to-discover-drugs-really/> (arguing that if the NIH were to invest in drug repurposing, "successes are going to be rare," and that "[t]he NIH should let industry do the applied R&D for drug discovery and focus its resources on the crucial basic research that is

have little incentive to repurpose off-patent drugs.²⁷¹ Moreover, while the NIH is undoubtedly imperfect, the available empirical studies still point to large social returns from the agency's past clinical-research programs.²⁷² The NIH's leadership is well aware of the desperate need for funding to test new uses of off-patent drugs.²⁷³ However, their budget is far too small to support a large-scale drug-repurposing program on top of the agency's existing core research commitments.²⁷⁴ Indeed, after years of stagnant or declining biomedical research funding from Congress, the NIH has had to significantly curtail its clinical-research programs, including trials for new uses of FDA-approved drugs.²⁷⁵ This Part describes Congress' failure to provide the NIH with adequate funding to repurpose old drugs for new uses, and hypothesizes that this failure is attributable to political economy problems that may be difficult to correct.

A. The NIH's Potential to Develop New Uses for Existing Drugs

The NIH undoubtedly has the institutional capacity to develop new uses for FDA-approved drugs. Unlike de novo drug development, drug repurposing does not involve engineering a novel drug compound or testing it in preclinical studies—which requires labor and resources located primarily within the private sector.²⁷⁶ When researchers identify a potential new indication for a drug that is already on the market, the NIH can move that treatment directly into clinical trials. Since the NIH has access to a wealth of clinical researchers at NIH and university hospitals, it can carry out those trials without industry support.²⁷⁷ And since physicians are free to prescribe FDA-approved drugs off-label for new indications,²⁷⁸ the NIH does not need to secure FDA approval for that new use, which otherwise might require finding an industry partner.²⁷⁹

Although the government generally has a poor track record in managing large-scale commercial R&D projects,²⁸⁰ the NIH's clinical-research programs seem to be an exception. The available empirical evidence suggests that these types of NIH-funded clinical studies

desperately needed”), with Arjun Jayadev & Joseph Stiglitz, *Two Ideas To Increase Innovation and Reduce Pharmaceutical Costs and Prices*, 28 HEALTH AFFAIRS w165,w165 (2009) (“Public funding of clinical trials likewise can reduce both pharmaceutical costs and prices and direct research effort in a manner that is more socially productive than the current state of affairs.”).

271. See *supra* Part III.

272. See *infra* note 281.

273. See Austin, *supra* note 13, at 19.

274. See *infra* notes 286-301, and accompanying text.

275. See *infra* notes 295-297, and accompanying text.

276. See *supra* note 74, and accompanying text.

277. See IOM, *CANCER CLINICAL TRIALS*, *supra* note 185.

278. See *supra* note 163, and accompanying text.

279. See Erdmann, *supra* note 181, at 1493-94 (explaining that academic clinical research centers often have insufficient resources to comply with the FDA's “tremendous regulatory requirements” when carrying out drug trials).

280. See generally LINDA R. COHEN & ROGER G. NOLL, *THE TECHNOLOGY PORK BARREL* (1991) (using a series of case studies to explore the substantial political economy problems that plague large-scale commercial development projects run by the government); cf. Congressional Budget Office (CBO), *Federal Support for Research and Development* xi (2007) (noting that “[a] number of studies have found no economic return associated with [the] spending” on “federally funded development work”).

generate significant social returns on average.²⁸¹ The NIH has a relatively limited budget for clinical research, but it has always used some of that funding for clinical trials on new indications.²⁸² Given the high costs of those trials, the agency understandably is cautious in funding them and strongly prefers pharmaceutical companies to pay for clinical trials establishing new indications for existing drugs.²⁸³ However, the NIH recognizes that industry is often unwilling to test potential new indications that are worthwhile investments from the public's perspective²⁸⁴ and does its best to provide the necessary funding.²⁸⁵

B. The Funding Problem

Unfortunately, Congress does not provide enough clinical-research funding for the NIH to sustain a meaningful drug-repurposing program.²⁸⁶ The government spends only about one-tenth of what the pharmaceutical industry spends on drug trials.²⁸⁷ This small pool of taxpayer funding must cover a variety of clinical-research areas that private industry currently shuns, ranging from proof-of-concept trials for novel drug targets to comparative-efficacy studies.²⁸⁸

281. See S. Claiborne Johnston, et al., *Effect of a US National Institutes of Health Programme of Clinical Trials on Public Health and Costs*, 367 LANCET 1319, 1324 (2006); Bhaven N. Sampat, *The Impact of Publicly Funded Biomedical and Health Research: A Review*, in MEASURING THE IMPACTS OF FEDERAL INVESTMENTS IN RESEARCH: A WORKSHOP SUMMARY 159-69 (NATIONAL ACADEMY OF SCIENCES 2011) (reviewing the literature).

282. See IOM, CANCER CLINICAL TRIALS, *supra* note 185, at 75 (noting that the National Cancer Institute (NCI) tends to fund clinical trials “to extend the indications of already approved drugs”); Bernard Ravina, et al., *Funding Evidence: The National Institute of Neurological Disorders and Stroke Clinical Trials Program*, 1 NEURORX 317, 321-22 (2004).

283. See Michael Privitera, *Large Clinical Trials in Epilepsy: Funding by the NIH versus Pharmaceutical Industry*, 68 REVIEWS/EPILEPSY RES. 19-94 (2006); Reed, et al., *supra* note 46, at 18 (“Clearly, resources must be deployed cautiously when projects reach the clinic due to the high costs associated with clinical trials.”); Salim Yusuf, et al., *Sensible Guidelines for the Conduct of Large Randomized Trials*, 5 CLINICAL TRIALS 38, 38 (2008) (noting that randomized and controlled clinical trials are “extremely expensive,” and their high costs can “prevent the conduct of important trials of generic questions, especially those that are not supported by industry”). The NIH makes it more difficult to receive grants for large or complex clinical trials (or any grant request exceeding \$1.5 million) by imposing additional layers of administrative review on those applications. See Francis S. Collins, *National Institute of Health Fiscal Year 2013 Budget Request*, Testimony before the Senate Subcommittee on Labor, Health and Human Services, and Education Appropriations, March 28, 2012.

284. See Austin, *supra* note 13, at 19.

285. See IOM, TRANSFORMING CLINICAL RESEARCH IN THE UNITED STATES: CHALLENGES AND OPPORTUNITIES: WORKSHOP SUMMARY 21 & 48 (2010) (hereinafter “TRANSFORMING CLINICAL RESEARCH”).

286. See Alan L. Buchman, *The State of Clinical Research in America*, Symposium and Meeting Reports, The American Federation for Medical Research (2010); WM. KEVIN KELLY & SUSAN HALABI, EDS., ONCOLOGY CLINICAL TRIALS: SUCCESSFUL DESIGN, CONDUCT, AND ANALYSIS ix (2010); Roxanne Nelson, *Funding Cuts Threaten Modernization of Cancer Research*, MEDSCAPE TODAY NEWS, Jun. 1, 2013, at <http://www.medscape.com/viewarticle/805163>.

287. Kristy Beal et al., *Budget Negotiation for Industry-Sponsored Clinical Trials*, 99 ANESTHESIA & ANALGESIA 173, 173 (2004); Getz, *supra* note 1, at 3; Olivera Vragovic, *Developing Budgets for Research Projects with a Focus on Phase III Clinical Trials*, Boston University & Boston Medical Center (2010), at <http://www.bumc.bu.edu/crrro/files/2010/01/Vragovic-6-17-09.pdf>.

288. Charlie Schmidt, *Cooperative Groups Say NCI Trials Funding Inadequate; Some Turn to Industry*, 99 J. NAT'L CANCER INST. 830 (2007) (“While industry-sponsored trials focus chiefly on new-drug development, NCI’s trials tackle a broader social agenda, fueled by cancer prevention, quality-of-life issues for patients, and the competing benefits of different treatments or treatment combinations.”); see also IOM, TRANSFORMING CLINICAL RESEARCH,

Since the NIH funding environment is largely zero-sum, proposals to increase funding for certain types of clinical research inevitably meet with resistance from the other areas of clinical research.²⁸⁹ Moreover, the demand for NIH funding is continually increasing relative to the supply in all of these fields,²⁹⁰ since advances in medical science open up new avenues of research faster than they close old ones. Consequently, the NIH appears to fund only a small fraction of the socially valuable clinical trials in need of public support.²⁹¹

Despite countless calls for the government to increase the NIH's funding for clinical research, the trend runs sharply in the other direction.²⁹² The NIH's budget fell by 20% in real dollars between 2003 and 2013,²⁹³ forcing drastic cuts in the number of NIH-funded research projects.²⁹⁴ These budget cuts have been particularly detrimental to the public sector's capacity to carry out large phase III drug trials,²⁹⁵ since clinical-trial costs have skyrocketed while NIH funding levels have fallen.²⁹⁶ Consequently, the NIH has had to cut back dramatically on the

supra note 285, at 21 (2010); Nelson, *supra* note 286 (explaining that firms leave several crucial areas of clinical research for the public to fund, including trials to “compare effective and promising regimens with each other,” trials for non-drug therapies “such as surgery, radiation therapy, and ... specialties such as pathology,” and trials for “cancer prevention, screening, survivorship, and optimizing quality of life, all of which do not generate a lot of revenue”); Woodcock, *supra* note 52, at 11.

289. See IOM, TRANSFORMING CLINICAL RESEARCH, *supra* note 285, at 26-27 (explaining “that because NIH’s funding is relatively flat, if research site payments are increased [in one area], an equivalent decrease in funding in other areas will be necessary,” and that “[g]iven this zero-sum calculation, it will be politically difficult to increase payments” to any one area).

290. See William R. Brinkley, et al., *Increased Funding for NIH: A Biomedical Science Perspective*, 12 FASEB J. 1431 (1998); NIH Director’s Panel on Clinical Research Report: Executive Summary (1997), at http://www.oenb.at/de/img/executive_summary_nih_directors_panel_on_clinical_research_report_12_97_tcm14-48582.pdf (noting that the percentage of NIH grant applications that receive funding has been declining since the 1970s).

291. See, e.g., S. Claiborne Johnston & Stephen L. Hauser, *Basic and Clinical Research: What Is the Most Appropriate Weighting in a Public Investment Portfolio?*, 60 ANNALS OF NEUROLOGY 9A, 10A (2006).

292. See Matt Jones, *Slow, Steady Decline in NIH Funding Leads Researchers to Fear Future Cuts*, GENOMEWEB, Jul. 18, 2013, at <http://www.genomeweb.com/genomeweb-feature-slow-steady-decline-nih-funding-leads-researchers-fear-future>; Rosanne Spector, *The Competition: on the Hunt for Research Dollars*, STANFORD MEDICINE, Fall 2012, at 10.

293. See Meredith Wadman, *The NIH Faces Up to Hard Times*, NATURE, Sept. 26, 2012, doi:10.1038/nature.2012.11458; Hamilton Moses III & E. Ray Dorsey, *Biomedical Research in an Age of Austerity*, 308 JAMA 234, 235 (2012); *Bottom Line: Medicine’s Funding Pool is Drying Up*, STANFORD MEDICINE, Fall 2012, at 6.

294. See Wadman, *supra* note 293. These cutbacks have had a devastating effect on the academic biomedical research community. *Id.* at 10 (“[A]cross the country people are closing labs, retiring early. This is a crisis.”); Jones, *supra* note 292 (describing how the “slowly tightening fiscal belts” are causing “historically low success rates [in NIH grants to] build to a crescendo,” and many “people [are] essentially shutting their labs down, or shutting down particular areas of research”).

295. See Lelia Duley et al., *Specific Barriers to the Conduct of Randomized Trials*, 5 CLINICAL TRIALS 40, 41 (2008) (“These [funding] restrictions form major barriers to the conduct of large trials.”); Mike Mitka, *Scientists Warn NIH Funding Squeeze Hampering Biomedical Research*, 297 JAMA 1867, 1867 (2007) (noting that between 2003 and 2007, the NIH’s budget had fallen 16 percent in real dollars, but since clinical trials “take years to complete, [and] are often subject to higher costs as they occur in health care settings facing higher inflationary pressures,” the NIH’s “purchasing power in clinical trials is 35% less than 4 years ago”).

296. See Roger Collier, *Rapidly Rising Clinical Trial Costs Worry Researchers*, 180 CANADIAN MED. ASS’N J. 277 (2009); Schmidt, *supra* note 288, at 831-33; Yusuf et al., *supra* note 283, at 38.

number of phase III drug trials it supports,²⁹⁷ and many of the established grant programs now cover less than half of trial costs, leaving academic research centers to make up the difference.²⁹⁸

Following a 2007 workshop hosted by the Society for Clinical Trials, participants reported that “[t]here is widespread concern in the academic trials community that only studies supported by industry, plus a few trials funded through public or charity funds, are now practical.”²⁹⁹ NIH funding for clinical research fell even further in the five years following that conference, and the NIH is at risk of further budget cuts in the near future.³⁰⁰ Given the federal government’s large budget deficit and long-term fiscal troubles, most experts anticipate that NIH funding levels will stay flat or decline for at least another decade.³⁰¹

There is a growing consensus within the clinical research community that the public must find alternative funding sources for public-sector research, including clinical trials for new indications.³⁰² Given the high costs of Phase III clinical trials, private-sector investment is one of the few viable alternatives to government grants.³⁰³ University clinical researchers are already

297. See Jennifer Couzin, *Tight Budget Takes a Toll on U.S.-Funded Clinical Trials*, 315 SCIENCE 1202 (2007); Steve Frandzel, *Revamping the NCI Clinical Trials Cooperative Groups*, CLINICAL ONCOLOGY NEWS, vol. 6, issue 11, pg 6 (2011) (explaining that “continued lower funding levels—a consequence of the economic and political climate ... means fewer clinical trials,” mostly through a “drop in the number of Phase III trials”); IOM, A NATIONAL CANCER CLINICAL TRIALS SYSTEM FOR THE 21ST CENTURY: REINVIGORATING THE NCI COOPERATIVE GROUP PROGRAM 165 (2010) (hereinafter “NCI COOPERATIVE GROUP PROGRAM”) (recommending that in response to the funding shortages from public sources, “the total number of trials undertaken by the Cooperative Groups should be reduced to a quantity that can be adequately supported”); *Revamping the Clinical Trials System*, 1 CANCER DISCOVERY 194 (2011); Schmidt, *supra* note 288, at 832; Spector, *supra* note 292, at 9. The NIH is not alone in reducing its funding for large phase III drug trials. The analogous funding bodies in most other developed countries have done the same thing. See Duley et al., *supra* note 295, at 41.

298. Schmidt, *supra* note 288, at 830; see also Erdmann, *supra* note 181, at 1492; IOM, RARE DISEASES AND ORPHAN PRODUCTS: ACCELERATING RESEARCH AND DEVELOPMENT 247-48 (2010) (hereinafter “RARE DISEASES”) (noting that most of the grants available for clinical trials on rare diseases are insufficient for running trials that comply with FDA regulations, including the grants that come from the FDA).

299. Duley et al., *supra* note 295, at 41; see also J. Hearn & R. Sullivan, *The Impact of the ‘Clinical Trials’ Directive on the Cost and Conduct of Non-Commercial Cancer Trials in the UK*, 43 EUROPEAN J. CANCER 8, 12-13 (2007).

300. See David Malakoff, *The Future is Flat in White House’s 2015 Spending Request*, 343 SCIENCE 1186 (2014); Kwame Boadi, *Erosion of Funding for the National Institutes of Health Threatens U.S. Leadership in Biomedical Research*, Center for American Progress, Mar. 24, 2014.

301. Steve Usdin, *Lost in Translation*, BIOCENTURY, Feb. 14, 2011 (noting “that the chances of obtaining new money for science for the foreseeable future are slim to none,” and researchers are “fighting an uphill battle just to achieve flat funding”); see also Spector, *supra* note 292, at 10-11 (“The widespread assumption is that U.S. federal spending for medical research will stay flat, or maybe continue to drop.”).

302. See Spector, *supra* note 292, at 13 (“Ultimately, however, unless the federal grants boom again — and no one interviewed for this article was counting on that, or even expecting it — medical research must find other sources of support or risk atrophy.”); cf. Joseph Loscalzo, *The NIH Budget and the Future of Biomedical Research*, 354 N. ENGL. J. MED. 1665, 1666 (2006) (arguing that even if the government begins funding clinical research adequately, “it would be preferable for academic medical centers to cease relying so heavily on the NIH for research funding” given Congress’s inability to maintain steady funding levels).

303. Moses & Dorsey, *supra* note 293, at 2342 (explaining that because of “the reduction in federal funding, which is now approaching a decade in duration, ... [n]ew private sources of research support are needed.”); Jennifer L. Kellen, 3 *Clinical Trials Budgeting Methods & Best Practices*, University of California San Francisco, 52 (2010) at <http://or.ucsf.edu/cg/7893-DSY/version/default/part/4/data/> (“[P]artnerships with industry ... are expected to increase”).

turning to the pharmaceutical industry for funding,³⁰⁴ but this strategy forces them to work on clinical trials meant to be profitable to the sponsoring company,³⁰⁵ which rarely includes trials on new uses for off-patent drugs. And with limited funding available for late-stage clinical trials, the NIH and academic research centers generally limit their investments in investigational treatments to ones likely to attract an industry sponsor who will pay for those trials.³⁰⁶

C. *Underlying Political-Economy Problem*

Unless Congress significantly increases its funding for clinical research, which is unlikely in the foreseeable future, the public cannot rely on the NIH for investments in developing new uses for existing drugs. Although leaders from both parties express strong support for public-sector biomedical research, Congressional funding for that research continues to decline (in real dollars).³⁰⁷ Indeed, the recent NIH budget cuts have merely accelerated a long-term trend dating back to the mid-1960s of declining government support for R&D as a percentage of GDP, and a growing reliance on private industry for the nation's R&D investments.³⁰⁸ The duration of this trend suggests that the government's failure to provide adequate funding for drug repurposing reflects a broader political-economy problem.

In general, the political incentives for politicians to spend taxpayer dollars on R&D programs are probably far lower than the social returns from those investments.³⁰⁹ Although increased government funding for R&D might generate substantial benefits for the public, those benefits take many years to arrive, which is well beyond the relevant political time-horizon for

304. See, e.g., Peggy Eastman, *IOM Report Recommends Rethinking Phase III Clinical Trials & NCI Cooperative Groups*, ONCOLOGY TIMES, Vol. 31, Issue 6, pp. 35-37, Mar. 25, 2009; Heather Lindsey, *Study: Industry-Funded ASCO Meeting Abstracts Get More Prominence, Higher Peer-Review Scores*, ONCOLOGY TIMES, vol. __, Jul. 17, 2013 (explaining that the increased prominence of industry-funded clinical trials relative to publicly funded trials “reflects the steady shift from federally funded clinical research to industry-funded research,” and that “[t]his trend has been going on for a number of years as federal funding has diminished and as industry has stepped in to take its place”).

305. See Frandzel, *supra* note 297 (explaining that as the NIH's budget woes worsen, the NCI cooperative groups have starting conducting phase III trials in partnership with pharmaceutical companies, but only “with great reluctance,” since studies “funded by the pharmaceutical industry ... may not address the types of questions that the cooperative groups have historically addressed”).

306. See Barbara J. Culliton, *Interview: Extracting Knowledge From Science: A Conversation With Elias Zerhouni*, __ HEALTH AFFAIRS W94, W97 (2006); Reed et al., *supra* note 46, at 18-19 (“Clearly, resources must be deployed cautiously when projects reach the clinic due to the high costs associated with clinical trials. ... In general, all efforts should be made to partner clinical-stage projects with the biopharmaceutical industry at the earliest opportunity....”).

307. See Jones, *supra* note 292; Brad Plumer, *The Coming R&D Crash*, WASHINGTON POST WONKBLOG, Feb. 26, 2013, at <http://www.washingtonpost.com/blogs/wonkblog/wp/2013/02/26/the-coming-rd-crash/>.

308. See CONGRESSIONAL BUDGET OFFICE (CBO), *FEDERAL SUPPORT FOR RESEARCH AND DEVELOPMENT* vii-viii, 3-7 (2007) (noting that “[s]ince [1964], with the exception of a period in the 1980s—when an expansion of national defense activities prompted more funding for research and development—federal R&D spending has generally declined as a share of GDP”). The past ten years greatly accelerated this trend in the field of clinical research, but did not change its trajectory. See Linda Bressler, *Industry Collaboration in Cancer Clinical Trials*, in ONCOLOGY CLINICAL TRIALS: SUCCESSFUL DESIGN, CONDUCT, AND ANALYSIS 315 (WM. Kevin Kelly & Susan Halabi, eds., 2010).

309. See COHEN & NOLL, *supra* note 280, at 55-63.

most elected officials.³¹⁰ Meanwhile, the political pressure to expend government resources elsewhere—including for tax cuts, social-service programs, or any other spending project meant to deliver immediate and observable benefits to the public—could be tremendous.³¹¹ If the government underfunds R&D because elected officials receive greater political gains from spending the money elsewhere, the resulting harm to the public may be immense.³¹² But this harm would be essentially invisible to voters because people cannot observe innovations that do not exist. Since the public is probably unaware of any social welfare losses attributable to inadequate government R&D spending, voters are unlikely to punish elected officials for those failures. When legislators are under pressure to reduce the budget deficit without increasing taxes or cutting entitlement programs, cuts to “discretionary” R&D spending may be inevitable.³¹³

V. THE IMMENSE SOCIAL COSTS OF THE PROBLEM OF NEW USES

The lack of incentives for developing new indications of FDA-approved drugs is a longstanding—albeit somewhat arcane—problem in the incentives for pharmaceutical innovation. Over the past decade, this seemingly inevitable gap in industry’s incentives has become a major impediment to medical progress. Recent technological advances suggest that the existing pharmacopeia could provide effective treatments for many of our major unmet medical needs. Developing new indications for existing drugs is also by far the most efficient route of drug development. As a result, it could allow pharmaceutical firms to develop medical treatments for smaller markets and more challenging pathologies. Creating a viable business model for the development of new indications would also help overcome the ongoing productivity crisis in the pharmaceutical industry, by providing an alternative to the increasingly unsustainable *de novo* model. At the same time, it would offer the NIH an invaluable bridge across the “valley of death,” allowing the NIH to translate breakthroughs in basic research into actual medical treatments. Without effective incentives to develop new therapeutic uses for older drugs, all these benefits are lost. And because the number of off-patent drugs will continue to

310. See Stuart Minor Benjamin & Arti K. Rai, *Fixing Innovation Policy: A Structural Perspective*, 77 GEORGE WASHINGTON L. REV. 1, 13 (2008). This distortion affecting the incentives for elected officials to finance R&D is well known in the political economy literature. As Linda Cohen and Roger Noll explain:

From the perspective of the elected official, the implication of retrospective evaluation is that, all else being equal ... , a project with earlier realization of politically relevant benefits will be preferred to longer-term projects. That is, to the extent that citizens heavily discount future plans of programs and engage in retrospective evaluations, they create an incentive for political officials to be too impatient in evaluating proposed programs. Because R&D projects are usually long term, they will normally face an uphill struggle in the battle for budgets with operating programs that provide current benefits.

COHEN & NOLL, *supra* note 280, at 61.

311. See Moses & Dorsey, *supra* note 293, at 2342.

312. See *supra* note 281.

313. Cf. Emmanuel Jimenez, *Human and Physical Infrastructure: Public Investment and Pricing Policies in Developing Countries*, in 3 HANDBOOK OF DEVELOPMENT ECONOMICS 2792-93 (J. Behrman & T.N. Srinivasan eds. 1995) (“When countries have had to make difficult spending decisions, they have tended to start by cutting longer-term capital investment.”).

grow, as will researchers' ability to identify potential new uses, this already severe problem will only get worse.

A. Losing a Wealth of New Medical Treatments

Commentators have long recognized that private industry is unwilling to develop new indications for off-patent drugs. But only recently has the tremendous range of new uses for existing drugs become apparent, revealing the true magnitude of this public policy failure. As of 2011, there were 2,356 distinct FDA-approved drug compounds,³¹⁴ the vast majority of which are off patent.³¹⁵ Using new screening technologies, researchers have identified hundreds of potential new uses for these off-patent drugs to treat unmet medical needs.³¹⁶ But without private industry to finance the clinical development of these potential new medical treatments, few will ever be tested.

The recent discovery that the drug bexarotene, an FDA-approved therapy for cutaneous T-cell lymphoma, might also provide an effective treatment for Alzheimer's disease highlights the potential social costs of this policy failure.³¹⁷ Paige Cramer and co-authors reported in *Science* that bexarotene is remarkably effective against Alzheimer's in several important preclinical models.³¹⁸ Although this discovery attracted a great deal of attention, it remains uncertain whether the treatment will work in humans.³¹⁹ The clinical trials needed to test bexarotene for this indication would take five to seven years and hundreds of millions of dollars.³²⁰ With only a few years of patent life remaining on bexarotene, finding industry sponsors for these trials will be difficult, if not impossible.³²¹

The potential loss of a breakthrough treatment for Alzheimer's disease would be a major public policy concern even if it were an isolated occurrence.³²² But Cramer et al.'s discovery is

314. See Huang et al., *supra* note 32, at 80ps16.

315. See *supra* note 67.

316. See *supra* note 32; *infra* notes 327-330, and accompanying text.

317. See Warren J. Strittmatter, *Old Drug, New Hope for Alzheimer's Disease*, 335 *SCIENCE* 1447 (2012); Frank M. LaFerla, *Clinical Success Against Alzheimer's Disease with an Old Drug*, 367 *N. ENG. J. MED.* 570 (2012).

318. See Paige E. Cramer et al., *ApoE-Directed Therapeutics Rapidly Clear β -amyloid and Reverse Deficits in AD Mouse Models*, 335 *SCIENCE* 1503 (2012).

319. See Strittmatter, *supra* note 317, at 1448; LaFerla, *supra* note 317, at 571-72.

320. See Chuck Soder, *Next Up for CWRU Docs' Alzheimer's Drug: Trials*, *CRAIN'S CLEVELAND BUSINESS*, Apr. 16, 2012, at 20 ("If a phase I clinical trial was to start today, it still would take five to seven years [to] ... finish testing the drug in Alzheimer's patients and win FDA approval to start selling bexarotene for use in treating Alzheimer's," and "there's no telling whether the drug will make it through clinical trials or whether the company will attract the 'hundreds of millions of dollars' that will be needed to complete all of them").

321. See Guatam Naik, *New Attack on Alzheimer's: Cancer Drug Reverses Disease's Symptoms in Mice; Human Tests to Start Soon*, *WALL ST. J.*, Feb. 10, 2012 ("Patents on the drug [bexarotene]—and hence its profitability—will start to expire this year, one reason drug companies may be reluctant to jump on bexarotene as a possible Alzheimer's treatment.").

322. See generally William Thies & Laura Bleiler, *Alzheimer's Association Report: 2013 Alzheimer's Disease Facts and Figures*, 9 *ALZHEIMER'S & DEMENTIA* 208 (2013) (discussing the social cost and disease burden of Alzheimer's disease in the United States).

just the tip of the iceberg.³²³ The medical literature contains hundreds of other examples of old drugs with preclinical evidence suggesting valuable new indications.³²⁴ The popular press is even starting to carry stories on the opportunities to develop new medical treatments through drug repurposing.³²⁵

The growing awareness that many older drugs may have valuable new uses stems in part from technological advances in drug-screening technology. Historically, researchers discovered most new uses for existing drugs either through serendipity, clinician investigation, or selective testing of individual drugs in cell-based or animal disease models.³²⁶ Over the past decade, scientists developed a variety of new computational tools to screen known-drug compounds in silico for new indications.³²⁷ Using chemoinformatics, genomic screening, and literature mining, researchers can now search for new medical treatments by utilizing large data sets of published information about diseases and known drug compounds, including data about genomic expression profiles, protein structures, drug structure similarities, disease pathways, phenotypic disease networks, drug-protein connectivity maps, drug-disease networks, and side-effect similarities.³²⁸ These screening tools have shown that existing drugs are much more likely than

323. See Stephen Ornes, *Using Old Drugs in New Ways*, 4 CANCER TODAY _ (2014); Gupta et al., *supra* note 35; Irene Seunghyun Hong et al., *Medication Repurposing: New Uses for Old Drugs*, 27 J. PHARMACY TECH. 132 (2011).

324. See *infra* notes 331-340.

325. See, e.g., Jessica Berman, *Scientists Find New Uses for Old Drugs*, VOICE OF AMERICA, Dec. 10, 2013, at <http://www.voanews.com/content/scientists-find-new-uses-for-old-drugs/1807326.html>; Ted Greenwald, *Hiding in Plain Sight: Finding New Targets for Old Drugs*, WIRED, Nov. 14, 2013; Amy Dockser Marcus, *Dilemma: When 1 Drug Treats 2 Diseases*, WALL ST. J., Feb. 14, 2012; Sarah Zhang, *You Can Teach an Old Drug New Tricks*, DISCOVER, Mar. 21, 2012, at <http://discovermagazine.com/2012/mar/20-you-can-teach-an-old-drug-new-tricks>.

326. See Chong & Sullivan, *supra* note 84, at 645 (“[M]ost successful crossovers have been the result of chance observations or educated guesses.”); Hee Sook Lee et al., *Rational Drug Repositioning Guided by an Integrated Pharmacological Network of Protein, Disease and Drug*, 6 BMC SYSTEMS BIOLOGY 80 (2012); Yvonne Y. Li et al., *A Computational Approach to Finding Novel Targets for Existing Drugs*, 7 PLOS COMPUTATIONAL BIOLOGY (2011) e1002139. doi:10.1371/journal.pcbi.1002139; Qu et al., *supra* note 44, at S4-S5.

327. See Chong & Sullivan, *supra* note 84, at 645; Ekins et al., *supra* note 33; Oprea & Mestres, *supra* note 9, at 759 (“Novel computational methods, which can estimate the target profile of small molecules with increasing levels of recall and precision, have significantly increased the scope of target space that can be explored, thus facilitating the identification of new targets for old drugs.”); Nair, *supra* note 56, at 2431; THOMSON REUTERS, WHITE PAPER: KNOWLEDGE-BASED DRUG REPOSITIONING TO DRIVE R&D PRODUCTIVITY 7 (2012) (“The process of drug repositioning is greatly enhanced by using computational methods.”).

328. See Dakshanamurthy et al., *supra* note 38; Keiser et al., *supra* note 33; Paul A. Novick et al., *SWEETLEAD: an In Silico Database of Approved Drugs, Regulated Chemicals, and Herbal Isolates for Computer-Aided Drug Discovery*, 8 PLOS ONE e79586, 1 (2013); Yves A. Lussier & James L. Chen, *The Emergence of Genome-Based Drug Repositioning*, 3 SCI. TRANSLATIONAL MED. 96ps35, 1 (2011); Wermuth, *supra* note 148; Kinnings et al., *supra* note 159; Monica Campillos et al., *Drug Target Identification Using Side-Effect Similarity*, 321 SCIENCE 263 (2008); Liu et al., *supra* note 44; Jiao Li et al., *Building Disease-Specific Drug-Protein Connectivity Maps from Molecular Interaction Networks and PubMed Abstracts*, 5 PLOS COMPUTATIONAL BIOLOGY e1000450 (2009); Christos Andronis et al., *Literature Mining, Ontologies and Information Visualization for Drug Repurposing*, 12 BRIEF BIOINFORM. 357-368 (2011); Justin Lamb et al., *The Connectivity Map: Using Gene-Expression Signatures to Connect Small Molecules, Genes, and Disease*, 313 SCIENCE 1929 (2006); Lun Yang & Pankaj Agarwal, *Drug Repositioning Based on Clinical Side-Effects*, 6 PLOS ONE e28025 (2011); Guanghui Hu & Pankaj Agarwal, *Human Disease-Drug Network Based on Genomic Expression Profiles*, 4 PLOS ONE e6536 (2009); Yong Li & Pankaj Agarwal, *A Pathway-Based View of Human Diseases and Disease Relationships*, 4 PLOS ONE e4346 (2009); César A. Hidalgo et al., *A Dynamic Network Approach for the Study of Human Phenotypes*, 5 PLOS COMPUTATIONAL BIOLOGY e1000353 (2009); Francesco Iorio et al., *Discovery of Drug Mode of Action and Drug Repositioning from Transcriptional Responses*, 107 PROC NAT’L ACAD SCI USA 146221 (2010); Joel T. Dudley et al., *Drug Discovery in a Multidimensional World: Systems,*

the average novel drug candidate to be active in multiple targets, pathways, and cellular phenotypes—factors indicative of greater potential for multiple uses.³²⁹ Moreover, many of the most promising tools only work for existing drugs because they function by screening databases of published information about drugs’ observed clinical effects and known mechanisms of action.³³⁰

Although researchers are just beginning to use these screening tools, they have already identified hundreds of potential new uses for drugs in the existing pharmacopeia.³³¹ These include possible treatments for cancer,³³² Alzheimer’s disease,³³³ diabetes,³³⁴ stroke,³³⁵

Patterns, and Networks, 3 J. CARDIOVASCULAR TRANSLATIONAL RES. 438 (2010); Ekaterina Kotelnikova et al., *Computational Approaches for Drug Repositioning and Combination Therapy Design*, 8 J. BIOINFORMATICS COMPUT. BIOL. 593 (2010); Simon J. Cockell et al., *An Integrated Dataset for In Silico Drug Discovery*, J. INTEGR BIOINFORM 116 (2010); Josef Scheiber et al., *Gaining Insight into Off-Target Mediated Effects of Drug Candidates with a Comprehensive Systems Chemical Biology Analysis*, 49 J. CHEM. INF. MODEL 308 (2009); Soyang Ha et al., *IDMap: Facilitating the Detection of Potential Leads with Therapeutic Targets*, 24 BIOINFORMATICS 1413 (2008); AP Chiang & AJ Butte, *Systematic Evaluation of Drug-Disease Relationships to Identify Leads for Novel Drug Uses*, 86 CLIN. PHARMACOL. THER. 507 (2009); V Joachim Haupt & Michael Schroeder, *Old Friends in New Guise: Repositioning of Known Drugs with Structural Bioinformatics*, 12 BRIEFINGS IN BIOINFORMATICS 312 (2011); Avi Ma’ayan et al., *Network Analysis of FDA Approved Drugs and Their Targets*, 74 MT. SINAI J. MED. 27 (2007); William Loging et al., *Cheminformatic/Bioinformatics Analysis of Large Corporate Databases: Application to Drug Repurposing*, 8 DRUG DISCOVERY TODAY: THERAPEUTIC STRATEGIES 109 (2011); Divya Sardana et al., *Drug Repositioning for Orphan Diseases*, 12 BRIEFINGS IN BIOINFORMATICS 346 (2011); S. Joshua Swamidass, *Mining Small-Molecule Screens to Repurpose Drugs*, 12 BRIEFINGS IN BIOINFORMATICS 327 (2011).

329. See Huang et al., *supra* note 32; Kinnings et al., *supra* note 159.

330. This is the case, for example, with literature mining and side effect-similarity screening. See Andronis et al., *supra* note 328, at 358; Campillos et al., *supra* note 328, at 263-64; Li et al., *supra* note 328, at 1; Liu et al., *supra* note 44; Wermuth, *supra* note 148; Yang & Agarwal, *supra* note 328, at 1 (noting that while some drug repositioning “strategies focus primarily on using preclinical information[,] ... clinical therapeutic effects are not always consistent with preclinical outcomes. ... Clinical phenotypic information comes from actual patient data, which mimics a phenotypic ‘screen’ of the drug effects on human, and can directly help rational drug repositioning.”).

331. See *supra* note 33.

332. See Telleria, *supra* note 35, at ix; Luisa Cimmino & Iannis Aifantis, *Fingerprinting Acute Leukemia: DNA Methylation Profiling of B-Acute Lymphoblastic Leukemia* 2 CANCER DISCOV. 976 (2012); Daichi Shigemizu et al., *Using Functional Signatures to Identify Repositioned Drugs for Breast, Myelogenous Leukemia and Prostate Cancer*, 8 PLOS COMPUT. BIOL. e1002347 (2012); Bradley, *supra* note 157, at 446 (childhood brain tumors, breast cancer, leukemia, and sarcomas); Lekka et al., *supra* note 69 (multiple sclerosis); Jinesh S. Gheeya et al., *Screening a Panel of Drugs with Diverse Mechanisms of Action Yields Potential Therapeutic Agents Against Neuroblastoma*, 8 CANCER BIOL. THER. 2386 (2009); Ekins & Williams, *supra* note 33 (neuroblastoma, retinoblastoma); Christopher Antczak et al., *Revisiting Old Drugs as Novel Agents for Retinoblastoma: In Vitro and In Vivo Antitumor Activity of Cardenolides*, 50 INVEST. OPHTHALMOL. VIS. SCI. 3065 (2009); Huafeng Zhang et al., *Digoxin and Other Cardiac Glycosides Inhibit HIF-1 α Synthesis and Block Tumor Growth*, 105 PNAS 19579 (2008); Sarah C. Garrett et al., *A Biosensor of S100A4 Metastasis Factor Activation: Inhibitor Screening and Cellular Activation Dynamics*, 47 BIOCHEMISTRY 986 (2008); Julie Blatt & Seth J. Corey, *Drug Repurposing in Pediatrics and Pediatric Hematology Oncology*, 18 DRUG DISCOVERY TODAY 4 (2012); Naris Nilubol, et al., *Four Clinically Utilized Drugs were Identified and Validated for Treatment of Adrenocortical Cancer Using Quantitative High-Throughput Screening*, 10 J. TRANSLATIONAL MED. 1 (2012); Li-Fan Zeng et al., *Repositioning HIV-1 Integrase Inhibitors for Cancer Therapeutics: 1,6-naphthyridine-7-carboxamide as a Promising Scaffold with Drug-Like Properties*, 55 J. MED. CHEM. 9492 (2012); Lisa Zhang et al., *Quantitative High-Throughput Drug Screening Identifies Novel Classes of Drugs with Anticancer Activity in Thyroid Cancer Cells: Opportunities for Repurposing*, 97 J. CLINICAL ENDOCRIN. METAB. E319 (2012); Mahadeo A. Sukhai et al., *New Sources of Drugs for Hematologic Malignancies*, 117 BLOOD 6747 (2011).

333. See Paige E. Cramer et al., *ApoE-Directed Therapeutics Rapidly Clear β -amyloid and Reverse Deficits in AD Mouse Models*, 335 SCIENCE 1503 (2012); Anne Corbett et al., *Drug Repositioning for Alzheimer’s Disease*, 11 NAT. REV. DRUG DISCOV. 833 (2012).

tuberculosis,³³⁶ malaria,³³⁷ multi-drug resistant bacteria,³³⁸ and a host of other unmet medical needs.³³⁹ Every recorded effort to screen libraries of FDA-approved drugs for activity against a particular disease uncovered one or more potential new treatments for the condition.³⁴⁰ Many researchers now suspect that our current arsenal of drugs could provide important treatments for many of the remaining major unmet medical needs.³⁴¹

Unfortunately, because the new screening tools were unavailable when pharmaceutical companies first developed these existing drugs, they were not tested for other indications.³⁴² Now that these drugs are off patent, firms lack the incentive to fund the necessary clinical research for

334. See Denise L. Faustman et al., *Proof-of-Concept, Randomized, Controlled Clinical Trial of Bacillus-Calmette-Guerin for Treatment of Long-Term Type 1 Diabetes*, 7 PLOS ONE e41756 (2012); Domokos Gerö et al., *Cell-Based Screening Identified Paroxetine as an Inhibitor of Diabetic Endothelial Dysfunction*, 62 DIABETES 953 (2013); Bradley, *supra* note 157.

335. See David C. Hess & Susan C. Fagan, *Repurposing an Old Drug to Improve the Use and Safety of Tissue Plasminogen Activator for Acute Ischemic Stroke: Minocycline*, 30 PHARMACOTHERAPY 55S (2010); Jennifer M. Plane et al., *Prospects for Minocycline Neuroprotection*, 67 ARCH NEUROL. 1442 (2010); 67(12):1442-1448; Susan C. Fagan, *Drug Repurposing for Drug Development in Stroke*, 30 PHARMACOTHERAPY 51S (2010).

336. See Kinnings et al., *supra* note 159; Juan Carlos Palomino & Anandi Martin, *Is Repositioning of Drugs a Viable Alternative in the Treatment of Tuberculosis?*, 68 J. ANTIMICROB. CHEMOTHER. 275 (2013).

337. See Ekins et al., *supra* note 33; Jing Yuan et al., *Chemical Genomic Profiling for Antimalarial Therapies, Response Signatures, and Molecular Targets*, 333 SCIENCE 724 (2011) (32 new potential antimalaria drugs); Jennifer L. Weisman et al., *Searching for New Antimalarial Therapeutics Amongst Known Drugs*, 67 CHEM BIOL DRUG DES. 409 (2006) (19 potential antimalarial therapeutics); Brian T. Grimberg & Rajeev K. Mehlotra, *Expanding the Antimalarial Drug Arsenal—Now, but How?*, 4 PHARMACEUTICALS (BASEL) 681 (2011); Anna Rosa Sannella et al., *New Uses for Old Drugs: Auranofin, a Clinically Established Antiarthritic Metallodrug, Exhibits Potent Antimalarial Effects In Vitro: Mechanistic and Pharmacological Implications*, 582 FEBS LETTERS 844 (2008).

338. See Francesco Imperi et al., *Repurposing the Antimycotic Drug Flucytosine for Suppression of Pseudomonas aeruginosa Pathogenicity*, 110 PNAS 16694 (2013); Sidharth Chopra et al., *Repurposing FDA-Approved Drugs to Combat Drug-Resistant Acinetobacter Baumannii*, 65 J. ANTIMICROB CHEMOTHER. 2598 (2010).

339. See Benjamin Alman, *Investigating the Potential for Nefopam in Fibromatosis Treatment*, 1 IMS MAGAZINE 17 (2013) (normal scarring and aggressive fibromatosis); Bessoff et al., *supra* note 46 (Cryptosporidiosis); Muthyala, *supra* note 36, at 71 (multidrug-resistant parasites, progressive multifocal leukoencephalopathy, bacterial pathogens, drug-resistant infections and a range of neurological disorders); Ekins & Williams, *supra* note 33 (C. parvum); Ekins et al., *supra* note 33 (trypanosomal and Chagas disease); Plane et al., *supra* note 335 (spinal cord injuries and Parkinsons, Alzheimer's and Huntington's disease); Allen S. Kaplan, *Investigating the Potential of Olanzapine in Anorexia Nervosa Treatment*, 1 IMS MAGAZINE 19 (2013) (anorexia nervosa); Qu et al., *supra* note 44 (systemic lupus erythematosus); Dakshanamurthy et al., *supra* note 38 (rheumatoid arthritis); Autumn S. Downey et al., *Efficacy of Pyriminium Pamoate Against Cryptosporidium Parvum Infection In Vitro and in a Neonatal Mouse Model*, 52 ANTIMICROB AGENTS CHEMOTHER 3106 (2008) (C. parvum); Jill Heemskerk, *Screening Existing Drugs for Neurodegeneration: the National Institute of Neurologic Disorders and Stroke (NINDS) Model*, 25 RETINA S56 (2005) (Huntington's disease, ALS); Peter B. Madrid et al., *A Systematic Screen of FDA-Approved Drugs for Inhibitors of Biological Threat Agents*, 8 PLOS ONE e60579, at 3 (2013) (high containment and biodefense pathogens); Henry C. Ou et al., *Identification of FDA-Approved Drugs and Bioactives that Protect Hair Cells in Zebrafish (Danio Rerio) Lateral Line and Mouse (Mus Musculus) Utricle*, 10 JARO. 191 (2009) (hearing loss); Syed Ahmad et al., *Potential Repurposing of Known Drugs as Potent Bacterial β -glucuronidase Inhibitors*, 17 J. BIOMOL SCREEN. 957 (2012) (severe diarrhea).

340. Ekins et al., *supra* note 33; see also Chong & Sullivan, *supra* note 84; Boguski et al., *supra* note 13; Muthyala, *supra* note 36; Ekins & Williams, *supra* note 33; Telleria, *supra* note 35.

341. See *supra* notes 35-37, and accompanying text; cf. Wermuth, *supra* note 148, at 161 (stating “there is only a limited chemical universe of small molecules that can be safely administered to humans,” and “this universe can be adequately covered with currently available drugs”).

342. See Mizushima, *supra* note 155, at 499.

potential new uses identified in screening by NIH and academic researchers, and the vast majority of these promising candidates will likely remain untested hypotheses. Over time, the number of off-patent drugs will increase, and the screening technologies for identifying potential new indications will get better. As a result, the social costs of this failure in the incentives for pharmaceutical R&D will continue to increase.

B. Losing the Most Efficient Way to Develop New Medical Treatments

Developing new uses for FDA-approved drugs is far and away the most efficient route for producing new medical treatments.³⁴³ New indications take only a fraction of the time, cost, and risk involved in developing new drugs.³⁴⁴ This makes it possible to deliver new medical treatments to the public faster, to pursue treatments for smaller populations that otherwise would be unprofitable, and to pursue treatments for more challenging pathologies or novel drug targets that involve a higher risk of failure.³⁴⁵

Developing new uses for existing drugs is generally much faster and cheaper than developing a novel drug compound.³⁴⁶ It allows firms to skip the drug discovery and preclinical development stages,³⁴⁷ which typically constitute between one third and one half of the cost and time of developing a drug.³⁴⁸ In some cases, firms can also skip the early clinical development stages.³⁴⁹ This dramatically reduces the cost of bringing a new medical treatment to market.³⁵⁰ Whereas de novo drug development typically costs in excess of \$1.2 billion per drug,³⁵¹ the development of a new indication for an existing drug costs on average \$300 million or less.³⁵² Moreover, while de novo drug development takes an average of twelve to sixteen years,³⁵³

343. See Barratt & Frail, *supra* note 5, at 1; Dakshanamurthy et al., *supra* note 38 (“The most effective way to move from target identification to the clinic is to identify already approved drugs with the potential for activating or inhibiting unintended targets (repurposing or repositioning).”); Mullard, *supra* note 38, at 400 (referring to the development of new indications as “a route to cost-effective drug development”).

344. See *supra* notes 38-44, and accompanying text.

345. See *supra* notes 45-47, and accompanying text.

346. See *supra* note 38 & 175-180, and accompanying text.

347. See *supra* notes 42 & 177, and accompanying text; Mullard, *supra* note 148, at 1 (noting that when firms develop new indications for drugs, they “have leapfrogged over 6 or 7 years of preclinical and early-stage research and \$30 million or so of investment with these compounds — that’s where the time saving is”).

348. See *supra* note 41.

349. See *supra* notes 175-180 and accompanying text; see also Chong & Sullivan, *supra* note 84, at 645 (“Because existing drugs have known pharmacokinetics and safety profiles and are often approved by regulatory agencies for human use, any newly identified use can be rapidly evaluated in phase II clinical trials”); Oprea & Mestres, *supra* note 9 (“The other advantage is that the NME subject to repositioning is an already-approved drug, and thus, there is no need to conduct phase I and phase IIa clinical trials.”).

350. See Chong & Sullivan, *supra* note 84, at 645 (stating, with respect to new indications, that “drug developers can bypass almost 40% of the overall cost of bringing a drug to market by eliminating much of the toxicological and pharmacokinetic assessments.”).

351. See *supra* note 39 and accompanying text.

352. See Sahoo, *supra* note 89, at 28.

353. See *supra* note 40 and accompanying text.

pharmaceutical companies can almost always develop a new indication within twelve years, and it often take as little as three.³⁵⁴

Developing new uses for an existing drug is also much less risky than de novo drug development.³⁵⁵ High failure rate in developing new drugs is one of the largest hurdles in pharmaceutical innovation.³⁵⁶ Much of this risk stems from the difficulty of predicting the pharmacological properties of untested drug compounds, including how patients will absorb the active ingredient and whether it has an acceptable toxicity profile.³⁵⁷ The risk of failure is much lower when developing new indications for established drugs, since pharmaceutical companies start with a chemical compound known to be safe and therapeutically effective in humans.³⁵⁸ Indeed, a recent study found that the likelihood of success in late-stage clinical trials is several times greater for drugs in their second or third indication than a novel drug compound in late-stage trials for a first indication.³⁵⁹

The time, cost, and risk advantages of developing new therapeutic uses for existing drugs (as opposed to new drugs) could allow pharmaceutical companies to pursue critical areas of medical research that they currently neglect.³⁶⁰ Many commentators have expressed concern over the pharmaceutical industry's tendency to overlook treatments for diseases that affect smaller or poorer populations—drugs for which firms would have greater difficulty recovering the substantial costs of de novo drug development.³⁶¹ Over the past decade, experts have also become increasingly worried that industry is failing to pursue potential breakthrough treatments aimed at novel disease targets because of the higher risk of failure.³⁶² The lower cost and risk involved in developing new indications make it more attractive for pharmaceutical companies to invest in treatments for especially challenging diseases (e.g., Alzheimer's),³⁶³ for serious but uncommon conditions (e.g., rare cancers),³⁶⁴ and for diseases that primarily afflict the uninsured

354. See Ashburn & Thor, *supra* note 56, at 673 (“The advantage of the indication-focused approach, by contrast, is that it has the potential to move the compounds very quickly through clinical trials on the basis of previously collected data.”); Dudley et al., *supra* note 155, at 303 (“The drug development cycle for a repositioned drug can be as short as 3–12 years compared to the traditional 10–17 years required to bring a new chemical entity to market.”); Elvidge, *supra* note 261, at 8; THOMSON REUTERS, *supra* note 327, at 1 (“drug repositioning has a number of R&D advantages including a reduction of R&D timelines by up to 3-5 years”).

355. See *supra* notes 44 & 48-55, and accompanying text.

356. See Scannell et al., *supra* note 58, at 199.

357. See *supra* notes 48-49 and accompanying text.

358. See *supra* note 44, and accompanying text; THOMSON REUTERS, *supra* note 327, at 1 (2012) (explaining that “drug repositioning has a number of R&D advantages including ... the repositioned drug will have passed a significant number of toxicology and safety assessments and so the chances of failure are greatly reduced”).

359. See Joseph A. DiMasi et al., *Clinical Approval Success Rates for Investigational Cancer Drugs*, 94 CLINICAL PHARMACOLOGY & THERAPEUTICS 329 (2013); Michael Hay et al., *BIO/BioMedTracker Clinical Trial Success Rates Study*, BIO CEO & Investor Conference, Feb. 15, 2011, at <http://insidebioia.files.wordpress.com/2011/02/bio-ceo-biomedtracker-bio-study-handout-final-2-15-2011.pdf>.

360. See *supra* note 45, and accompanying text; Hemphill, *supra* note 13, at 6-7.

361. See, e.g., Erdmann, *supra* note 181, at 1492.

362. See *supra* notes 76 & 79-81, and accompanying text; *infra* Part V.D.

363. See Corbett et al., *supra* note 37.

364. See Xu & Coté, *supra* note 55.

poor (e.g., multi-drug resistant tuberculosis).³⁶⁵ At the same time, the faster development period offers hope to patients with rapidly advancing conditions that may not survive the duration of a de novo drug development project.³⁶⁶ But without an incentive for firms to developing new uses for existing drugs, society loses these opportunities to spur R&D spending in neglected areas.

C. Losing a Solution to the Pharmaceutical Industry's Productivity Crisis

For much of the past decade, the pharmaceutical industry has faced a productivity crisis.³⁶⁷ After years of increased R&D spending with no commensurate increase in drugs reaching the market,³⁶⁸ and a persistently high failure rate in expensive late-stage trials,³⁶⁹ many industry executives have concluded that their current business model of de novo drug development is unsustainable.³⁷⁰ If pharmaceutical companies were given a viable drug development strategy based on establishing new indications for FDA-approved drugs, it could help revitalize a struggling industry that the public depends on to produce life saving medications.³⁷¹

Tremendous advances in the scientific fields underlying drug discovery and development over the past half century created the hope of a new golden age of pharmaceutical innovation,³⁷² but the reality has been a disappointment.³⁷³ While the pharmaceutical industry invested heavily in R&D to take advantage of new scientific opportunities, their increased R&D spending did not yield commensurate increases in new drugs reaching the market.³⁷⁴ A recent study found that, since the 1950s, the number of FDA-approvals for new drugs per inflation-adjusted dollar of

365. See Juan Carlos Palomino & Anandi Martin, *Is Repositioning of Drugs a Viable Alternative in the Treatment of Tuberculosis?*, 68 J. ANTIMICROBIAL CHEMOTHERAPY 275, 279-80 (2013).

366. See Collins, *Therapeutic Gold*, *supra* note 81, at 397; Weir et al., *supra* note 9, at 1056-57 (“First and foremost, repurposing approved and abandoned drugs for cancer represents an opportunity to rapidly advance to patients promising drug therapies by capitalizing on existing data and experience.”).

367. See Scannell et al., *supra* note 58.

368. See *supra* notes 57-60, and accompanying text.

369. See *supra* note 65.

370. In a 2011 survey of pharmaceutical industry executives, 68% of respondents either agreed or strongly agreed with the statement, “the current commercial pharmaceutical model is broken and needs significant repair.” BOOZ & COMPANY, PHARMACEUTICAL SALES AND MARKETING TRENDS 2011: KEY INSIGHTS 2 (2012), at <http://www.booz.com/media/file/BoozCo-Pharmaceutical-Sales-Marketing-Trends-National-Analysts-2011.pdf>; see also Reed, *supra* note 74, at 6; Fabio Pammolli et al., *The Productivity Crisis in Pharmaceutical R&D*, 10 NATURE REV. DRUG DISCOVERY 428, 436 (2011); DHANKHAR ET AL., *supra* note 61, at 3 (“Recent years have seen a collapse in the industry’s R&D productivity and a loss of faith in its innovation model. ... A recent McKinsey analysis calculates that the average economic return on R&D has dropped from between 13 and 15 percent in the 1990s to between 4 and 9 percent in the past decade. This suggests that much of the current investment in R&D is not creating value. We estimate that cumulative success rates have fallen by as much as 50 percent as the number of drug development programs and the cost per program have doubled.”); Paul et al., *supra* note 39, at 203; ANDY PASTERNAK ET AL., BRIDGING THE SHAREHOLDER RETURN GAP IN BIG PHARMA: MEANINGFUL COST TRANSFORMATION CAN DELIVER RESULTS 1 (2012).

371. See *supra* note 56.

372. See *supra* note 57.

373. See *supra* notes 56-65, and accompanying text.

374. See *supra* note 59, and accompanying text.

R&D spending has fallen by half approximately every nine years since the 1950s.³⁷⁵ The market capitalization of pharmaceutical companies has declined in concert (by \$550 billion between 2000 and 2010),³⁷⁶ with the inevitable result of facility closures,³⁷⁷ job cuts,³⁷⁸ and reductions in R&D investment as firms become more risk averse.³⁷⁹

Many commentators and industry insiders attribute this productivity crisis to a severe—and perhaps irreparable—breakdown in the pharmaceutical industry’s primary business model of de novo drug development.³⁸⁰ Firms spend in excess of one billion dollars on R&D to deliver a single new drug to the market,³⁸¹ but their products are not generating that much revenue.³⁸² As one commentator noted back in 2004, near the beginning of the industry’s downturn, “[t]he cost of [de novo] drug development is so great that new medicines are in danger of becoming unaffordable for ... manufacturers to develop.”³⁸³

Much of the pharmaceutical industry’s current troubles stem from the scientific hurdles involved in de novo drug discovery.³⁸⁴ Firms spend hundreds of millions of dollars creating and optimizing novel drug compounds to maximize a drug’s chance of success in clinical trials.³⁸⁵ Nevertheless, the vast majority of the compounds entering clinical trials fail to reach the market,³⁸⁶ usually because of problems related to their toxicity or efficacy.³⁸⁷ Medicinal chemists

375. See Scannell et al., *supra* note 58, at 191. There is some evidence of recent turn-around in the industry. See Munos, *supra* note 66 (“The last couple of years have seen an encouraging rise in new drug approvals, including many based on novel modes of action.”).

376. See DHANKHAR ET AL., *supra* note 61, at 3 (“In the past 25 years the industry has created in excess of \$1 trillion of shareholder value, but destroyed around \$550 billion of value during the “decade of doubt” from 2000 to 2010. That value destruction coincided with a 60 percent increase in the R&D spending rate from 10 to 16 percent of sales, and with an even higher increase in absolute spend as worldwide sales grew from \$200 billion in 1995 to \$800 billion in 2009.”); Jean-Pierre Garnier, *Rebuilding the R&D Engine in Pharma*, HARV. BUS. REV., May 1, 2008.

377. See, e.g., Andrew Jack, *Innovation: Pharmaceutical Groups Become Victims of their Own Success*, FINANCIAL TIMES, Jun. 19, 2013.

378. See, e.g., Bennani, *supra* note 49, at S31-32 (reporting “dramatic numbers of job losses over the past three years” as well as “increasing rates of mergers and acquisitions”); Oprea & Mestres, *supra* note 9, at (citing an “overall reduction of in-house workforce”).

379. See Ben Hirschler, *Drug R&D Spending Fell in 2010, and Heading Lower*, REUTERS, Jun. 26, 2011; Martin Grueber, *2012 Global R&D Funding Forecast: Stable Growth of U.S. R&D*, R&D MAGAZINE, Dec. 16, 2011; Jack, *supra* note 377; Reed, *supra* note 74.

380. See *supra* note 370; Shelley DuBois, *Novartis CEO: We Need to Re-Think the Blockbuster*, CNN MONEY, Mar. 4, 2013 (“Big Pharma is still big, but its business model is dying. For years, the game in pharmaceuticals has been to research, discover and then fiercely defend billion-dollar drugs The old blockbuster-finding strategy hasn’t been sustainable.”); Bennani, *supra* note 49, at S32.

381. See *supra* note 39 and accompanying text.

382. See *supra* note 370.

383. Rawlins, *supra* note 60, at 360; see also SA Morris et al., *The PCAST Report: Impact and Implications for the Pharmaceutical Industry*, 94 CLINICAL PHARMACOLOGY & THERAPEUTICS 300, 300 (2013) (“To continue bringing value to society, we must find ways to substantially increase the number and quality of innovative, cost-effective new medicines while stemming unsustainable R&D costs.”).

384. See *supra* notes 48-55, and accompanying text.

385. See *supra* note 41.

386. See *supra* notes 52-53, and accompanying text.

387. See *supra* note 54.

now recognize that it is extremely difficult to design a compound that can be safely administered to patients in a therapeutically effective dose.³⁸⁸ Many believe that the universe of potentially safe and efficacious drug compounds is quite limited, and a significant portion of those compounds may already be known.³⁸⁹

An obvious solution to these problems plaguing their industry would be for firms to develop new uses of FDA-approved drugs.³⁹⁰ As noted in Part V.B above, developing new indications is cheaper, faster, and less risky than de novo development.³⁹¹ It also allows firms to take advantage of the extensive body of knowledge from prior research and clinical experience with existing drugs.³⁹² New indications for existing drugs could offer firms a pipeline of attractive business opportunities that would help revitalize the pharmaceutical industry while providing the public with a wealth of new medical treatments.³⁹³ However, the patent system fails to provide almost any meaningful protection over new indications developed after a drug's initial FDA-approval.³⁹⁴ As a result, the development of new drugs not previously approved by the FDA remains the dominant business model, with much less spent on developing new uses for recently approved drugs, and virtually no investment in new uses for drugs available as generics.³⁹⁵

D. Losing a Solution to the Valley-of-Death Problem in Biomedical Research

For the past decade, the NIH has struggled to overcome a pervasive failure to translate advances in basic research into new medical treatments.³⁹⁶ NIH-funded research has identified underlying molecular causes for thousands of human diseases, revealing new biological targets for pharmacological intervention.³⁹⁷ “This array of new opportunities should portend a revolution in therapeutics,” notes Francis Collins, the NIH’s Director, but “clinical advances ... have been frustratingly slow to arrive: Therapies exist for only about 200 of the ~4000 conditions with

388. See *supra* note 51, and accompanying text. Finding compounds with drug-like properties has become a key challenge in drug discovery because the potency needed for the prospective drug to be efficacious often conflicts with the characteristics of a compound that successfully functions as a drug in humans (*e.g.*, absorption, distribution, metabolism, excretion and toxicity). See Bennani, *supra* note 49; Hann & Keserü, *supra* note 49. Moreover, medicinal chemists still struggle to predict the pharmacological properties of new drugs before costly clinical trials. See Colombo & Peretto, *supra* note 54, at 677; Kaitin, *supra* note 48.

389. See Mizushima, *supra* note 155, at 499; Muthyala, *supra* note 36; Wermuth, *supra* note 148.

390. See *supra* note 56.

391. See *supra* notes 346-351, and accompanying text.

392. See Qu et al., *supra* note 44, at S4.

393. See *supra* note 56.

394. See *supra* Part III.

395. See *supra* Part III.D. The pharmaceutical industry does develop new indications for failed drug compounds that were abandoned before receiving FDA approval and, therefore, never marketed. See *infra* note 426, and accompanying text. The number of such FDA approvals is increasing but does not represent a large portion of new approvals. See James Netterwald, *Recycling Existing Drugs*, _ DRUG DISC DEV 16 (Jan. 2008).

396. See Collins, *Translational Science*, *supra* note 60; Elias A. Zerhouni, *US Biomedical Research: Basic, Translational, and Clinical Sciences*, 294 JAMA 1352 (2005); Moses & Dorsey, *supra* note 293, at 1333; Nancy S. Sung et al., *Central Challenges Facing the National Clinical Research Enterprise*, 289 JAMA 1278 (2003); Elias Zerhouni, *The NIH Roadmap*, 302 SCIENCE 63 (2003).

397. See *supra* notes 331-340, and accompanying text; see also Meredith Wadman, *The Bridge Between Lab and Clinic: Q&A Francis Collins*, 468 NATURE 877 (2010).

defined molecular causes.”³⁹⁸ The pharmaceutical industry’s productivity crisis left “a large research and funding gap” at “the crucial early stages of preclinical R&D—the research necessary to ‘translate’ promising discoveries made in laboratories into optimize candidate therapeutics ready for testing in clinical trials.”³⁹⁹ The NIH lacks the resources and institutional capacity to fill in this gap directly by advancing novel drug compounds through preclinical R&D.⁴⁰⁰ Consequently, most newly discovered targets languish in the so-called valley of death between academia and industry,⁴⁰¹ where neither public nor private funding is available to advance the research to the point of commercial viability.⁴⁰² By testing FDA-approved drugs against new targets, the NIH could skip preclinical R&D to move quickly from target discovery to early-stage clinical trials, leapfrogging the valley of death in biomedical research.⁴⁰³ Many experts argue that drug repurposing is the NIH’s best opportunity to translate breakthroughs in basic research into commercialized products.⁴⁰⁴ However, with limited public sector funding for clinical research, the NIH must attract industry sponsors to finance the late-stage clinical trials needed to repurpose old drugs successfully, which is nearly impossible without effective monopoly protection for these treatments.⁴⁰⁵ As a result, the NIH has been unable to take advantage of drug repurposing as a solution to its valley-of-death problem.⁴⁰⁶

Historically, when researchers discovered a new target, they could usually rely on the pharmaceutical industry to invest in discovering and developing novel drug compounds to hit that target.⁴⁰⁷ These projects are more likely to result in a medical breakthrough than drugs designed to hit established targets, since they provide an entirely different pathway for treating disease.⁴⁰⁸ However, developing new drugs based on unvalidated targets also involves more uncertainty, and thus a higher failure rate.⁴⁰⁹ After years of declining productivity and

398. Collins, *Translational Science*, *supra* note 60, at 2; *supra* notes 56-65.

399. Reed, *supra* note 74.

400. *See infra* note 413 and accompanying text.

401. *See, e.g.*, Butler, *supra* note 77, at 841; Mary Carmichael, *Desperately Seeking Cures*, NEWSWEEK, May 14, 2010; FASTER CURES, *supra* note 79; Collins, *Translational Science*, *supra* note 60.

402. *See* Muthyala, *supra* note 36; Press Release: U.S. Department of Health and Human Services, National Institutes of Health, *NIH Announces New Program to Develop Therapeutics for Rare and Neglected Diseases*, NIH NEWS, May 20, 2009, at <http://www.nih.gov/news/health/may2009/nhgri-20.htm>; Nuala Moran, *Public Sector Seeks to Bridge ‘Valley of Death’*, 25 NATURE BIOTECH. 266 (2007); Reed, *supra* note 74.

403. *See supra* note 55 and accompanying text.

404. *See supra* note 81; Reed et al., *supra* note 46; Boguski et al., *supra* note 13; O’Connor & Roth, *supra* note 84.

405. *See supra* note 84; Weir et al., *supra* note 9 (discussing the importance of public-private partnerships for repurposing known drugs for new indications, but noting that “[a] particular development challenge exists in repurposing off-patent drugs” because “regulatory approval often requires expensive and complex clinical trials, but limited returns on investment make it difficult to attract private sector financing and expertise.”).

406. *See infra* notes 425 & 426.

407. *See* Butler, *supra* note 77.

408. *See* Brian W. Metcalf & Susan Dillon, *Preface*, in TARGET VALIDATION IN DRUG DISCOVERY vii (Brian W. Metcalf & Susan Dillon Eds. 2007).

409. *Id.*; Amy P. Patterson, *Target Selection and Validation: A More Strategic and Collaborative Approach*, December 8-9, 2011 Advisory Committee to the Director, National Institutes of Health, 5-8 at http://acd.od.nih.gov/reports/TargetValidationReport_122011.pdf.

diminishing returns on their R&D investments, pharmaceutical companies are increasingly reluctant to pursue these higher-risk projects, leaving a crucial funding gap at preclinical R&D.⁴¹⁰

At the same time, support from the public sector remains insufficient to advance breakthroughs in basic research into viable candidates for industry development.⁴¹¹ In addition to the NIH's budget constraints,⁴¹² the NIH and universities generally lack the facilities and expertise for the medicinal chemistry necessary to optimize novel drug compounds, the exploratory pharmacology necessary to evaluate their drug-like properties, and the rigorous preclinical toxicology testing necessary to advance them into clinical trials.⁴¹³ As former NIH director Elias Zerhouni candidly admits, "such 'bench to bedside' research is more difficult than he [originally] thought," and "[a]t the end of the day, there's a gap in translation."⁴¹⁴

The NIH could overcome this problem by repurposing FDA-approved drugs for newly identified targets, since this approach bypasses the preclinical R&D stages constituting the valley of death. When researchers identify a novel biological target, they can use the new screening technologies (discussed in Part V.A above) to search for any FDA-approved drugs that may be active against that target.⁴¹⁵ Since those drugs are already on the market and have established safety and efficacy profiles,⁴¹⁶ the NIH could quickly move any promising leads into early-stage clinical trials, avoiding the need to design a novel drug compound and test it in preclinical studies.⁴¹⁷ This shortcut across preclinical R&D would drastically reduce the time and expense of moving from target discovery to human trials,⁴¹⁸ which, as Francis Collins explains, "can enable the rapid testing of new clinical hypotheses, leading to remarkable health outcomes."⁴¹⁹

Unfortunately, the NIH generally cannot utilize this seemingly ideal solution to the valley-of-death problem unless there are incentives for private industry to fund clinical trials on new uses for off-patent drugs. If the NIH's clinical-research programs were adequately funded, the NIH might be able to repurpose FDA-approved drugs without support from private industry.⁴²⁰

410. Elias A. Zerhouni, *Turning the Titanic*, 6 SCI. TRANSLATIONAL MED. 221 (2014); Reed, *supra* note 74; see also Butler, *supra* note 77, at 840; Metcalf & Dillon, *supra* note 408; Patterson, *supra* note 409; Collins, *Translational Science*, *supra* note 60; Rai et al., *supra* note 76.

411. See *supra* note 402; Moran, *supra* note 401; FASTER CURES, *supra* note 79; Scott F. Roberts et al., *Transforming Science Into Medicine: How Clinician-Scientists Can Build Bridges Across Researcher's 'Valley of Death'*, 87 ACAD. MED. 266, 268 (2012).

412. See *supra* Part IV.B.

413. See *supra* note 74; Reed, *supra* note 74; Woodcock, *supra* note 52, at 19-20.

414. See, e.g., Shirley S. Wang, *Sanofi's Zerhouni on Translational Research: No Simple Solution*, WSJ HEALTH BLOG, May 20, 2011; Roberts et al., *supra* note 411, at 268.

415. See Huang et al., *supra* note 32.

416. See *supra* note 44, 358 & 392, and accompanying text.

417. See Huang et al., *supra* note 32 (noting that the development of new indications for existing drugs "obviate[s] the need for NME development, a long and expensive process.").

418. See *supra* notes 346-354, and accompanying text.

419. Collins, *Therapeutic Gold*, *supra* note 81, at 397; see also Hemphill, *supra* note 13, at 6-7; Cimmino & Aifantis, *supra* note 332, at 976 ("Repurposing existing drugs for the treatment of different diseases is part of a new initiative by the NIH to speed up the translation of research findings into new treatment regimens.").

420. See Rai, *supra* note 13, at 491-92; Elie Dolgin, *Nonprofit Disease Groups Earmark Grants for Drug Repositioning*, 17 NATURE MED. 1027, 1027 (2011). Partnering with private industry to develop new indications for off-patent

However, as discussed in Part IV.B above, government funding for clinical trials is always (and increasingly) in short supply, particularly for the costly late-stage clinical trials.⁴²¹ In the medical literature on drug repurposing, researchers—predictably—describe “an unmet critical need to fund repurposing projects into phase IIb and phase III [trials].”⁴²² University or NIH researchers generally must find an industry sponsor to pay for these studies.⁴²³ Since firms have little or no incentive to invest in drugs once generics are on the market,⁴²⁴ public-private partnerships of this sort are infeasible when repurposing an off-patent drug.⁴²⁵ As a result, the NIH is increasingly reluctant to initiate drug-repurposing projects involving off-patent drugs, preferring to spend its money on projects that might ultimately find an industry sponsor to complete their development.⁴²⁶

drugs might have significant benefits even if the NIH could finance those projects on its own, since pharmaceutical companies are much more experienced navigating many aspects of the drug-development process. *See* Butler, *supra* note 74, at 158-159 (“[T]ranslational research requires skills and a culture that universities typically lack, says Victoria Hale, chief executive of the non-profit drug company the Institute for OneWorld Health”); Colvis et al., *supra* note 59, at 25; Nair, *supra* note 56, at 2431; Woodcock, *supra* note 52, at 19 (noting that from the FDA’s perspective, studies funded by pharmaceutical companies are superior to academic studies in their “rigor”).

421. *See supra* notes 292-301, and accompanying text.

422. Oprea & Mestres, *supra* note 9; Weir et al., *supra* note 9, at 1056-57 (explaining that academic drug development still relies on the for-profit sector to take drugs through the more expensive later-stage clinical trials, giving the example of auranofin for chronic lymphocytic leukemia); Brewer, *supra* note 74.

423. *See supra* notes 302, and accompanying text; Mark S. Boguski et al., *Repurposing For Neglected Diseases: Response*, 326 SCIENCE 935, 935 (2009) (noting that “the [high] cost of repurposing projects underscores the real need for novel business models and/or regulatory and legal reforms in order to capitalize on the candidate drugs that are identified[, which] is especially true in the case of generic drugs or drugs that cannot otherwise be patented.”) (quotation marks omitted).

424. *See supra* Part III.D.

425. *See* Mullard, *supra* note 38, at 400 (“In the case of the abandoned and off-patent products — for which lack of patent protection can make commercialization of an eventual product difficult — the NIH faces the inverse problem of attracting private partners who will run with POC [proof of concept] data to the finish line.”).

426. The NIH recently created a new institute for translational research, the National Center for Advancing Translational Research (NCATS), with a major initiative for funding early-stage clinical trials on new indications for known drug compounds. *See* Collins, *Therapeutic Gold*, *supra* note 81. Since the public and private sector both lack an effective funding model to support drug repurposing, NCATS is pursuing an alternative (and second-best) strategy to drug repurposing known as drug rescuing. *See* Nair, *supra* note 56, at 2431; Colvis et al., *supra* note 59, at 24-25; Jocelyn Kaiser, *NIH’s Secondhand Shop for Tried-and-Tested Drugs*, 332 SCIENCE 1492 (2011); Mullard, *supra* note 148. While drug repurposing involves developing new uses for FDA-approved drugs, drug rescuing involves developing new uses for drug compounds that failed in clinical trials for their original indication and thus never reached the market. *See* NIH Office of Science Policy, NIH-Industry Roundtable: Exploring New Uses for Abandoned and Approved Therapeutics, April 21-22, 2011: Executive Summary 1 n.1 (2012), at http://www.ncats.nih.gov/files/exploring_new_uses_for_abandoned_and_approved_therapeutics.pdf. These failed drug candidates are far less likely to prove safe and effective for a new indication than an FDA-approved drug. *See* DiMasi et al., *supra* note 359 (finding that, among oncology drugs, clinical trials for a second indications are “more likely than not” to succeed if the lead indication succeeded, but “if the lead indication fails, then the likelihood of success for a second indication is only 2.5%”). But failed drug candidates have one crucial advantage over FDA-approved drugs: they remain eligible for effective monopoly protection against generic entry through new-use patents and FDA-exclusivity periods, and therefore may attract an industry sponsor to finance their late-stage clinical trials. *See* Diamond, *supra* note 44; Smith, *supra* note 217 (“Previously shelved APIs [active pharmaceutical ingredients] can provide some of the most attractive opportunities for repositioning because under the right circumstances they can offer excellent product exclusivities and protection from generics and modified versions of the product.”).

VI. THE INFORMATION BARRIERS UNDERLYING THE PROBLEM OF NEW USES

Industry's unwillingness to repurpose off-patent drugs is not the only gap in the incentives for pharmaceutical innovation, but it is seemingly the hardest to fix. The standard policy options for promoting private sector drug development all seem ill suited to the task, including temporary monopoly rights to block generic entry, consumer subsidies for prescription-drug costs or insurance, and monetary prizes for manufacturers. NIH leaders have asked for help in devising a "new funding paradigm" to support drug repurposing,⁴²⁷ preferably through "[n]ew paths to exclusivity and pricing/reimbursement strategies ... to promote private sector engagement."⁴²⁸ But the existing literature on the problem of new uses offers little help in this regard. It treats the problem as a binding constraint on private sector incentives rather than as a problem to be solved.⁴²⁹ This pessimism stems from having framed the problem improperly. The public does not need a new incentive mechanism to promote drug repurposing, as assumed in the literature. Any of the standard policy options could be effective were it not for a simple information problem—the difficulty observing utilization rates for new indications. Pharmaceutical companies are free to patent newly discovered uses for off-patent drugs, but because they do not know when physicians prescribe that off-patent drug for the patented new use, they cannot enforce their new-use patents to charge payers for those prescriptions.⁴³⁰ Likewise, when the government does not observe physicians prescribing off-patent drugs for new indications, it cannot create alternative incentive mechanisms that tie the rewards for developing new indications to their utilization rate, which is necessary for linking rewards to social value.⁴³¹ Solving the problem of new uses therefore requires a mechanism for observing new indications' utilization rates.

Despite significant attention from experts in the field,⁴³² the existing literature on the problem of new uses offers few suggestions for solving it.⁴³³ Rebecca Eisenberg ends her 2005 article *The Problem of New Uses* without offering any solutions, merely stating that "[h]ow to motivate firms to make socially efficient investments in studying the effects of [old] drugs in

427. See Austin, *supra* note 13, at 19.

428. See Weir et al., *supra* note 9, at 1057.

429. See Eisenberg, *New Uses*, *supra* note 13, at 739; Hemphill, *Repurposing Pharmaceuticals*, *supra* note 108, at 1250016-4 n.7; Rai, *supra* note 13, at 492; Milne & Bruss, *supra* note 13; Grabowski, et al., *supra* note 13.

430. See *supra* Part III.C.

431. See *infra* notes and text accompanying notes 446-454.

432. See, e.g., Eisenberg, *supra* note 13; Rai, *supra* note 13; Grabowski, et al., *supra* note 13; Milne & Bruss, *supra* note 13; Hemphill, *supra* note 13; Walson, *supra* note 2; Gelijns et al., *supra* note 13; Boguski et al., *supra* note 13; *Change of Purpose*, *supra* note 13; Weir et al., *supra* note 9; Chong & Sullivan, *supra* note 84.

433. See *supra* note 114, and accompanying text. Some scholars support offering pharmaceutical companies an additional year or two of market exclusivity over their new drugs if they develop one or more additional indications for the product before generics enter. See, e.g., Gelijns et al., *supra* note 13. The European Union already has such a policy, offering firms a one-year extension on their market exclusivity for developing over a new drug for obtaining approval for one or more new indications. See Art. 10(1), Directive 2001/83/EC. Needless to say, this approach is not a comprehensive solution to the problem of new uses. It only works for new indications discovered prior to generic entry, and because firms may claim no more than one extension per drug, it does not encourage them to develop anything more than two indications.

patients is thus a major challenge for the legal system.”⁴³⁴ *Nature*’s editorial board issued a call in 2010 for “the United States [to] protect investments used to find new uses for old drugs,” but instead of offering solutions, it describes the problem as “a difficult conundrum ... that warrants serious thought and creativity from researchers, agencies and policy-makers alike.”⁴³⁵ Arti Rai essentially gives up on creating incentives for private industry to repurpose off-patent drugs, and instead calls for the government to fund that research directly,⁴³⁶ despite the grim outlook for public sector clinical-research funding.⁴³⁷

Unlike new uses for off-patent drugs, most other areas of under-investment in drug development are amenable to correction through one or more of the established policy levers for incentivizing industry investment in pharmaceutical R&D—namely, patents, FDA-exclusivity periods, and consumer subsidies. Some new drugs receive inadequate monopoly protection through the existing Hatch-Waxman framework, either because they are unpatentable⁴³⁸ or because they take too long to develop given the fixed 20-year patent term.⁴³⁹ In these cases, the underlying problem is that the standard monopoly protection for new drugs is either unavailable or too short for firms to recoup their R&D investment. Consequently, the government could remedy that problem by amending the patent laws or lengthening FDA-exclusivity periods to provide an adequate term of standard monopoly protection for those under-protected drugs.⁴⁴⁰ Other socially valuable drugs fail to reach the public because market demand for them is too

434. Eisenberg, *New Uses*, *supra* note 13, at 739; *cf.* Hemphill, *Repurposing Pharmaceuticals*, *supra* note 108, at 1250016-4 n.7.

435. *Change of Purpose*, *supra* note 13, at 267 & 268.

436. *See* Rai, *supra* note 13, at 492.

437. *See supra* notes 286-305 and accompanying text.

438. *See* Roin, *Unpatentable Drugs*, *supra* note 18, at 515-45. Over the years, researchers have disclosed millions of compounds with potentially valuable therapeutic properties through journal articles and older patent applications, the vast majority of which have never been tested in clinical trials and are unavailable to the public. *See* Richard Van Noorden, *Chemistry’s Web of Data Expands*, 483 NATURE 524 (2012) (reporting that between 1976 and 2011, the pharmaceutical industry patented at least 10 million distinct molecules with potentially beneficial therapeutic properties); Paul D. Leeson & Stephen A. St. Gallay, *The Influence of the ‘Organizational Factor’ on Compound Quality in Drug Discovery*, 10 NATURE REV. DRUG DISCOVERY 749, 751 box.1 (2011) (finding that the 18 largest pharmaceutical companies filed a total of 14,335 drug patents published between 2000 and 2009, and these patents together disclosed 791,722 unique compounds along with some of their potential therapeutic uses). These prior disclosures generally render the drugs either non-novel or obvious, and thus unpatentable. *See* Roin, *Unpatentable Drugs*, *supra* note 18, at 517-544 (explaining how drugs can—and often do—become unpatentable because of prior disclosures that render them either non-novel or obvious). As drug-discovery tools improve and researchers gain better knowledge of human and disease biology, they sometimes discover that these once-discarded compounds are much more promising drug candidates than previously assumed. *See supra* notes 326-330, and accompanying text. According to both the trade literature on drug development and the scientific literature on medicinal chemistry, these patentability concerns heavily influence firms’ choice of drug compounds to pursue in their de novo drug development programs. *See* Roin, *Unpatentable Drugs*, *supra* note 18, at 545-47 (collecting sources).

439. *See* Benjamin N. Roin, *Drug Patent Length* (2009) (hereinafter Roin, *Drug Patent Length*), at <http://www.law.harvard.edu/faculty/faculty-workshops/faculty-workshop-secure/roin.workshop.paper.summer.2009.pdf>; Eric Budish et al., *Do Fixed Patent Terms Distort Innovation? Evidence from Cancer Clinical Trials*, NBER Working Paper No. 19430 (2013), at <http://www.nber.org/papers/w19430>; *infra* notes 548-556 and accompanying text (explaining how the fixed 20-year patent term distorts private-sector drug development).

440. *See* Roin, *Unpatentable Drugs*, *supra* note 18, at ; Budish et al., *supra* note 439, at .

low,⁴⁴¹ possibly including treatments for malaria.⁴⁴² In these cases, because the underlying problem is inadequate market demand for socially valuable drugs, the government can remedy it with consumer subsidies (perhaps through subsidized prescription drug insurance or advanced purchase commitments) to bolster market demand for those products.⁴⁴³

None of these market-based mechanisms for encouraging pharmaceutical innovation offer an appealing solution to the problem of new uses because they would break the link between a new indication's social value and the incentive to develop it. Granting firms the standard monopoly protection over off-patent drugs through patents or FDA-exclusivity periods—which block generics from the market entirely—would allow those firms to charge consumers for that drug's new and old uses alike.⁴⁴⁴ Similarly, using consumer subsidies to incentivize drug repurposing would support purchases of the drug for any use. Both approaches link the incentives to repurpose old drugs to their overall sales volume instead of the new indication's sales volume.⁴⁴⁵ Indeed, almost any market-based mechanism for incentivizing drug repurposing will be problematic when the market fails to differentiate between sales for drugs' old and new indications.⁴⁴⁶

A prize system to promote drug repurposing would encounter essentially the same problem.⁴⁴⁷ Many scholars have argued that the government should award firms monetary prizes instead of patents to incentivize the development of new drugs.⁴⁴⁸ In theory, the

441. See William Fisher & Talha Syed, *Chapter 7: Prizes*, 1 (2012) at http://cyber.law.harvard.edu/people/tfisher/Drugs_Chapter7.pdf; AIDAN HOLLIS & THOMAS POGGE, *THE HEALTH IMPACT FUND: MAKING NEW MEDICINES ACCESSIBLE FOR ALL* (2008).

442. See Owen Barder et al., *Advance Market Commitments: A Policy to Stimulate Investment in Vaccines for Neglected Diseases*, *ECONOMISTS VOICE*, Feb. 2006; Ernst R. Berndt et al., *Advance Market Commitments for Vaccines Against Neglected Diseases: Estimating Costs and Effectiveness*, 16 *HEALTH ECON.* 491 (2007).

443. See Roin, *Intellectual Property versus Prizes*, *supra* note 111, at 164-67.

444. In theory, the government could use the standard monopoly protection to promote drug repurposing without breaking the link between incentives and social value by tailoring the length of protection to each new indication's social value. *Cf.* Michael Abramowicz, *Orphan Business Models: Toward a New Form of Intellectual Property*, 124 *HARV. L. REV.* 1362, 1396-1420 (2011) (outlining a system for awarding temporary monopoly rights over unpatentable drugs in need of further clinical development involving an auction, in which pharmaceutical companies would bid against one another for the right to develop the drug (or indication) for the shortest market-exclusivity period).

445. See *supra* notes 228-229, and accompanying text.

446. See *supra* notes 252-254, and accompanying text.

447. *Cf.* Amy Kapczynski & Talha Syed, *The Continuum of Excludability and the Limits of Patents*, 122 *YALE L.J.* 1900, 1955 (2013) (acknowledging that so long as “prize mechanisms operate by using the sales of some discrete good as their substrate measure of social value, ... nonexcludability analysis presents an Achilles heel for prizes that is similar to the one it presents for patents,” since “[m]any nonexcludable innovations—such as ... changes in eating habits or exercise or other lifestyle behavior—will not be linked to any commodifiable good or otherwise easily traceable uses”). According to Kapczynski and Syed, the government might avoid this problem by setting prize payouts “us[ing] quite intricate methods for assessing impact, which may ultimately sever their measurement of social value from any reliance on indirect proxies such as sales data, and look instead directly at observed outcomes in terms of specific indications, e.g., reduced disease incidence or improved health in a target population after the introduction of an innovation.” *Id.* To this author's knowledge, no one has yet described how such a system might work—perhaps because, as Kapczynski and Syed admit, “the complexity and costs in establishing [such a system] may ultimately prove insurmountably high, due in part to the presence of confounding variables.” *Id.* at 1956.

448. See Roin, *Intellectual Property versus Prizes*, *supra* note 111, at 106 n.19 (collecting sources).

government could use this same approach to solve the problem of new uses, paying firms a monetary prize as a reward for repurposing off-patent drugs. But prize systems require a mechanism for the government to calculate appropriate prize payouts.⁴⁴⁹ Virtually all of the proposed prize systems for pharmaceuticals base their prize payouts in part on drugs' actual or expected sales volume,⁴⁵⁰ which would conflate sales of off-patent drugs for their old and new indications.⁴⁵¹

Ultimately, without a way to measure the utilization rate for a new indication distinct from the drug's overall sales, designing an efficient incentive system of any type to encourage repurposing off-patent drugs is extremely difficult.⁴⁵² In any reward-based system for encouraging innovation, including patents, prizes, and any other financial inducement for investing in R&D, the rewards for inventions should be linked to their social value.⁴⁵³ An invention's social value is mostly a function of how often people use it and the value generated by each use. Since an invention's utilization rate is a critical component of its social value, a reward-based incentive system for innovation generally requires a mechanism to link the reward for inventions to their utilization rate (either actual, estimated or expected).⁴⁵⁴ Consequently, unless the government can observe when patients are using an old drug for a new indication as opposed to its other uses, there is no easy way to tie the incentives for developing new indications to their social value.

449. *Id.* at 136-39.

450. *Id.* at 160 & n.254-255.

451. Aidan Hollis and Thomas Pogge's proposed Health Impact Fund ("HIF") demonstrates how the same information problem affects both patent and prize-based incentive mechanisms for drug repurposing. *See* HOLLIS & POGGE, *supra* note 441. Hollis and Pogge argue that, under their proposed prize system, "firms will be able to make use of patents issued for new uses" because "the HIF reward mechanism does not require exclusion: it only requires that the patentee provide evidence that the existing drug was in fact used for the new indication." *Id.* But the mechanism they propose for calculating prize payouts requires information about utilization rates. *Id.* at 24 (describing how a firm that develops a new indications for an existing drug "will receive payments based on the effects of the product for the [new] treatment ... [and] on its own sales as well as on sales made by generics [for that new use].") And they do not specify how the government or pharmaceutical companies might acquire that information. *See id.* at 32-34. Terry Fisher and Talha Syed's proposed drug-prize system is similar. *See* Fisher & Syed, *supra* note 441. They describe a prize system encompassing new uses for off-patent drugs, *id.* at 46, in which the government bases prize payouts in part on inventions' utilization rates, *id.* at 21-32, without specifying how the government might observe a new indication's utilization rate to calculate its prize. *Id.* at 45-48.

452. The government could fund drug-repurposing efforts directly through grants without knowing the subsequent utilization rates for the new indications it develops. But if the government were to initiate a large-scale funding program for drug repurposing, it would probably want to observe utilization rates *ex post* to evaluate the social returns from those investments and guide future funding decisions. *Cf.* Albert N. Link & Nicholas S. Vonortas, *Introduction to the Handbook*, in *HANDBOOK ON THE THEORY AND PRACTICE OF PROGRAM EVALUATION 2* (Albert N. Link & Nicholas S. Vonortas, eds.) (2013) (emphasizing the importance of carrying out *ex post* economic evaluations of large government-funded R&D programs, explaining that *ex post* evaluations help in "measuring [the program's] performance; supporting performance-based management and performance-based budgeting; enhanced accountability and transparency; [and] improving the communication of program activities and outcomes to policy decision-makers and sponsors").

453. *See* Shavell & van Ypersele, *supra* note 111, at 530.

454. *See supra* note 111, and accompanying text. Most incentive systems rely on inventions' sales volume as a proxy for their utilization rate because it is usually difficult to observe consumers directly when they use an invention. *See* Roin, *Intellectual Property versus Prizes*, *supra* note 111, at 106.

The longstanding problem of new uses therefore stems from information barriers, not a problem with the existing incentive mechanisms for promoting pharmaceutical innovation. The government and pharmaceutical companies do not know the utilization rate for new indications because they do not observe the prescribed indications for drugs.⁴⁵⁵ If they knew when physicians prescribed off-patent drugs for a new indication as opposed to an older one (or at least had a reliable estimate of new indications' utilization rates), then the government could deploy a variety of different incentive systems to encourage firms to repurpose off-patent drugs, including patents, FDA-exclusivity periods, and prizes. But policymakers do not need to create new incentive mechanisms to promote drug repurposing. If the government and pharmaceutical companies could observe the prescribed indications for drugs, pharmaceutical companies could enforce their patents on new uses for older drugs, providing them an incentive to develop those new medical treatments.

VII. THE PROBLEM OF NEW USES RECAST AS A PRICE-DISCRIMINATION PROBLEM

The existing literature on the problem of new uses generally attributes the problem to the finite monopoly term for new drugs,⁴⁵⁶ overlooking the underlying information barriers preventing firms from enforcing their new-use patents.⁴⁵⁷ This framing causes scholars to overlook the problem of new use's true nature and scope. Ultimately, industry's unwillingness to develop new uses for off-patent drugs is about impediments to price discrimination. Each of the different indications for drugs is essentially a distinct product. They require separate clinical trials to establish,⁴⁵⁸ benefit a different group of patients, and have different cost-benefit profiles.⁴⁵⁹ Pharmaceutical companies cannot separate the markets for a drug's different indications because they do not observe when physicians prescribe that drug for one indication as opposed to another.⁴⁶⁰ Consequently, they have no choice but to charge the same price for these otherwise distinctive goods.⁴⁶¹ This barrier to differential pricing by indication creates an acute incentive problem once generics enter the market, since the resulting low prices and limited market power give firms little reason to invest in costly clinical trials.⁴⁶² But the problem extends

455. See *supra* notes 252-254, and accompanying text.

456. See, e.g., Eisenberg, *New Uses*, *supra* note 13, at 721 (attributing the problem of new uses to "patent protection on drugs typically begin[ing] and end[ing] too early" to motivate drug repurposing, and generally "does a better job of motivating the initial R&D that is necessary to bring new products to market than it does of motivating the development of new information about old drugs.").

457. See *supra* note 108.

458. See *supra* Part II.C.

459. Gregson et al., *supra* note 463, at 123 ("Different indications generally involve distinct customers, value propositions and competing (reference) products, as well as different doses.").

460. See *supra* notes 252-254, and accompanying text.

461. See SAHOO, *supra* note 89, at 83 ("[A] drug must be priced at the same rate for all indications (otherwise consumers would simply purchase the lowest priced version of the drug and use it for any approved indication.);"; Gregson et al., *supra* note 463, at 123 ("Although the value-based approach might theoretically justify appreciably different prices in each indication, in reality it is not viable to achieve large price spreads in a given country for the same molecule on the basis of differing indications, unless a differing dose relationship supports this.").

462. See *supra* Part III.D.

beyond inadequate incentives for investing in off-patent drugs. The same underlying information barriers that prevents pharmaceutical companies from enforcing their new-use patents also prevents them from pricing drugs with multiple indications efficiently. This Part offers a first look at this price-discrimination problem in the market for prescription drugs, speculating that it reduces firms' incentive to invest in new indications for their patented drugs and probably reduces patients' access to drugs with multiple indications.

The impediments to differential pricing by indication likely discourage firms from developing some socially valuable indications for their on-patent drugs. Pharmaceutical companies are usually aware of several possible indications for their new drug compounds while they are in development and shortly after their initial FDA approval.⁴⁶³ The inability to price drugs by indication necessarily diminishes incentives to develop these new indications because firms cannot charge the profit-maximizing price for each different use. This distortion is probably most acute for new indications with significantly different therapeutic values than the drug's established use.⁴⁶⁴ Insurers will have a very different willingness-to-pay for those indications.⁴⁶⁵ As a result, pharmaceutical companies would be unable to market the drug effectively for its lower-value indication without greatly underpricing the high-value indication.⁴⁶⁶ The same problem can arise for new indications requiring substantially different doses than the drug's original indication, since patients may be able to take advantage of the high-dose

463. Nigel Gregson et al., *Pricing Medicines: Theory and Practice, Challenges and Opportunities*, 4 NATURE REV DRUG DISCOVERY 121, 122 (2005) ("Development generally starts with a molecule that might have potential uses in several, often very different, indications.").

464. In a recent trade book on drug repurposing, the authors note that when given the option to develop a second indication with a significantly different therapeutic value, firms instead often develop "a 'backup' NCE [i.e., a new drug] for the second indication, despite the efficiency advantages that result from parallel development of the alternative indication with the 'lead' candidate." Barratt & Frail, *supra* note 5, at 54.

465. Ideally, patented medical treatments should be priced according to the severity of the disease they treat, the efficacy of that treatment, and the availability, price, and effectiveness of alternative treatments. See Gregson, *supra* note 463, at 122. The negotiations between pharmaceutical companies and PBMs over drug prices should have this effect to the extent that the market is working properly. Of course, no market is perfect, and the health care system has more than its fair share of distortions and market failures. Nevertheless, industry consultants report that a drug's perceived therapeutic value over competing products heavily influences its price. See Analysis Group, *Healthcare Consulting: Pricing and Payer Strategies* 3 (2013); IMS CONSULTING GROUP, PRICING & MARKET ACCESS OUTLOOK: 2012 EDITION 21-24 (2012); Michael D. Miller, *Drug Pricing Principles*, in THE ENTREPRENEUR'S GUIDE TO A BIOTECH STARTUP 58 (Peter Kolchinsky ed. 2004). Moreover, there is ample qualitative evidence that when pharmaceutical companies and payers negotiate drug prices, their negotiations center on questions regarding the drug's therapeutic value relative to alternative treatments. See Gregson et al., *supra* note 463, at 122; Miller, *supra* at 58; E.M. (MICK) KOLASSA, THE STRATEGIC PRICING OF PHARMACEUTICALS 55 (2009); Everett Neville, *A PBM Calls the Plays*, MEDICAL MARKETING & MEDIA, Feb. 2013, at 38-39.

466. See SAHOO, *supra* note 89, at 83 (explaining that when a potential second indication would call for a significantly lower price than the initial indication, "[m]ost commonly, ... this situation would represent such a significant competitive threat as to render an indication expansion not worthwhile"). Interestingly, the trade literature on drug pricing suggests that this distortion may be most pronounced for new indications targeted at niche markets with significantly higher pricing points, since pharmaceutical companies usually cannot raise their drug's price substantially (presumably because of pricing regulations). See ELLERY & HANSEN, *supra* note 89, at 128 ("[I]t will be almost impossible to obtain premium pricing for a high-unmet need niche follow-on indication if the drug is already marketed in a mass indication at an (inevitably) lower price."); PHARMA FUTURES, PATHWAYS TO VALUE: PHARMA IN A CHANGING WORLD 15 (2013) ("Companies seek the highest possible price for a medicine knowing that it cannot later be adjusted upwards if the drug proves more effective.").

indication by dividing it into multiple treatments to save on the low-dose indication.⁴⁶⁷ However, if pharmaceutical companies could price drugs by their prescribed indication instead of at a flat rate, they could invest in developing new indications for on-patent drugs without worrying about reducing the profits from their drugs' original indications.

The barriers to differential pricing by indication also likely cause a second distortion. When firms develop new indications for their on-patent drugs (despite the lower anticipated returns from needing to set a single price), insurers often restrict patients' access to some of those indications.⁴⁶⁸ Pharmaceutical companies frequently price drugs to reflect their most valuable indications,⁴⁶⁹ which can make them too expensive for uses offering smaller therapeutic benefits or that are experimental.⁴⁷⁰ Insurers typically exclude these lower-value indications from their plan's coverage.⁴⁷¹ The pharmacy benefit managers (PBMs) that administer insurers' prescription drug plans use a variety of tools to discourage physicians from prescribing patented drugs for excluded indications,⁴⁷² including prior authorization and step therapy.⁴⁷³ These

467. Genentech likely refused to develop its chemotherapy drug bevacizumab (Avastin) for a new use in macular degeneration—at least in part—for this reason, and instead developed a new drug for the indication, ranibizumab (Lucentis). Both drugs are effective against macular degeneration, but a single vial of bevacizumab sold for chemotherapy creates roughly 20 macular-degeneration treatments, making it next-to-impossible for Genentech to profit from developing bevacizumab for that indication. See Daniel F. Martin et al., *Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration*, 364 N ENGL J MED. 1897, 1907 (2011).

468. Price discrimination by monopolists is generally associated with reductions in consumer deadweight loss, but it can increase consumer deadweight loss under certain circumstances. See Lars A. Stole, *Price Discrimination and Competition*, in III HANDBOOK OF INDUSTRIAL ORGANIZATION (Mark Armstrong & Robert H. Porter, eds. 2007). Given the prevalence of prescription-drug insurance and its mitigating effect on the deadweight loss from monopoly drug pricing, see *supra* note 234, differential pricing by indication probably avoids many of the potentially adverse effects from price discrimination by monopolists, suggesting that it would reduce consumer deadweight loss. As noted in the text below, pharmaceutical companies and payers could negotiate lower prices for lower-value indications, lessening the need for insurers to use prior authorization and step therapy to reduce patients' access to those medical treatments. See *infra* text accompanying notes 469-475. But there are two countervailing considerations. First, differential pricing by indication would allow pharmaceutical companies to charge more for some higher-value uses, which could reduce patients' access to those medical treatments. However, these higher prices will only reduce insured patients' access to high-value uses if insurers stop covering them, which should be unusual given the pressure on insurers to cover clinically validated indications of high therapeutic value. See Ha T. Tu & Divya R. Samuel, *Limited Options to Manage Specialty Drug Spending*, Center for Studying Health System Change, Research Brief 22, at 3-5 (2012). Second, to the extent that differential pricing by indication increases insurers total outlays to pharmaceutical companies, it could increase consumer deadweight loss by raising prices for prescription-drug insurance, forcing some consumers to remain uninsured. However, national health insurance policies will often minimize this effect by promoting (or ensuring) that most or all consumers have prescription-drug insurance. See Roin, *Intellectual Property versus Prizes*, *supra* note 111, at ___. To the extent that the public absorbs the cost of higher prescription-drug spending, differential pricing by indication might create additional deadweight loss from raising tax revenue. A full analysis of how differential pricing by indication would affect consumer deadweight loss is beyond the scope of this article.

469. See ELLERY & HANSEN, *supra* note 89, at 128; PHARMA FUTURES, *supra* note 466, at 15; Gregson et al., *supra* note 463, at 123.

470. See ELLERY & HANSEN, *supra* note 89, at 128.

471. See Neville, *supra* note 465, at 38-39.

472. See James C. Robinson, *Comparative Effectiveness Research: From Clinical Information to Economic Incentives*, 29 HEALTH AFFAIRS 1788, (2010); Tu & Samuel, *supra* note 468.

473. See *supra* note 124.

coverage restrictions can severely limit patients' access to those therapies,⁴⁷⁴ although they may offer meaningful therapeutic benefits to some of those patients, despite having a lower value than the drug's primary indication.⁴⁷⁵ Insurers would have less need to restrict coverage for drugs with multiple indications if they could demand pricing concessions for experimental or lower value uses commensurate with their lesser value.

VIII. REMOVING INFORMATION BARRIERS TO SOLVE THE PROBLEM OF NEW USES

The various impediments to pharmaceutical innovation discussed in Part V and VII all stem from the same underlying information problem. If physicians reported indications to pharmaceutical companies (as well as pharmacists and PBMs), the pharmaceutical companies could enforce their new-use patents against pharmacists⁴⁷⁶ and (probably) PBMs.⁴⁷⁷ Pharmacists would then be required to dispense the pharmaceutical companies' more expensive, brand name drug instead of a low-cost generic when physicians prescribe that drug for a patented indication. Alternatively, the pharmacist could dispense the low-cost generic and then report the sale to the PBM and pharmaceutical company, allowing the pharmaceutical company to bill the insurer directly for the sale. In either case, pharmaceutical companies could charge insurers when physicians prescribe an off-patent drug for a patented indication, thereby providing a financial

474. See Shoemaker et al., *supra* note 124, at S5-S6 (reviewing the literature); Michael A. Fischer et al., *Medicaid Prior-Authorization Programs and the Use of Cyclooxygenase-2 Inhibitors*, 351 N. ENG. J. MED. 2187 (2004).

475. Although experts often speculate that certain prior authorization policies are associated with negative clinical patient outcomes, the existing empirical literature on this question is sparse and (thus far) inconclusive. See Laura E. Happe et al., *A Systematic Literature Review Assessing the Directional Impact of Managed Care Formulary Restrictions on Medication Adherence, Clinical Outcomes, Economic Outcomes, and Health Care Resource Utilization*, 20 J. MANAGED CARE PHARM. 677 (2014) (reviewing the literature).

476. See *supra* notes 248 and accompanying text (explaining that pharmacists would be liable for indirectly infringing a new-use patent if they knowingly fill a prescription with a low-cost generic for a patented indication). Since the pharmacist would not be liable for indirectly infringing a new-use patent unless it knows of that patent or is willfully blind to its existence, pharmaceutical companies may need to notify pharmacists of their new-use patents to enforce them. Alternatively, the government could require that pharmacy software for submitting insurance authorization requires notify pharmacists when a prescribed indication is covered by a new-use patent. Since pharmaceutical companies generally must list those patents in the FDA's Orange Book, pharmacies' software could link to that information. See *Caraco Pharm. Labs. v. Novo Nordisk*, 132 S.Ct. 1670, 1672 (2012) ("[T]he Hatch-Waxman Amendments require a brand manufacturer to submit its patent numbers and expiration dates, [21 U.S.C.] § 355(b)(1); and FDA regulations require a description of any method-of-use patent, known as a use code, see 21 CFR §§ 314.53(c)(2)(ii)(P)(3), (c)."); Mahn, *supra* note 240 (explaining that the FDA could ensure that pharmacists have the requisite knowledge of new-use patents to establish liability for inducing infringement by "adopting therapeutic equivalence codes that ... automatically alerts pharmacists (and doctors) to the possibility that the generic may not be approved for the intended uses and, thus, may not be fully substituted for the pioneer. Such codes already exist (B-ratings) and perhaps should be used here.").

477. See *supra* note 248 (discussing whether insurers would be liable for indirect patent infringement if they knowingly authorize pharmacists to dispense a generic drug for a patented indication). PBMs and insurers might be accountable for pharmacists infringing new-use patents even if they are not liable for inducing infringement under 35 U.S.C. § 271(b). Pharmacists would presumably demand indemnification from insurers or PBMs for liability under these circumstances. Consequently, the real parties of interest in these disputes would be the pharmaceutical companies and insurers. If PBMs and insurers can escape liability under the existing § 271(b) rules and they do not contract into that liability by indemnifying pharmacists for their own liability under § 271(c), the government might need to amend the §271(b) standards.

incentive to develop those new uses. Moreover, if pharmaceutical companies could observe the intended indication for prescribed drugs, they could price each indication separately, thereby avoiding the static and dynamic inefficiencies caused by flat pricing across indications.⁴⁷⁸ But pharmaceutical companies do not have this information. When pharmacists fill a prescription for a drug that has more than one potential medical use, pharmaceutical companies do not know which of those indications the physician prescribed the drug to treat.⁴⁷⁹ As a result, they cannot separate the markets for a drug's different indications.

Fortunately, a proven solution to this information problem already exists—prior authorization. As discussed above, most insurers limit their coverage for drugs by the prescribed indication.⁴⁸⁰ The PBMs administering prescription-drug plans use a system known as prior authorization to enforce the coverage restrictions.⁴⁸¹ When physicians prescribe a drug subject to prior authorization, they must submit a form listing the indication to the PBM, which uses that information to determine whether the patient's plan covers the prescription.⁴⁸² Although physicians could misreport indications to skirt insurers' coverage restrictions, that misreporting would be fraud,⁴⁸³ and PBMs can check patients' medical records to verify physicians' reported indications.⁴⁸⁴ PBMs claim they have “had great success at preventing payments for drugs not provided for medically accepted indications by using prior authorization.”⁴⁸⁵ This success indicates that prior authorization is generally an effective means for third parties to observe prescribed indications, even when physicians have an incentive to misreport. Prior authorization therefore provides both a model for solving the problem of new uses and proof-of-concept for that solution's effectiveness.

The problem of new uses persists today because pharmaceutical companies do not have access to the basic information infrastructure PBMs use to observe indications. Unlike insurers and PBMs, pharmaceutical companies typically lack authority to require physicians to report

478. See *supra* Part VII.

479. Tewodros Eguale et al., *Enhancing Pharmacosurveillance with Systematic Collection of Treatment Indication in Electronic Prescribing*, 33 DRUG SAF. 559 (2010) (discussing the limited information available on prescribed indications).

480. See *supra* notes 167 & 468 and accompanying text.

481. See Robert P. Navarro & Rusty Hailey, *Overview of Prescription Drug Benefits in Managed Care*, in MANAGED CARE PHARMACY PRACTICE 28 (Robert P. Navarro ed., 2d Ed. 2009). Prior authorization requirements have become “nearly universal” in pharmacy benefit plans for expensive patented drugs. See Tu & Samuel, *supra* note 468, at 8-9.

482. See ELIZABETH HARGRAVE & JACK HOADLEY, COVERAGE AND PRICING OF DRUGS THAT CAN BE COVERED UNDER PART B AND PART D, 11-14, MedPAC No. 07-6 (2007); Bergeson et al., *supra* note 124, at 376.

483. See *Reminder: Physicians Must Verify Medical Necessity Before Signing Certification Forms*, Texas Academy of Family Physicians (2012), at www.tafp.org/news/stories/12.02.21/medical-necessity.

484. See CENTER FOR HEALTH TRANSFORMATION, ELECTRONIC PRIOR AUTHORIZATION AND ITS POTENTIAL IMPACT ON HEALTHCARE: HOW PAPER-BASED PRIOR AUTHORIZATION IMPEDES ELECTRONIC PRESCRIBING 13 (2012).

485. Wright, *supra* note 168, at 5; see also *id.* (“The PDP [prescription drug plan] sponsors indicated that prior authorization is the best tool they currently have to compare the diagnosis provided by the prescriber to the medically accepted indications contained in the compendia.”); ACADEMY OF MANAGED CARE PHARMACY, CONCEPTS IN MANAGED CARE PHARMACY: PRIOR AUTHORIZATION 1 (2012) at http://www.amcp.org/prior_authorization/ (describing prior authorization as “an essential tool that is used to ensure that drug benefits are administered as designed”).

indications to them or to review patients' medical records to verify those reports. Solving the problem of new uses is a simple matter of giving pharmaceutical companies these abilities.⁴⁸⁶

This Part sketches the basic contours of such a system, explaining how—with a few targeted policy changes—the government could use electronic prescribing (“e-prescribing”) software and electronic health (“e-health”) records to enable effective indication reporting and verification.⁴⁸⁷ With modern e-prescribing software, physicians can easily submit the indication for a drug when they write their prescriptions.⁴⁸⁸ The government could then require (or allow pharmaceutical companies to demand) that information be sent to them electronically, allowing them to link prices to reported indications. To reduce the risk of fraud, the government also must give pharmaceutical companies (restricted) access to patients' e-health records for the purpose of verifying reported indications. Admittedly, this strategy will not always be effective. Some indications are hard to distinguish based on patients' medical records, making it easy for physicians to misreport the indication. But PBMs' success with prior authorization suggests that the strategy will work for most indications. And as diagnostic technologies improve and become more widely utilized, verifying indications will get easier, since the diagnostic results in patients' medical records will more clearly signal prescribed indications. Once this information infrastructure is in place, pharmaceutical companies could enforce their new-use patents and separate the market for drugs' different indications, thereby solving the problem of new uses.

486. As an alternative to observing each prescription intended indication, pharmaceutical companies and payers could rely on a mechanism that merely estimates the overall utilization rate for new indications, such as physician surveys or random sampling. Assuming the mechanism is relatively accurate and difficult to manipulate, parties could link rewards for new indications to their estimated utilization rate to provide reasonably efficient incentives for drug repurposing. However, the government would need to amend the indirect patent infringement rules to allow firms to enforce new-use patents based on these estimated usage figures. Or the government could implement a prize system for new indications that links prize payouts to estimated utilization rates.

487. There is an expansive literature on the potential benefits of e-prescribing, but to this author's knowledge, none of it mentions the use of indication reporting to facilitate the enforcement of new-use patents or differential pricing by indication. See, e.g., Egualé et al., *supra* note 479, at 560; Andrew English et al., *A New Regulatory Function for E-Prescriptions: Linking the FDA to Physicians and Patient Records*, (June 19, 2013), Harvard Public Law Working Paper No. 13-44; Maria A. Friedman et al., *Interoperable Electronic Prescribing in the United States: a Progress Report*, 28 HEALTH AFFAIRS 393 (2009); Ed. J. Fotsch, *Electronic Health Records: the New Vehicle for Drug Labeling, Safety, and Efficacy*, 91 CLIN PHARMACOL THER. 917 (2012); Joy M. Grossman et al., *Transmitting and Processing Electronic Prescriptions: Experiences of Physician Practices and Pharmacies*, J. AM. MED. INFORM. ASSOC. (2011) doi:10.1136/amiajnl-2011-000515; Robert H. Miller & Ida Sim, *Physicians' Use of Electronic Medical Records: Barriers and Solutions*, 23 HEALTH AFFAIRS 116 (2004); R. Lamar Duffy et al., *Effects of Electronic Prescribing on the Clinical Practice of a Family Medicine Residency*, 42 FAMILY MEDICINE 358 (2010); E-PRESCRIBING: BARRIERS AND OPPORTUNITIES, CENTER FOR HEALTHCARE RESEARCH AND TRANSFORMATION (2011) at http://www.chrt.org/assets/policy-papers/CHRT_E-Prescribing-Barriers-and-Opportunities.pdf; Erika L. Abramson, *Electronic Prescribing Within an Electronic Health Record Reduces Ambulatory Prescribing Errors*, 37 JOINT COMMISSION JOURNAL ON QUALITY AND PATIENT SAFETY 470 (2011); Kevin B. Johnson et al., *Showing Your Work: Impact of Annotating Electronic Prescriptions with Decision Support Results*, 43 J. BIOMEDICAL INFORMATICS 321 (2010); Jesse C. Crosson et al., *Early Adopters of Electronic Prescribing Struggle to Make Meaningful Use of Formulary Checks and Medication History Documentation*, 25 J. AM. BOARD FAM. MED. 24 (2012); Robyn Tamblyn et al., *The Development and Evaluation of an Integrated Electronic Prescribing and Drug Management System for Primary Care*, 13 J. AM. MED. INFORM. ASSOC. 148 (2006).

488. See Egualé et al., *supra* note 479, at 559.

A. Physicians Reporting Prescribed Indications

The first step in solving the problem of new uses is to create an information infrastructure for indication reporting. Physicians must report the indications along with their prescriptions, and the relevant pharmacist, insurer and pharmaceutical company all must have access to that information. Fortunately, most of this information infrastructure already exists. The government requires physicians to report the indications for prescriptions covered under Medicare Part B,⁴⁸⁹ and private insurers widely use prior-authorization systems that require physicians to report indications for many prescriptions to pharmacists and insurers.⁴⁹⁰ The government could simply expand these systems to include pharmaceutical companies and new uses—first by requiring broader indication reporting, and second by affording pharmaceutical companies restricted access to those reports.

Mandatory indication reporting might have been overly burdensome before the information-technology revolution, but with modern e-prescribing software, physicians can record and transmit that information with minimal hassle.⁴⁹¹ Most U.S. physicians are already using e-prescribing to send prescriptions directly to pharmacists,⁴⁹² and U.S. regulators are pushing for universal e-prescribing adoption by 2017.⁴⁹³ At present, physicians usually enter little more than the drug's name and dosage when writing e-prescriptions.⁴⁹⁴ But e-prescribing software can—and sometimes does—require the physician to list the indication for their prescription, usually by selecting a diagnosis from a short scroll-down menu.⁴⁹⁵ Tewodros Egualé and co-authors studied the mandatory adoption of such a system among primary care physicians in Quebec.⁴⁹⁶ They found a high level of accuracy (97%) in the indications submitted by physicians through e-prescribing,⁴⁹⁷ suggesting that a mandatory indication-reporting system is feasible.

489. See Ankur Ramesh Shah, et al., *Adding Diagnosis Codes to Prescriptions: Lessons Learned from a Quality Improvement Project*, 15 J MANAGED CARE PHARMACY 508 (2009).

490. See *supra* note 124.

491. See Egualé et al., *supra* note 479; Tamblyn et al., *supra* note 487, at 153 (finding that with two-weeks experience, physicians became adept at quickly entering indications with their e-prescriptions); cf. C. Douglas Monroe et al., *Kaiser Permanente's Evaluation and Management of Biotech Drugs: Assessing, Measuring, and Affecting Use*, 25 HEALTH AFF. 1340 (2006) (describing the success of existing electronic health records systems employed by some health insurers to track indications reported at the time of prescription).

492. See Fotsch, *supra* note 487 at 917 (reporting that, as of November 2011, “more than 50% of community-based providers were using e-prescribing”).

493. See 78 FED. REG. 21308, 21311, 42 C.F.R. part 411, Apr. 10, 2013.

494. See MICHAEL VAN ORNUM, ELECTRONIC PRESCRIBING: A SAFETY AND IMPLEMENTATION GUIDE 155-56 (2008).

495. See Egualé et al., *supra* note 479; Tamblyn et al., *supra* note 487, at 149-51; VAN ORNUM, *supra* note 494, at 63.

496. See Egualé et al., *supra* note 479, at 559.

497. See *id.* at 566 (reporting the success of physician e-prescribing at “correctly identifying the treatment indication was 97.0% (95% CI 94.2, 98.6). Among the ten false positives, errors in selection (clicking a different indication than intended) is a probable cause in three cases since the correct indication was just above or below the incorrect indication”).

The more advanced e-prescribing software not only records the indications for prescribed drugs. It can also record and report the supporting evidence necessary to document those indications by integrating with patients' e-health records and their PBMs' prior-authorization systems.⁴⁹⁸ Traditional prior-authorization systems are mostly manual, requiring physicians telephone and fax information to PBMs to document the intended indications for their prescriptions.⁴⁹⁹ Not surprisingly, physicians often complain that these procedures are “costly and burdensome.”⁵⁰⁰ The newer electronic prior-authorization (“e-prior authorization”) programs allow physicians to submit the information PBMs require for prior authorization along with their prescriptions, and the programs even auto-complete most of the data fields by linking to patient's e-health records.⁵⁰¹ These e-prior authorization programs are meant to streamline that review process for physicians and PBMs.⁵⁰² But they also provide an efficient electronic system for indication reporting and documentation that could easily transmit that information to parties other than PBMs when necessary, including pharmaceutical companies.

Allowing pharmaceutical companies to observe indications for prescriptions through e-prescribing and e-prior authorization software probably requires two policy changes. First, the government must ensure that physicians are using these programs. The Centers for Medicare and Medicaid Services (CMS) could easily accomplish this goal. It already administers a set of financial incentives for physicians to use e-prescribing software and e-health records.⁵⁰³ CMS would only need to alter its specifications for qualifying software to require indication reporting

498. See *The New Standard for Electronic Prior Authorization*, Pharmacy Town Hall Series (hereinafter *The New Standard for E-Prior Authorization*), 18-34 (Apr. 10, 2014) at <http://www.himss.org/files/FileDownloads/Pharmacy%20Town%20Hall%20Series%20April%2010%202014-2a.pdf> (discussing new programs that integrate e-prescribing and e-prior authorization that avoid the time-consuming process of phone or fax-based prior authorization); cf. Julie C. Jacobson Vann et al., *Pharmacist and Physician Satisfaction and Rates of Switching to Preferred Medications Associated with an Instant Prior Authorization Program for Proton Pump Inhibitors in the North Carolina Medicaid Program*, 16 J. MANAGED CARE PHARMACY 250, 252 (2010) (describing the growing use by insurers of “instant approval process (IAP) [as an] ... alternative to traditional PA [prior authorization] for managing access to specific types of prescription drugs”);

499. See American Medical Association (AMA), *Standardization of Prior Authorization for Medical Services White Paper* 2-3 (2011); *The New Standard for E-Prior Authorization*, *supra* note 498.

500. Wright, *supra* note 168, at 6; see also Vann et al., *supra* note 498, at 251-52; AMA, *supra* note 499. Although prior authorization requirements undoubtedly impose some burden on physicians and their staff, the size of that burden is unclear. The estimated average time spent by physicians and their staff per week on prior-authorization requirements ranges from 1.15 hours to 56.2 hours. See John W. Epling et al., *Practice Characteristics and Prior Authorization Costs: Secondary Analysis of Data Collected by SALT-Net in 9 Central New York Primary Care Practices*, 14 BMC HEALTH SERVICES RES. 109 (2014). Similarly, the estimated average cost to each full-time practicing physician annually from prior-authorization requirements ranges from \$2,161 to \$85,000. See Christopher P. Morley et al., *The Impact of Prior Authorization Requirements on Primary Care Physicians' Offices: Report of Two Parallel Network Studies*, 26 J. AM. BOARD FAM. MED. 93, 94 (2013).

501. See *The New Standard for E-Prior Authorization*, *supra* note 498, at 24; Marc Nyarko et al., *Electronic Prior Authorization Initiatives at the Point of Care: Moving the Industry Forward*, AMCP 24th Annual Meeting and Expo, San Francisco, CA (2012).

502. See Jennifer Webb, *Real Time Prior Auth Standards Approved*, MANAGED HEALTHCARE EXECUTIVE, Jul. 1, 2013.

503. See 42 U.S.C. § 1395w4(o)(2)(A)(i); Medicare Improvement for Patients and Providers Act of 2008 (MIPPA), Pub. L. 110-275, sec. 132; see also Seth B. Joseph et al., *E-Prescribing Adoption and Use Increased Substantially Following the Start of a Federal Incentive Program*, 32 HEALTH AFFAIRS 1221 (2013); Fotsch, *supra* note 487, at 917.

and e-prior authorization.⁵⁰⁴ Software vendors would then need to incorporate this functionality into their systems.⁵⁰⁵

Second, the government must provide pharmaceutical companies with the right to demand indication reporting (perhaps along with additional privacy safeguards)⁵⁰⁶ when they need that information to enforce their monopoly right over a new use or a differential pricing scheme. There is some precedent for such a policy. The FDA currently uses its Risk Evaluation and Mitigation Strategies (REMS) authority to require pharmaceutical companies to demand indication reporting (along with other information) for drugs with serious safety concerns.⁵⁰⁷ Legislators could broaden that authority to include any drug with one or more protected indications, and allow the pharmaceutical companies with those monopoly rights to require indication reporting whenever physicians prescribe that drug. A more restrictive version of this proposal would give pharmaceutical companies the right to require physicians to report indications to them only when the prescribed drug has one or more FDA-approved uses still subject to a new-use patent (or FDA-exclusivity period).⁵⁰⁸

B. Allowing Firms to Verify Reported Indications Through Access to Health Records

The second step in permitting pharmaceutical companies to enforce patents on new uses for drugs is to give them access to patient-level information that will allow them to verify the accuracy of reported indications. Needless to say, pharmaceutical companies would be reluctant to develop a new indication for an older drug if they think physicians will falsely report their

504. See 21 C.F.R. § 1311.205 (listing the required elements for an e-prescribing software program to qualify for federal incentive benefits); MARYLAND HEALTH CARE COMMISSION, RECOMMENDATIONS FOR IMPLEMENTING ELECTRONIC PRIOR AUTHORIZATION 14-15 (2011) (advising CMS to use its EHR (e-health records) Incentive Program, under which “providers must be meaningful users of HER by January 1, 2015, or they will face penalties in their Medicare reimbursement rates,” such “that by January 1, 2015, providers should be required to use electronic methods to submit prior authorization requests”).

505. See Egualé et al., *supra* note 156.

506. Since disclosing to pharmaceutical companies a patient’s identify along with the indication for their prescriptions would likely violate HIPAA privacy laws, the disclosed prescription might need to be de-identified. See 45 CFR 164.502(d)(2). Pharmaceutical companies would know the intended indication for each prescription, but pharmacists would replace the patient’s name with a unique identifier code. See U.S. Department of Health and Human Services, *Guidance Regarding Methods for De-identification of Protected Health Information in Accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule* 21-22 (2012), at http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/De-identification/hhs_deid_guidance.pdf (noting that covered entities may disclose the unique identifier codes for patients as part of their de-identified data as long as the data still meets the de-identification requirements). This de-identification could create a problem for pharmaceutical companies trying to verify reported indications by checking patients’ medical records, which might not use the same unique identifier code for those patients. Consequently, the system for de-identifying indication reporting to pharmaceutical companies might need to be connected in some way with the system for de-identifying patient’s medical records. Alternatively, the government could amend HIPAA to classify drug manufacturers (or at least their billing activities) as “covered entities.” Pharmaceutical companies would then be subject to HIPAA’s privacy rules, which would permit them restricted access to patients’ individually identifiable health information. See 45 CFR 164.502 (2007).

507. See 21 USC §355-1(f)(3)(D).

508. This approach would prevent pharmaceutical companies from enforcing new-use patents over new indications for generic drugs without demonstrating the safety and efficacy of those treatments in clinical trials. See *infra* notes 536-541.

prescribed indication to avoid the higher price. To discourage fraud, both PBMs and pharmaceutical companies would need access to patients' e-health records, although that information could be de-identified (and perhaps subject to other restrictions on use) to protect patients' privacy.

The government already provides insurers with access to patient's health records⁵⁰⁹ to use for their coverage determinations.⁵¹⁰ As discussed above, PBMs use this information to verify the accuracy of reported indications through prior authorization, and report "great success" at discouraging prescriptions for excluded indications.⁵¹¹ Their success suggests that insurers can generally deduce the actual indication for a prescription when they have access to patient health records. It also suggests that having access to that information effectively deters most fraudulent reporting of indications. If pharmaceutical companies also had access to patients' medical records, they would be in the same position as insurers to verify reported indications for prescriptions.

Of course, patients have legitimate privacy interests in their medical records that should be protected under such a system. The government could limit pharmaceutical companies' access to patients' medical records by requiring de-identification of the records.⁵¹² It could also prohibit pharmaceutical companies from using those medical records for anything other than billing. If the government believes these privacy safeguards are inadequate, it could expand its existing HIPAA framework to include pharmaceutical companies as "covered entities," which would impose strict regulations on pharmaceutical companies' use of patients' confidential medical information.⁵¹³

Pharmaceutical companies cannot depend on patients' medical records to prevent physicians from misreporting indications under all circumstances. Some diagnoses are hard to distinguish from others based on the information contained in a patient's medical records (e.g., many psychiatric conditions),⁵¹⁴ leaving room for fraudulent reporting not susceptible to audit. In these cases, enforcing new-use patents may be cost-prohibitive, and pharmaceutical companies may remain unwilling to develop these new indications. Likewise, if the drug is on patent and the pharmaceutical company already developed both indications, it would probably negotiate a single price for both indications because it could not prevent arbitrage—even if the two indications have substantially different therapeutic values.

However, in many (and perhaps most) circumstances, this system should allow pharmaceutical companies to enforce new-use patents over new indications—as evidenced by PMS's success with prior authorization. Pharmaceutical companies could distinguish many indications based on the prescribing physicians' specialty or records of concomitant and follow-

509. See 45 C.F.R. § 164.508(a)(2).

510. See Mark A. Rothstein, *Access to Sensitive Information in Segmented Electronic Health Records*, 40 J.L. MED. & ETHICS 394, 396 (2012).

511. See *supra* notes 480-485 and accompanying text.

512. Indeed, pharmaceutical companies are already allowed to purchase such de-identified patient-level health records for marketing and research purposes. See *supra* note 254.

513. Health Insurance Portability and Accountability Act (HIPAA) of 1996, 42 U.S.C. § 1320d.

514. See J. Morris, *The Use of Observational Health-Care Data to Identify and Report on Off-Label Use of Biopharmaceutical Products*, 91 CLINICAL PHARMACOLOGY & THERAPEUTICS 937, 940 (2012).

up treatments. When physicians use laboratory and imaging tests to diagnose a condition, those test results are available for review in patients' medical files, clearly signaling the indication in most cases. As diagnostic technology advances and medicine becomes more personalized, such testing will become increasingly common, making it easier to verify reported indications.⁵¹⁵ When pharmaceutical companies can detect fraud easily through access to patients' medical records, physicians would be reluctant to misreport indications, allowing pharmaceutical companies to enforce their new-use patents.

The practical limitations to relying on e-prescribing software and electronic health records to overcome the problem of new uses will also benefit people in developing countries. This proposal can only be implemented in countries with a sufficiently sophisticated IT structure surrounding the delivery of healthcare. E-prescribing software and electronic health records must be widely used by practicing physicians. These conditions are much more likely to be present in developed countries. As a result, pharmaceutical companies could enforce their new-use patents only in the wealthy nations. In most or all developing countries, patients could still purchase off-patent drugs at generic prices even if they are taking them for patented new indications. Using e-prescribing software and electronic health records to make new-use patents enforceable should result in a mostly beneficial form of international price discrimination.⁵¹⁶ Moreover, encouraging pharmaceutical companies to finance more clinical trials for new uses will free up NIH funding for drug-repurposing projects aimed at tropical diseases.⁵¹⁷

IX. THE LIMITATIONS OF EXISTING MONOPOLY RIGHTS FOR NEW INDICATIONS

This Article does not attempt to identify the optimal incentive mechanism for encouraging private sector investment in drug repurposing. Rather, it proposes a mechanism for observing new indications' utilization rates. This system would allow pharmaceutical companies to enforce new-use patents (and perhaps FDA-exclusivity periods)⁵¹⁸ on off-patent drugs, providing them an incentive to invest in drug repurposing. The Article assumes that the

515. Cf. PERSONALIZED MEDICINE COALITION, *THE CASE FOR PERSONALIZED MEDICINE 2* (3rd Ed. 2011) ("In the future, personalized medicine will become embedded in every hospital, clinic and medical practice, supported by electronic health records, a clinical decision support system, tailored blood and tissue tests aimed at very early and precise diagnosis, and a personal genomic sequence linked to every patient's medical record."); Lola Butcher, *Employers Struggle to Cope with the Rising Use of Biologics*, 8 BIOTECHNOLOGY HEALTHCARE 21, 24 (2011) ("As more diagnostic tests become available, expect those tests to be required before high-cost specialty drugs are authorized.").

516. The potential benefits from international price discrimination in pharmaceutical markets have been discussed extensively elsewhere. See, e.g., Patricia M. Danzon & Adrian Towse, *Differential Pricing for Pharmaceuticals: Reconciling Access, R&D and Patents*, 3 INT'L J. HEALTH CARE FINANCE & ECON. 183 (2003); Sean Flynn et al., *An Economic Justification for Open Access to Essential Medicine Patents in Developing Countries*, 37 J.L. MED. & ETHICS 184 (2009); William Jack & Jean O. Lanjouw, *How Much Should Poor Countries Contribute?*, 19 WORLD BANK ECON. REV. 45 (2005); Patricia M. Danzon, *At What Price?*, 449 NATURE 176 (2007).

517. Cf. Muthyala, *supra* note 36; Boguski et al., *supra* note 13. Of course, because patents on new indications will continue to be unenforceable in undeveloped countries, this system would not create an incentive for developing new treatments for diseases like malaria that primarily afflict those countries.

518. See *infra* text accompanying notes 568-569 (discussing the additional regulatory changes needed to make FDA-exclusivity periods enforceable monopoly rights over new indications when generics are on the market).

government would use drug patents and/or FDA-exclusivity periods to incentivize drug repurposing, since those monopoly rights for new uses already exist. But the proposed mechanism to measure utilization rates for new indications would be equally valuable in a prize system.⁵¹⁹ Indeed, as discussed in Part VI, for any reward-based system for encouraging innovation (be it patents, FDA-exclusivity periods, prizes, or consumer subsidies), the government would want information about utilization rates to provide appropriate incentives for drug repurposing.⁵²⁰ However, because enforceable monopoly rights over new indications implicate slightly different policy considerations than normal drug patents, these issues warrant further discussion. Without making any claims about optimal incentive mechanisms, this Part compares new-use patents to FDA-exclusivity periods as tools for promoting drug repurposing, examining their relative strengths and weaknesses, and suggests a few areas for reform.

A. Over- and Under-Inclusiveness Problems in Patent Protection for New Indications

The goal in providing firms with effective monopoly protection over new uses for FDA-approved drugs is to motivate the development of new medical treatments that the public would not otherwise receive. As discussed in Part II.E, the basic economics of drug repurposing provide a strong prima facie case for patent protection.⁵²¹ Physicians are generally reluctant to prescribe drugs for potential new indications without any supporting clinical-trial evidence,⁵²² especially if the new indication is for an entirely different disease than the drug's established uses.⁵²³ Public sector funding for these clinical trials is scarce,⁵²⁴ and given the costs of these trials and the ease of imitation by generic manufacturers, firms rarely pay to test drugs in clinical trials without strong monopoly protection.⁵²⁵ The potential social-welfare gains from drug repurposing⁵²⁶ and private industry's current unwillingness to fund this research⁵²⁷ together suggest that providing enforceable patent rights over new uses is preferable to the status quo. But new-use patents will not provide perfect incentives for drug repurposing.⁵²⁸ In some cases, the system will be over-

519. See *supra* notes 447-450 and accompanying text.

520. See *supra* notes 453-454 and accompanying text.

521. See *supra* Part II.E.

522. See *supra* notes 162-168 and accompanying text.

523. See *supra* note 162 and accompanying text.

524. See *supra* Part IV.

525. See *supra* Part III.D.

526. See *supra* Part V.

527. See *supra* Part III.D.

528. The incentives for drug repurposing provided by new-use patents will have many of the same deficiencies as the incentives for de novo drug development provided by product patents. Pharmaceutical companies typically capture only a small portion of the social value generated by their drugs. See Dana P. Goldman, et al., *The Value of Specialty Oncology Drugs*, 45 HEALTH SERVICE RESEARCH 115 (2010); Tomas J. Philipson & Anupam B. Jena, *Who Benefits from New Medical Technologies? Estimates of Consumer and Producer Surpluses for HIV/AIDS Drugs*, FORUM HEALTH ECON. & POL'Y, vol. 9, art. 3 (2006). Consequently, they will limit their investments to new indications with a lower risk of failure, larger market size, and higher reimbursement rate relative to what the public would prefer. Moreover, because pharmaceutical companies do not capture the social value of information about adverse drug effects or inefficacy, they may be reluctant to test a new indication for one of their patented drugs if those trials might uncover harmful side effects, or if the trial outcome might be negative and physicians are already prescribing the drug off-label for that use. See Eisenberg, *New Uses*, *supra* note 13, at 718.

inclusive, awarding protection for new indications without any beneficial incentive effects from those monopoly rights. In other cases, the system will be under-inclusive, failing to protect new indications that need that protection to motivate their development.

The classic over-inclusiveness problem in patent law, which occurs when the government awards patents for inventions that the public will receive anyway,⁵²⁹ should be relatively rare for new uses of older drugs. If the problem occurs, it would most likely involve patents on new indications that do not require validating clinical studies.⁵³⁰ Some new indications are so closely related to the drug's original FDA-approved use that physicians quickly recognize that new indication's potential and feel comfortable prescribing it off-label without any supporting clinical-trial evidence.⁵³¹ Assuming physicians are correct in their assessment of that new treatment's probable safety and efficacy, the social costs of awarding enforceable monopoly rights over that new use may be greater than the social value of testing the new use in clinical trials. However, the existing patent laws should deny protection to most indications fitting this description. If a new indication does not require any supporting clinical-trial evidence (that is, if physicians can reasonably infer that a drug is likely safe and effective for a new use based on the clinical-trial data supporting the drug's older use), then researchers should also be aware of the new indication when they discover the drug's original use. As a result, most closely related new indications that do not require any clinical-trial evidence should also fail the nonobviousness standard for patentability.⁵³² Even if the new indication is nonobvious, and thus patentable, pharmaceutical companies will be under intense pressure to file those patents as early as possible to prevent rivals from patenting the new use first.⁵³³ Since the patent term starts running on the filing date,⁵³⁴

529. See Benjamin N. Roin, *The Case for Tailoring Patent Awards Based on Time-to-Market*, 61 UCLA L. REV. 672, 691-92 (2014) (hereinafter *Case for Tailoring*) (framing patent policy as a trade-off between over- and under-inclusiveness).

530. Making new-use patents on off-patent drugs enforceable might lead to two additional manifestations of the classic over-inclusiveness problem, but for reasons discussed above, these two concerns are probably insignificant. First, a policy that makes new-use patents enforceable could create unnecessary deadweight loss to the extent that firms patent and develop new indications that the public otherwise would have received because the public sector would have been developed them. However, given the paucity of public funding for drug-repurposing trials, see *supra* Part IV.B., and the fact that any public funding crowded out of drug-repurposing trials by private sector funding is likely to be reallocated toward other socially valuable clinical research projects neglected by private industry, see *supra* notes and text accompanying notes 288-291, this concern seems minor. Second, it is conceivable that firms might be willing to develop some new indications without any monopoly protection, but given the economics of drug development, such situations should be rare. See *supra* text accompanying notes 189-194. A more plausible scenario for this over-inclusiveness problem would involve secondary indications for new drugs discovered shortly before or after the new drugs' approval. In these cases, firms sometimes develop the secondary indications without needing any additional monopoly protection from new-use patents because the remaining patent life on their new drug offers enough protection. See *supra* notes and text accompanying notes 255-259. However, since firms still need some monopoly protection to invest in these new uses, this manifestation of the over-inclusiveness problem ultimately concerns the questions of optimal patent length, and thus warrants correction through other policy levers—as discussed (briefly) below. *Infra* text accompanying note 566.

531. See *supra* note 174.

532. The nonobviousness standard of patentability, as applied to drug patents, is whether “there was a ‘reasonable expectation’ that the drug ‘would work for its intended purpose’ at the time it was invented and if there is inadequate ‘[e]vidence of unexpected results’ in the drug’s performance.” Roin, *Unpatentable Drugs*, *supra* note 18, at 532-33 (*quoting* Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1368-69 (Fed. Cir. 2007)).

533. Pharmaceutical companies usually file their patent applications as early as possible in the R&D process because if they delay, they risk allowing a competitor to patent the drug first, or that subsequent disclosures will

patents on closely related new uses are unlikely to extend significantly beyond the drug's original patent term.⁵³⁵

While the classic over-inclusiveness problem in patent law may not be a serious concern for new indications, there is a substantial risk of a different over-inclusiveness problem—firms may enforce their new-use patents without testing the patented indication in clinical trials. The primary justification for awarding enforceable monopoly rights over new indications is to motivate private sector investment in their clinical development.⁵³⁶ But there is no guarantee that the firms will invest in clinical trials to establish the patented indications' safety and efficacy, since they do not need that evidence to acquire or enforce the patent.⁵³⁷ If physicians are willing to prescribe the drug off-label for a patented indication without any supporting clinical-trial evidence, firms could earn significant revenues from a new-use patent without ever paying for clinical trials.⁵³⁸ The patentee might choose to invest in clinical trials anyway, since a positive outcome could boost sales for the new indication⁵³⁹ and justify fewer formulary restrictions and higher reimbursement rates from PBMs.⁵⁴⁰ But the more physicians are willing to prescribe a drug off-label for a new indication without supporting clinical-trial evidence, the less the patentee has to gain from a positive outcome in the trials, and the more it has to lose by risking a negative outcome that would jeopardize the drug's existing sales.⁵⁴¹ When off-label prescribing without clinical-trial evidence is common enough that patentees are unwilling to invest in clinical trials, the public will suffer the social costs of the patent monopoly without any corresponding benefit. This over-inclusiveness problem may warrant additional restrictions on firms' right to enforce patents claiming new indications, such as requiring clinical-trial evidence.

The current patentability standards also likely suffer from a serious under-inclusiveness problem for new indications, denying patent protection to many such treatments even though firms will not develop them without that protection. The patent laws are designed to reward and

undermine the drug's novelty or nonobviousness for purposes of patentability. See GARETH THOMAS, *MEDICINAL CHEMISTRY* 571 (2nd ed. 2007); GRAHAM L. PATRICK, *AN INTRODUCTION TO MEDICINAL CHEMISTRY* 257 (3d Ed. 2005); Richard A. Kaba et al., *Intellectual Property in Drug Discovery and Biotechnology*, in 2 BURGER'S *MEDICINAL CHEMISTRY & DRUG DISCOVERY* 706 (Donald J. Abraham ed., 6th 2003); EDWARD D. ZANDERS, *THE SCIENCE AND BUSINESS OF DRUG DISCOVERY: DEMYSTIFYING THE JARGON* 322-23 (2011).

534. See 35 U.S.C. § 154(a)(2).

535. At the latest, firms must file their new use patents for closely related indications just before the drug reaches the market, since the new use will not be a novel invention once physicians begin prescribing the drug for that purpose. See 35 U.S.C. § 102(a).

536. See *supra* Part II.E.

537. See *In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1324-25 (Fed. Cir. 2009).

538. See Berman & Melnick, *supra* note 173.

539. A positive outcome would lessen any doubts among physicians about the treatments safety and efficacy. See *supra* note 162 and accompanying text. Moreover, if the FDA approves the new indication, the patentee could market the treatment directly to physicians and patients to further increase sales. See *supra* note 164 and accompanying text.

540. See *supra* note 465.

541. See ELLERY & HANSEN, *supra* note 89, at 118 ("When assessing how much a potential tactic could increase the patient and sales potential of a brand ... [f]or indication expansions, the key question is what proportion of the potential target patients will already be using the drug 'off-label' and what the value of the label change to include the indication will really be."); Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 N. ENG. J. MED. 1427 (2008); Eisenberg, *New Uses*, *supra* note 13, at 718; Kapczynski & Syed, *supra* note 447.

protect the creation of new inventions, not their subsequent development or commercialization.⁵⁴² As a result, the mere disclosure of an idea for an invention may render it unpatentable for want of novelty or non-obviousness, even if the lack of protection will discourage others from developing that invention from an idea into a commercialized product.⁵⁴³ Researchers have already disclosed many potentially valuable new indications in published journal articles, albeit without any clinical-trial evidence to support their use in medical practice.⁵⁴⁴ Those disclosures are probably sufficient to render the new indications unpatentable.⁵⁴⁵ Some new indications may also be unpatentable under the inherent anticipation rules, since patients using the drug for its original indication may have unwittingly benefited from the new use.⁵⁴⁶ These gaps in the patent coverage for new indications weigh against relying exclusively on the patent system to encourage drug repurposing.⁵⁴⁷

The current patent term generates further—and potentially quite serious—over- and under-inclusiveness problems for new indications. Patents run for 20 years from their filing date.⁵⁴⁸ Since pharmaceutical companies file their patents early in R&D,⁵⁴⁹ they often lose a significant portion of their product’s patent life before it reaches the market.⁵⁵⁰ Drug-development projects that take longer to complete generally involve higher total R&D costs, and thus usually need a longer monopoly period to incentivize their development.⁵⁵¹ But the current

542. See Roin, *Unpatentable Drugs*, *supra* note 18, at 515-45.

543. See *id.*

544. See *supra* notes 331-339

545. See Ashburn & Thor, *supra* note 56, at 677-78 (noting that “because the candidate is usually not new to the scientific community, prior art might exist that can render a repositioned idea unpatentable”); Oprea & Mestres, *supra* note 9 (noting that the “[r]ecent academic enthusiasm in this field [of drug repurposing] has resulted in the publication of relatively long lists of drugs that could potentially be repurposed for a variety of indications,” but “[a]s this information is now public domain, even if experimentally confirmed, it still constitutes ‘prior art.’”). Cf. Roin, *Unpatentable Drugs*, *supra* note 18, at 515-44 (describing how the patentability standards deny protection to drugs that have not yet been tested in clinical trials based on prior disclosures of the idea for the drug).

546. See Roin, *Unpatentable Drugs*, *supra* note 18, at 525-26 (explaining that “[u]nder the doctrine of inherent anticipation, ... the disclosure of a drug in some unrecognizable form is still sufficient to invalidate a later filed patent on that drug because the prior ‘lack of knowledge [about the drug] is wholly irrelevant to the question of whether the ... patent claims something ‘new’ over the [earlier] disclosure.’”); *id.* at 553 (noting that the Patent and Trademark Office (PTO) would not grant a patent on a method of using finasteride (Proscar) to prevent prostate cancer because finasteride was already being used as a treatment for benign enlarged prostates, and anyone who used it for that purpose would inherently (albeit unknowingly) benefit from its chemopreventative effects) (*citing* *In re Gormley*, No. 1997-2801, 2001 WL 1049136, at *3, *3-4 (B.P.A.I. Jan. 1, 2001)).

547. Cf. *id.* at 557-60 & 564-568 (arguing that FDA-exclusivity periods are preferable to patent reform as a means to protect currently unpatentable drugs).

548. See 35 U.S.C. § 154(a)(2).

549. See *supra* note 533.

550. See Michael K. Dunn, *Timing of Patent Filings and Market Exclusivity*, 10 NATURE REV. DRUG DISCOVERY 487, 488 (2011); ZANDERS, *supra* note 533, at 322-23.

551. See Roin, *Drug Patent Length*, *supra* note 439, at 42-44 (arguing that drugs with longer R&D times typically need a longer patent term than drugs with shorter R&D times, since longer R&D times correspond to higher out-of-pocket expenses due to more extensive clinical trials, higher costs of capital because of the time-value of money, and reduced future sales revenues because of greater discounting); Budish et al., *supra* note 439; cf. Roin, *Case for Tailoring*, *supra* note 529, at 723-46 (arguing that inventions’ time-to-market is strongly correlated with their optimal patent strength).

patent system does the opposite, offering firms a variable monopoly period of a term inversely related to their product's development time.⁵⁵² As a result, treatments with lengthy R&D times are more likely to receive insufficient protection to motivate their development, while treatments with short R&D times are more likely to receive too much protection.⁵⁵³ Patent-term extensions partially offset this distortionary effect for new drugs,⁵⁵⁴ but those extensions are not available for new indications of FDA-approved drugs.⁵⁵⁵ Given the tremendous variance in R&D times for new indications,⁵⁵⁶ the over- and under-inclusiveness problems caused by the fixed patent-term could be substantial.

B. Over- and Under-Inclusiveness Problems in FDA-Exclusivity Periods for New Indications

In light of these limitations in the protection afforded by new-use patents, the government might want to rely on FDA-exclusivity periods in addition to (or instead of) the patent system to encourage investment in new indications for off-patent drugs. Federal law already grants firms a three-year data-exclusivity term over any new indication approved by the FDA, and a seven-year market-exclusivity term over new indications for orphan diseases.⁵⁵⁷ Unlike patents, which protect novel and nonobvious inventions for 20-years from the filing date,⁵⁵⁸ these FDA-exclusivity periods protect new medical treatments approved by the FDA based on clinical-trial evidence demonstrating their safety and efficacy, for a duration that runs from the date of FDA approval.⁵⁵⁹ Since the government grants monopoly protection over new indications (primarily) to motivate investment in clinical trials,⁵⁶⁰ FDA-exclusivity periods offer a tighter link between

552. See Roin, *Drug Patent Length*, *supra* note 439, at 44-46; Budish et al., *supra* note 439, at .

553. See Roin, *Drug Patent Length*, *supra* note 439, at 46-52; Budish et al., *supra* note 439. Numerous reports from the medical literature confirm that pharmaceutical companies shy away from drugs requiring lengthy clinical trials because they lose too much patent life before reaching the market. See, e.g., Jay Cohn et al., *Unconventional End Points in Cardiovascular Clinical Trials: Should We Be Moving Away from Morbidity and Mortality?*, 15 J. CARDIAC FAILURE 199, 201 (2009); Stephen I. Rennard, *The Many 'Small COPDs': COPD Should Be an Orphan Disease*, 134 CHEST 623 (2008); Tom Rooney, *Addressing the R&D Challenges*, at Facing the Future: Developing an EU Strategy on Alzheimer's, Sept. 21, 2011, available at <http://www.theparliament.com/fileadmin/theParliament/pdfs/ThomasRooney.pdf>; Rena Conti, *Balancing Safety, Effectiveness, and Public Desire: The FDA and Cancer*, ISSUE BRIEF #615, 2, April 2003; Frank L. Meyskens Jr. et al., *Regulatory Approval of Cancer Risk-Reducing (Chemopreventive) Drugs: Moving What We Have Learned into the Clinic*, 4 CANCER PREV. RES. 311 (2011); Zaven S. Khachaturian et al., *A Roadmap for the Prevention of Dementia: The Inaugural Leon Thal Symposium*, 4 ALZHEIMERS DEMENT. 156 (2008).

554. See Mossinghoff, *supra* note 13. Once their drug is approved in the U.S., firms can extend the term of their patent by the sum of (1) one-half of the time the firms spent testing the drug in clinical trials, and (2) the full amount of time the FDA spent reviewing their new drug application. However, the total amount of time added back to the patent life cannot exceed five years, and in no case can the extension result in the drug having an effective patent life of more than 14 years. See 35 U.S.C. § 156.

555. See *Photocure ASA v. Kappos*, 603 F.3d 1372 (Fed. Cir. 2010).

556. See Dudley et al., *supra* note 155, at 303 ("The drug development cycle for a repositioned drug can be as short as 3–12 years compared to the traditional 10–17 years required to bring a new chemical entity to market.").

557. See *supra* notes 221-222, and accompanying text.

558. See 35 U.S.C. §§ 102, 103 & 154(a)(2).

559. See *supra* notes 218-223, and accompanying text.

560. See *supra* Part II.E.

the criteria for granting monopoly protection and the justification for those awards.⁵⁶¹ That link is not perfect, however, and FDA-exclusivity periods therefore have their own over- and under-inclusiveness problems.

With their closer link between the eligibility criteria for receiving monopoly protection and the economic need for that protection, FDA-exclusivity periods avoid all three of the patent system's over- and under-inclusiveness problems discussed above. Since FDA-exclusivity periods only protect new indications once the FDA approves them, firms cannot take advantage of those monopoly rights over new indications without investing in clinical trials to establish their safety and efficacy. FDA-exclusivity periods also avoid the under-inclusiveness problem caused by patent law's novelty and nonobviousness requirements because they protect any new use developed in clinical studies, regardless of whether the ideas for those indications were previously disclosed to the public.⁵⁶² And since FDA-exclusivity periods provide monopoly rights that run from the FDA-approval date, they avoid the fixed patent-term distortion—which results in too much monopoly protection for treatments with shorter development times and too little protection for treatments with longer development times.⁵⁶³

However, FDA-exclusivity periods have three potentially important drawbacks relative to patent protection for new uses. First, they may suffer from patent law's classic over-inclusiveness problem—protecting inventions the public would receive anyway—because they cover any new indication approved by the FDA, including closely related indications that may not need or warrant costly clinical trials.⁵⁶⁴ To avoid this problem, the government might wish to condition regulatory-exclusivity periods for new indications on the indications being genuinely distinct from the original indication. Second, FDA-exclusivity periods for new indications will be under-inclusive because they only protect investments in clinical trials that satisfy the FDA's stringent safety and efficacy standards. Some indications have small markets that are unlikely to generate enough sales revenue to justify a full clinical-development program compliant with FDA requirements.⁵⁶⁵ FDA-exclusivity periods offer no incentive for firms to carry out less costly (and less rigorous) clinical-development programs for these indications, even though those studies could still provide useful information to guide treatment decisions. Third, the current 3-year exclusivity period for new indications might be too short to motivate investment in many drug-repurposing projects that require large or lengthy clinical trials, creating an additional under-inclusiveness problem. As this author has argued elsewhere, the government may want to tailor

561. See Roin, *Unpatentable Drugs*, *supra* note 18, at 565 (“[S]ince the FDA’s regulatory requirements are themselves what drive much of the need for protection in the pharmaceutical industry, linking the reward of exclusivity to successfully completing clinical trials is a sensible approach to promoting innovation.”).

562. Cf. *id.* at 564-68 (proposing that the government use “FDA-administered exclusivity periods [to] fill the gaps left by the novelty and nonobviousness requirements by guaranteeing and adequate period of market exclusivity to any drug that successfully completes the FDA’s clinical-trial requirements[,] ... since the FDA’s regulatory requirements are themselves what drive much of the need for protection in the pharmaceutical industry”).

563. See *supra* notes 548-556 and accompanying text.

564. See *supra* text accompanying notes 529-531.

565. See *supra* note 188.

the term of protection based on features indicative of the incentive required to motivate the new indication's development (*e.g.*, the size and duration of clinical trials).⁵⁶⁶

In addition to these three drawbacks, relying on regulatory-exclusivity periods to protect new indications would require additional government action beyond the reforms discussed in Part VIII. The existing regulatory-exclusivity periods operate against generic manufacturers, preventing them from listing any protected indications on their generic-drug label.⁵⁶⁷ Consequently, even after pharmaceutical companies can detect when pharmacists dispense an off-patent drug for a new indication, they could not enforce their regulatory-exclusivity periods against insurers, pharmacists or patients. The government could modify existing FDA-exclusivity periods to make them an enforceable monopoly right against insurers, pharmacists and patients. A simpler solution might be for the FDA to require pharmacists to dispense drugs with the appropriate label for their prescribed indication if that indication is covered by a regulatory-exclusivity period.⁵⁶⁸ Pharmacists would then need to dispense branded drugs when prescribed for newly approved indications, since generics cannot list those indications on their label while that exclusivity period is in force.⁵⁶⁹

X. CONCLUSION

[To be completed]

566. See Roin, *Drug Patent Length*, *supra* note 439; Budish et al., *supra* note 439; Roin, *Case for Tailoring*, *supra* note 529, at 751-53.

567. 21 C.F.R. § 314.108; *supra* notes 244-245 and accompanying text.

568. The FDA could probably implement such a change through regulation, avoiding any need for Congressional action. See *Pharmaceutical Mfrs Ass'n v. Food & Drug Admin.*, 484 F. Supp. 1179 (D. Del. 1980) (upholding FDA regulations requiring pharmacists to include patient package inserts (PPIs) containing safety information for certain estrogen-containing drugs) (*aff'd* 634 F.2d 106 (3d Cir. 1980)).

569. The FDA could also discourage (but not prohibit) generic substitutions for new indications with its therapeutic equivalence codes by not listing any generic bioequivalents to brand-name drugs when prescribed for a new indication protected by a FDA-exclusivity period. Cf. Mahn, *supra* note 240.