

SOLVING THE PROBLEM OF NEW USES

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Abstract

Among the most pronounced 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. Unfortunately, there is no viable business model to support drug repurposing at present. Pharmaceutical companies invariably lose interest in developing new uses for drugs once generics enter the market because they cannot prevent patients from taking the generic version for the new indication. 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. The real problem is that 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 about impediments to price discrimination. Firms cannot prevent arbitrage between the markets for a drug’s different indications. Once the problem of new uses is reframed in this light, the solution becomes obvious. Health insurers have already developed a fairly effective system for observing indications when physicians prescribe drugs with multiple uses – known as “prior authorization.” If pharmaceutical companies had access to this same information, they could enforce their new-use patents on new indications, and thus would have an incentive to develop new uses for off-patent drugs.

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I. INTRODUCTION

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 While the industry struggles to deliver an average of 27 new drugs to the market annually through its massive R&D investments,³ there are approximately 2,000 off-patent drugs already on the market.⁴ Over the past few years,

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. 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)).

4. As of 2012, there were 2,356 distinct FDA-approved drug compounds (NMEs). See Huang et al., *supra* note 21, at 80ps16. Since the FDA approves has approved 27 NMEs on average each year since 2000, see Munos, *supra* note 3, and the average effective patent life for a new drug is about 12 years, see *infra* note 67, it is likely that between 300 and 350 of those NMEs are probably still under patent protection.

researchers have uncovered hundreds of potential new indications for these older drugs.⁵ There is evidence that the therapeutic value of new uses for existing drugs is usually on par with the value of original indications.⁶ There is a growing consensus among experts that testing old drugs for new uses (“drug repurposing”)⁷ is one of the most promising avenues for developing new medical treatments⁸—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.”⁹ The public generally foregoes these benefits unless someone tests the safety and efficacy of the potential new indications in clinical trials.¹⁰ Clinical trials are costly,¹¹ and the government offers limited funding for such studies.¹² The public primarily relies on private industry to pay for clinical trials of potential new medical treatments,¹³ particularly the expensive late-stage clinical trials necessary to complete a new treatment’s development.¹⁴ At present, pharmaceutical companies have little or no incentive to repurpose existing drugs once generics are available.¹⁵ This well-known gap in the incentives for pharmaceutical innovation¹⁶—known as “the problem of new uses”¹⁷—causes most (and perhaps

5. See *infra* notes 297-309 and accompanying text.

6. 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).

7. The National Institutes of Health (NIH) defines “repurposing” as “studying drugs that are already approved to treat one disease or condition to see if they are safe and effective for treating other diseases.” National Center for Advancing Translational Sciences, NIH, *What is Drug Repurposing?*, at <http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/rescue-repurpose.html> (last accessed Feb. 4, 2016).

8. 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 310-328 and accompanying text.

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

10. See JERRY AVORN, POWERFUL MEDICINES: THE BENEFITS, RISKS, AND COSTS OF PRESCRIPTION DRUGS 39-68 (2004) (discussing the importance of evaluating new treatments in clinical trials to inform medical practice); *infra* notes 155-165 and accompanying text.

11. *Infra* Part II.D.

12. 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 II.E.

13. 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 177.

14. See *infra* notes 185-188, and accompanying text.

15. See *infra* Part III.

16. See INSTITUTE OF MEDICINE (IOM), DRUG REPURPOSING AND REPOSITIONING: WORKSHOP SUMMARY (hereinafter (DRUG REPURPOSING) 26-27, 36 & 46-47 (2014); Christopher P. Austin, *Systematic Drug Repurposing*:

almost all) of these potential new medical treatments to remain untested hypotheses.¹⁸ Experts widely agree that this public-policy failure should be corrected,¹⁹ but thus far have been unable to identify a viable solution.²⁰

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.²¹ The new screening tools uncovered a wealth of potential treatments for unmet medical needs hidden within our existing arsenal of FDA-approved drugs.²² These findings have generated significant interest within the biomedical research community about the

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 12, 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); 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).

17. Eisenberg, *New Uses*, *supra* note 16.

18. See Oprea & Mestres, *supra* note 12.

19. NIH officials have called for “a new funding paradigm” to support repurposing generic drugs. Austin, *supra* note 16 at 19; see also Weir et al., *supra* note 12, 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 16, 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 16, at 73 (reserving judgment on specific reform proposals).

20. See *infra* notes 76-82, and accompanying text.

21. See *infra* notes 292-293, and accompanying text; Francesco Iorio, *Genome-Based Drug Discovery and Re-Purposing: 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).

22. See *infra* notes 297-309, and accompanying text; Oprea & Mestres, *supra* note 12 (“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 21.

possibility of repurposing existing drugs for new indications.²³ There is hope that developing new uses for existing drugs could help “convert cancer into a treatable chronic disease.”²⁴ 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.”²⁵ Furthermore, some experts believe that drug repurposing offers the best chance in the near-term to discover effective treatments for Alzheimer’s disease and many other central nervous system disorders.²⁶

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”).²⁷ Developing a new drug is a massive financial undertaking, costing an estimated \$1.2 billion²⁸ and taking 12 to 16 years on average.²⁹ Roughly one-third to one-half of

23. 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 IV.A.

24. 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 298.

25. 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.”).

26. 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 23 (“Repurposing drugs is particularly important in the treatment of CNS disorders, CVD, metabolic disorders, and cancer.”).

27. See Boguski et al., *supra* note 16; Barratt & Frail, *supra* note 8, 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).

28. 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*

the total cost is attributable to the drug-discovery and preclinical-development stages, with the remainder attributable to clinical development and FDA approval.³⁰ 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 the early clinical trials.³¹ Consequently, drug repurposing reportedly costs only \$300 million on average and takes between 3 and 12 years.³² Drug repurposing also has a significantly higher success rate than developing a new drug – 30% versus 10% – because of the greater information available to firms about the pharmacological properties of FDA-approved drugs.³³ 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.³⁴ Firms could also pursue treatments for smaller

‘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.

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

30. See DiMasi & Grabowski, *supra* note 28, 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 28, at 206; cf. THOMSON REUTERS, 2012 CMR INTERNATIONAL PHARMACEUTICAL R&D FACTBOOK: EXECUTIVE SUMMARY fg. 5 (2012) (reporting that the distribution of R&D costs between preclinical research (including drug discovery) and clinical research varies by therapeutic class).

31. See Corbett et al., *supra* note 26 (“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 312-314, and accompanying text.

32. See *infra* notes 169 & 319.

33. 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 320-328, and accompanying text.

34. 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” that underlie 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.”).

markets that would otherwise be unprofitable,³⁵ and they could rapidly deliver these new medical treatments to patients in need.³⁶

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.³⁷ 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).³⁸ Pharmaceutical companies rely on their medicinal chemists to create compounds that can be safely administered to humans at a therapeutically effective dose.³⁹ 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.⁴⁰ Researchers synthesize and evaluate thousands of novel drug compounds

35. 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.”).

36. See Huang et al., *supra* note 21 (“[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.”).

37. 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 ...”).

38. See Bennani, *supra* note 37, 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 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.”).

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

40. *Overcoming Bottlenecks in Drug Discovery*, *supra* note 38, at 8; see also Bennani, *supra* note 37, at S36 (“[T]he field is still plagued by clinical idiosyncratic toxicities.”); Kaitin, *supra* note 37, 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. Winkler et al., *The Fall and Rise of Pharmacology—(Re-)defining the Discipline?*, 87 CLINICAL PHARMACOLOGY 4 (2014).

to find a handful worthy of testing in clinical trials.⁴¹ 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.⁴² Many of these failures trace back to problems with drugs' chemical structures.⁴³ 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.⁴⁴

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.⁴⁵ Advances in molecular biology and genomics now permit researchers to identify the distinct molecular causes for human diseases.⁴⁶ These discoveries offer extraordinary opportunities to develop new treatments for unmet medical needs by identifying new molecular targets for therapeutic intervention.⁴⁷ Since the public sector generally lacks the resources and capacity to engineer novel drug compounds and complete their preclinical development,⁴⁸ the public largely relies on

41. See GAO, *supra* note 29, 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).

42. 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).

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

44. See Oprea & Mestres, *supra* note 12, 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.”).

45. See *infra* Part IV.C.

46. See Winquist et al., *supra* note 40, at 10-17; Francis S. Collins, *Reengineering Translational Science: the Time is Right*, 3 SCI. TRANSLATIONAL MED. 90cm17, at 1-2 (2011) (hereinafter, *Translational Science*).

47. See Collins, *Translational Science*, *supra* note 46, at 2.

48. 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 41, 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 25; 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*

private industry to carry out this research.⁴⁹ 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.⁵⁰ Consequently, preclinical R&D has become known as the “valley of death” in pharmaceutical innovation⁵¹—“the gap in drug development between where NIH-funded research typically leaves off and industry development begins.”⁵² A recent Institute of Medicine (IOM) 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.”⁵³ Indeed, of the approximately 4000 medical conditions with defined molecular causes, only 200 currently have drugs available to treat them.⁵⁴ Many commentators believe that testing old drugs against these new therapeutic targets is the best way to overcome this problem.⁵⁵ Public-sector researchers are already using the new screening technologies discussed above to find existing drugs that may be effective against a new target.⁵⁶ The NIH generally cannot afford the expensive late-stage clinical trials needed to establish a new treatment’s safety

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 38.

49. 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.”).

50. See Collins, *Translational Science*, *supra* note 46, 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).

51. 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).

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

53. 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.”).

54. 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-Hunt--Translational-Research-Feature/biotechniques-327542.html>; cf. Collins, *Translational Science*, *supra* note 46, at 2.

55. See, e.g., Hemphill, *supra* note 16, 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*); C.M. Colvis et al., *Partnering for Therapeutics Discovery*, 93 CLINICAL PHARMACOLOGY & THERAPEUTICS 24, 25 (2013).

56. See *supra* note 21-22 and accompanying text.

and efficacy.⁵⁷ 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),⁵⁸ and then attract an industry sponsor to finance the more expensive late-stage trials.⁵⁹

Unfortunately, there is no viable business model for repurposing old drugs at present.⁶⁰ The pharmaceutical industry, perhaps more than any other industry, depends on legal barriers to imitation to generate a return on its R&D investments.⁶¹ 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.⁶² With minimal R&D expenses, generic manufacturers sell their products for 15% to 25%

57. See *infra* notes 176-191, and accompanying text; Colvis et al., *supra* note 55, 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”).

58. See Muthyala, *supra* note 25; 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).

59. 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 12, 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 as an example the use of auranofin to treat chronic lymphocytic leukemia); Collins, *Better Drugs*, *supra* note 34.

60. See, e.g., Weir et al., *supra* note 12, 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 16, 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.”).

61. Pharmaceuticals is one of the few industries about which patent scholars widely agree that firms rely 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).

62. 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.”).

of the brand-name drug's price on average,⁶³ and usually capture 70% to 80% of the market within one to six months of launching.⁶⁴ 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. Legislators created a sui generis legal framework of drug patents and FDA-exclusivity periods to provide this protection⁶⁵ – the Drug Price Competition and Patent Term Restoration Act of 1984 (“Hatch-Waxman Act”).⁶⁶ Under this system, pharmaceutical companies usually enjoy 10 to 15 years of monopoly protection on their new drugs following FDA approval (12.5 years on average) before generics enter.⁶⁷ Once generics are on the market, it is nearly impossible for pharmaceutical companies to maintain an exclusive marketing position to recoup investments in clinical trials.⁶⁸ Pharmaceutical companies therefore have little incentive to invest in clinical trials testing new uses for off-patent drugs.⁶⁹ Since the 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.⁷⁰

The NIH's leadership is well aware of the need to compensate for industry's unwillingness to test new uses for off-patent drugs with public funding those clinical trials.⁷¹ Despite its limited clinical-research budget, the NIH has always used some of that funding for clinical trials on new indications.⁷² But its budget is far too small to support a large-scale drug-

63. 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.

64. See Rich Silver, *A Wall Street Perspective on Generics*, 2007 GPhA Annual Meeting, Phoenix, Mar. 1-3, 2007, at 6; Datamonitor, *US Most Susceptible to Brand Erosion Post Patent Expiry*, Jan. 13, 2011, at <http://about.datamonitor.com/media/archives/5293>.

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

66. 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).

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

68. See *infra* Part III.C & III.D; Austin, *supra* note 16, at 16 (“Difficulties in establishing exclusivity for approved drugs has deterred industry from drug repurposing.”).

69. See *supra* note 16.

70. See PCAST, *supra* note 16, 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: 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 275-279.

71. See Austin, *supra* note 16, at 19.

72. See INSTITUTE OF MEDICINE (IOM), *IMPROVING THE QUALITY OF CANCER CLINICAL TRIALS: WORKSHOP SUMMARY* 78-79 (2008) (hereinafter “CANCER CLINICAL TRIALS”) (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). IOM, *CANCER CLINICAL TRIALS*, *supra* note 72, at 75

repurposing program on top of its existing core research commitments.⁷³ 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.⁷⁴ As a result, members of the NIH leadership have become some of the loudest voices calling for policy reforms that will incentivize pharmaceutical companies to investment in drug repurposing.⁷⁵

Despite significant attention from experts in the field,⁷⁶ the prior literature on the problem of new uses offers few suggestions for solving it.⁷⁷ Rebecca Eisenberg ends her 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 patients is thus a major challenge for the legal system.”⁷⁸ The President’s Council of Advisors on Science and Technology notes that although the government could use a variety of different incentive mechanisms to promote drug repurposing (including patent extensions, longer FDA-exclusivity periods, and advanced market commitments),⁷⁹ they all have significant drawbacks, and finds that “there is currently insufficient knowledge on which to base wise policy decisions.”⁸⁰ Nature’s editorial board issued a call for us to find a way to “protect investments used to find new uses for old drugs,” describing the problem as “a difficult conundrum ... that warrants serious thought and creativity from researchers, agencies and policy-makers alike.”⁸¹ Likewise, an IOM report states that “[a]n alternative intellectual property approach may be needed” to

73. See *infra* notes 176-191, and accompanying text.

74. See *infra* notes 185-187, and accompanying text.

75. See Weir et al., *supra* note 12, at 1057 (noting that “New paths to exclusivity and pricing/reimbursement strategies [for repurposed drugs] are needed to promote private sector engagement.”); Austin, *supra* note 16 at 19 (calling for “a new funding paradigm” to support repurposing generic drugs).

76. See, e.g., Eisenberg, *supra* note 16; Rai, *supra* note 16; Grabowski, et al., *supra* note 16; Milne & Bruss, *supra* note 16; Hemphill, *supra* note 16; Walson, *supra* note 2; Gelijns et al., *supra* note 16; Boguski et al., *supra* note 16; *Change of Purpose*, *supra* note 16; Weir et al., *supra* note 12; Chong & Sullivan, *supra* note 58.

77. See *supra* note 108, 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 16. 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.

78. Eisenberg, *New Uses*, *supra* note 16, at 739; cf. Hemphill, *Repurposing Pharmaceuticals*, *infra* note 91, at 1250016-4 n.7. Likewise, Arti Rai seemingly gives up on creating incentives for private industry to repurpose off-patent drugs, and instead calls for the government to fund that research directly, despite the grim outlook for public sector clinical-research funding. Rai, *supra* note 16, at 492; see also Darren R. Flower, *Pharmacovigilance, Drug Repositioning, and Virtual Screening*, 1 J. PHARMACOVIGILANCE e103 doi:10.4172/2329-6887.1000e103 (2013) (noting that for repurposing off-patent drugs, “[t]he Pharmaceutical Industry is reluctant to invest in such undertakings without water-tight patent protection, perhaps necessitating public- private finance initiatives.”).

79. See PCAST, *supra* note 16, at 25.

80. *Id.* at 73

81. *Change of Purpose*, *supra* note 16, at 267 & 268.

incentivize investment in off-patent drugs, but does not specify how such a system might operate.⁸²

The existing literature on the problem of new uses generally frames it as a gap in the patent protection and FDA-exclusivity periods for drugs.⁸³ Pharmaceutical companies rely on temporary monopoly rights to block generics from the market for long enough to recoup their R&D investments.⁸⁴ But the government only offers monopoly protection capable of blocking generic entry as an incentive to develop new drugs.⁸⁵ Those rights normally expire from ten to fifteen years after the new drug launched.⁸⁶ 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.”⁸⁷ With few exceptions,⁸⁸ 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.⁸⁹ 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.⁹⁰ The literature 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. When discussing the inadequate incentives for drug repurposing, therefore, the literature attributes the problem to legal rules preventing firms from delaying generic entry as a reward for developing new uses for FDA-approved drugs.⁹¹

82. IOM, DRUG REPURPOSING, *supra* note 16, at 47. The IOM report briefly mentions “therapeutic only” exclusivity—which would offer FDA-exclusivity periods for new indications without blocking generic sales for drugs’ other uses, much like a new-use patent—as a possible strategy for promoting investment in off-patent drugs. *Id.* The report does not discuss how firms might enforce those exclusionary rights over new indications without observing when physicians prescribe old drugs for their new uses.

83. See Boguski et al., *supra* note 16, 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 16 (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 16, at 720-35; Mossinghoff, *supra* note 16, 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 16, 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]”).

84. See *infra* notes 61-64, and accompanying text.

85. See *infra* notes 207-255, and accompanying text.

86. See *supra* note 67, and accompanying text.

87. Eisenberg, *New Uses*, *supra* note 16, at 720.

88. See *infra* notes 245-246, and accompanying text.

89. See *infra* notes 234-255, and accompanying text.

90. See Eisenberg, *New Uses*, *supra* note 16, at 729.

91. See Eisenberg, *supra* note 16, at 720-30; Rai, *supra* note 16, at 491-92; Thomas A. Hemphill, *Repurposing Pharmaceuticals: Does United States Intellectual Property Law and Regulatory Policy Assign*

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—misidentifies the problem’s underlying cause. Legislators have good reason to withhold this type of monopoly protection as a reward for drug repurposing.⁹² 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.⁹³ 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.⁹⁴ Since monopoly rights that block generic entry are not the appropriate 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.⁹⁵ 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.⁹⁶ The government routinely grants method-of-use patents over newly discovered indications for FDA-approved drugs (“new use patents”).⁹⁷ These rights ostensibly provide the patentee with a monopoly over the act of taking or administering the existing drug for the new indication.⁹⁸ 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.⁹⁹ Since physicians do not disclose the indications for their prescriptions to pharmaceutical companies,¹⁰⁰ they rarely have access to the information needed to enforce new use patents if generics are available.¹⁰¹

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

Sufficient Value to New Use Patents?, 16 INT’L J. INNOVATION MANAGEMENT 1250016-1, 1250016-4 n.7 (2012); SAHOO, *supra* note 70, at 63; ELLERY & HANSEN, *supra* note 70, at 126.

92. *See infra* Part III.B.

93. *See infra* note 237, and accompanying text.

94. *See infra* notes 234-235, and accompanying text.

95. *See infra* Part III.C.

96. *See infra* notes 259-265, and accompanying text.

97. *See infra* notes 217-224, and accompanying text.

98. *See* THOMAS, *supra* note 65, at 44-46, 235-37.

99. *See* Grabowski et al., *supra* note 16, at 382.

100. *See id.*

101. *See infra* notes 262-265, and accompanying text.

patent system.¹⁰² 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 are prescribing a drug for its new or old use, they cannot enforce monopoly rights specific to that 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.¹⁰³

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.¹⁰⁴ 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.¹⁰⁵ 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.¹⁰⁶ The existing literature overlooks this underlying information problem, focusing instead on potential fixes to the legal protection

102. See *supra* note 83.

103. 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 16, 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 16, 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.”); Hemphill, *Repurposing Pharmaceuticals*, *supra* note 91 (“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 16, 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 70, 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 16, 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.”).

104. 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).

105. See Benjamin N. Roin, *Intellectual Property versus Prizes: Reframing the Debate*, 81 U. CHI. L. REV. 999, 1058 (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).

106. See *infra* Part V.

for new indications.¹⁰⁷ Not surprisingly, scholars have had trouble coming up with solutions, and usually end up portraying the problem of new uses as intractable.¹⁰⁸

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, affecting the market for patented drugs as well.¹⁰⁹ Ultimately, the problem of new uses is about pharmaceutical companies' inability to separate the markets for a drug's different indications with price discrimination. 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.¹¹⁰ 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.¹¹¹ 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, preventing some patients from gaining access to the treatments.¹¹²

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 tool for

107. 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 16, at 720-30; Gelijns et al., *supra* note 16 (“[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 16, 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 16, 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”).

108. See *supra* notes 76-82, and accompanying text.

109. See *infra* Part VI.

110. See *infra* note 398.

111. See *infra* notes 402-406, and accompanying text.

112. See *infra* notes 407-413, and accompanying text.

observing prescribed indications—their “prior authorization” systems.¹¹³ Most insurers limit their coverage for individual prescription drugs to a specified set of indications.¹¹⁴ PBMs use prior authorization 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.¹¹⁵ Since PBMs have access to patients’ health records, they can discourage physicians from fraudulently reporting indications by occasionally reviewing those records to verify reported diagnoses.¹¹⁶ Although this system is not foolproof,¹¹⁷ 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 have “had great success at preventing payments for drugs not provided for medically accepted indications by using prior authorization when permitted.”¹¹⁸ 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 temporary monopoly rights over new uses.¹¹⁹

113. See *infra* notes 420-427, and accompanying text.

114. See *infra* note 409.

115. *Id.*

116. See *infra* note 448, and accompanying text.

117. See *infra* note 447, and accompanying text.

118. 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).

119. 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>; Benjamin Roin, *Solving the Problem of New Uses*, Duke Law School Center for Innovation Policy, New Approaches and Incentives in Drug Development, Washington, D.C., Nov. 22, 2013, at http://law.duke.edu/sites/default/files/centers/cip/newapproachesconference/Duke-Law-CIP_22Nov13_P3b_Roin.pdf; Center for Innovation Policy, *New Approaches & Incentives in Drug Development, Panel 4*, at <http://www.youtube.com/watch?v=UKVP24pV4ZI>. 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.

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 reviews the recent scientific and industry literatures 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 V argues that the problem of new uses ultimately stems from information barriers that prevent pharmaceutical companies from observing prescribed indications, and that these information barriers are also an impediment using alternative incentive mechanisms (such as prizes) to promote drug repurposing. The inability to observe utilization rates for new indications even a problem for government funding for repurposing trials. Part VI recasts the problem of new uses as the outcome of impediments to differential pricing by indication, and argues that this broader problem also likely affects the market for patented drugs. Part VII outlines a possible solution to the information barriers underlying the problem of new uses based on existing prior-authorization systems. If implemented, this system would allow pharmaceutical companies to price discriminate by indication and to enforce their new-use patents (and possibly their FDA-exclusivity periods) on off-patent drugs, thereby creating incentives for drug repurposing. Part VIII examines some potential shortcomings in the existing patent laws and FDA-exclusivity periods as an incentive system for drug repurposing, and it discusses possible corrective measures. Part IX 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.¹²⁰ Scholars often explicitly assume that the discovery and development of novel drug compounds (i.e., NMEs) is the only important form of pharmaceutical innovation.¹²¹ 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.¹²² The available evidence suggests that the public receives substantial benefits from

120. 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).

121. See Berndt, et al., *Impact of Incremental Innovation*, *supra* note 6, 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.”).

122. See *infra* Part II.A.

industry's efforts to develop new indications for existing drugs.¹²³ However, many of these potential new indications are discovered long after pharmaceutical companies first developed the drugs.¹²⁴ The FDA does not prohibit physicians from prescribing older drugs off-label for new indications,¹²⁵ but without clinical-trial evidence to support those new uses, physicians and payers are much less likely to accept them as appropriate medical treatments.¹²⁶ 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,¹²⁷ and the government offers little funding to support those experiments.¹²⁸ Pharmaceutical companies could provide that funding, but their investments would be highly vulnerable to free riding by generics.¹²⁹ Consequently, 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.¹³⁰ Although some of these potential new indications are closely related to the original FDA-approved use,¹³¹ others involve the treatment of unrelated diseases.¹³² For example, the drug Tarceva (erlotinib) was originally developed to treat non-small-cell lung cancer¹³³ but subsequently approved for pancreatic cancer,¹³⁴ and is currently being tested for

123. See *supra* note 6.

124. See *infra* Part II.B.

125. See *infra* note 155, and accompanying text.

126. See *infra* Part II.C.

127. See *infra* Part II.D.

128. See *infra* Part II.E.

129. See *infra* Part II.F.

130. 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).

131. See ELLERY & HANSEN, *supra* note 70, at 123-30; SAHOO, *supra* note 70, 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.

132. See SAHOO, *supra* note 70, at 66-85.

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

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

breast and ovarian cancers.¹³⁵ 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.¹³⁶

Tarceva is not unusual in this regard.¹³⁷ Although pharmaceutical companies specifically engineer and test new drugs to treat a particular condition, their biological effects are complex and multidimensional.¹³⁸ The vast majority of drug compounds operate by targeting biological pathways that affect the progress or symptoms of a range of diseases,¹³⁹ and almost all drugs have “off-target” activity on other biological pathways that may affect a different set of diseases.¹⁴⁰ Consequently, drugs designed to treat one disease commonly have potential new indications for treating one or more entirely different conditions.¹⁴¹ According to some

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

136. 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).

137. 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).

138. 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 22, at 175 (reporting that “several lines of evidence suggest that drugs may have many physiological targets.”).

139. 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).

140. 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.”).

141. 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)); Prashant Nair, *Drug Repurposing Gets a Boost as Academic Researchers Join the Search for Novel Uses of Existing Drugs*, 110 PNAS 2430, 2431 (2013) (“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.

estimates, approximately 90 percent of FDA-approved drugs have one or more secondary indications.¹⁴²

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.¹⁴³ However, at the time pharmaceutical companies are initially developing their new drugs, they may recognize only a small fraction of the drugs' possible indications.¹⁴⁴

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,¹⁴⁵ including medical practice, where clinicians frequently identify potential new uses for drugs as they prescribe them.¹⁴⁶ Clinicians sometimes stumble upon these indications inadvertently, such as when patients report that a drug helped resolve an entirely unrelated condition.¹⁴⁷ In other cases, clinicians discover the new indications through deliberate experimentation, most often while attempting to treat patients for conditions without established therapies.¹⁴⁸

Researchers have also become increasingly adept at finding potential new indications for drugs, often by using scientific knowledge or technologies unavailable to pharmaceutical

142. See Gupta et al., *supra* note 24, 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 16.

143. See ELLERY & HANSEN, *supra* note 70, at 123 (2012).

144. See Gelijns et al., *supra* note 16 (“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. Jack W. Scannell et al., *Diagnosing the Decline in Pharmaceutical R&D Efficiency*, 11 NAT. REV. DRUG DISCOVERY 191, 197 (2012) (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”).

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

146. 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 16; Scannell et al., *supra* note 144, 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.”).

147. 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 33, 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.”).

148. See, e.g., Demonaco et al., *supra* note 146; Scannell et al., *supra* note 144; Tewodros Eguale et al., *Drug, Patient, and Physician Characteristics Associated with Off-Label Prescribing in Primary Care*, 172 ARCH. INTERNAL MED. 781 (2012).

companies at the time they developed those products.¹⁴⁹ 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.¹⁵⁰ These insights can reveal a drug's propensity to hit distinct biological targets that may affect other diseases.¹⁵¹ Scientific advances are continually revealing previously unknown commonalities in the underlying pathways for seemingly unrelated diseases, suggesting that treatments effective for one might work for the other.¹⁵² 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.¹⁵³

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

Clinical trials are an important stage in the development of new medical treatments. They help to separate the wheat from the chaff in medicine, which is valuable because most new treatments that seem promising in the laboratory or based on anecdotal experiences prove ineffective when tested.¹⁵⁴ The FDA requires extensive clinical trials demonstrating a new drug's safety and efficacy for at least one indication before that drug can enter the market. Once the FDA approves a new drug for a particular indication, physicians may prescribe it off-label for other uses, even without any supporting clinical-trial evidence.¹⁵⁵ But providing that evidence may still be important. Clinical trials testing the safety and efficacy of new uses for existing

149. 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 22 ("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.").

150. Cf. Oprea & Mestres, *supra* note 12 ("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.").

151. 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 (2009); Mizushima, *supra* note 147, at 499; Oprea & Mestres, *supra* note 12, 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.").

152. See, e.g., Csermely et al., *supra* note 139, 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.)").

153. See *infra* notes 292-296, and accompanying text (describing how researchers have recently identified hundreds of potential new indications for drugs through in silico screening technologies).

154. See *supra* note 42.

155. 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.*

drugs are likely to increase the utilization of therapeutically beneficial new uses and decrease utilization for new uses that are either unsafe or ineffective.¹⁵⁶

Many potential new uses for existing drugs are unlikely to work their way into medical practice without supporting clinical-trial evidence. Although the FDA does not prohibit physicians from prescribing drugs for unapproved indications, it does prohibit pharmaceutical companies from marketing their drugs for any such off-label uses.¹⁵⁷ 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.¹⁵⁸ Physicians would be especially unlikely to learn of new indications discovered by researchers through laboratory experimentation, since those experiments tend to be reported in specialty scientific journals that are primarily read by researchers, not physicians. Even if physicians are aware of a potential new indication, they may be reluctant to prescribe it,¹⁵⁹ particularly if it is a treatment for an entirely different disease than the drug's original indication. Insurer's coverage restrictions can also deter physicians from prescribing drugs for untested off-label uses,¹⁶⁰ as can the threat of tort liability.¹⁶¹

In some cases, physicians learn of a potential new use for an existing drug and are willing to prescribe it without any supporting evidence from clinical trials.¹⁶² However, this type of

156. See Gelijns et al., *supra* note 16; 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).

157. 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).

158. See Grabowski, et al., *supra* note 16, 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 61, 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.").

159. 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).

160. See *supra* note 118; Murray Aitken et al., *Prescription Drug Spending Trends in the United States: Looking Beyond the Turning Point*, 28 HEALTH AFFAIRS w151 (2008); P.G. Casali, *Executive Committee of ESMO: the Off-Label Use of Drugs in Oncology*, 18 ANNALS ONCOLOGY 1923, 1924 (2007) ("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 Wright, *supra* note 118, at 2-3 & 5.

161. See Casali, *supra* note 160, at 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).

162. 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).

prescribing is often thought to be problematic.¹⁶³ Some of these untested indications are probably beneficial to patients, but others are probably ineffective or even harmful.¹⁶⁴ There are constant calls for increased funding to test these medical treatments in clinical trials,¹⁶⁵ and some experts argue that the government should take action to discourage physician prescribing of untested off-label uses.¹⁶⁶

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.¹⁶⁷ At the very least, these development programs

163. See Aaron S. Kesselheim, *Off-Label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J. L. & MED. 225, 234-237 (2011); Casali, *supra* note 160; 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 141, 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.”).

164. See Rosoff & Coleman, *supra* note 163, at 653.

165. See Casali, *supra* note 160; 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 141. 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 163, at 1436.

166. See, e.g., Rosoff & Coleman, *supra* note 163 at 656 (calling for government restrictions of off-label prescribing that is not supported by high-quality evidence of safety and efficacy).

167. See Tudor I. Oprea et al., *Drug Repurposing from an Academic Perspective*, 8 DRUG DISCOVERY TODAY THERAPEUTIC STRATEGY 61, 61 (2011). FDA regulations for clinical trials significantly increase the administrative costs of those studies with requirements for additional testing, recordkeeping, and reporting. See IOM, CANCER CLINICAL TRIALS, *supra* note 72, 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). Putting together an application for FDA approval of a new indication is also very costly. See Mark Hovde, *Management of Clinical Development Costs*, in CLINICAL TRIALS OF DRUGS AND BIOPHARMACEUTICALS 90 (Chi-Jen Lee et al. eds. 2006). The filing fee alone for these applications is over \$1 million. See Department of Health and Human Services, Prescription Drug User Fee Rates for Fiscal Year 2014, 78 Fed. Reg. 46980, 46981 (proposed Aug. 2, 2013).

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 much less reliable than the ones used to support FDA approval for a new indication. See Harold C. Sox, *Evaluating Off-Label Uses of Anticancer Drugs: Time for a Change*, 150 ANNALS INTERNAL MED. 353, 354 (2009). The FDA forces sponsors to conduct more rigorous trials. See IOM, CANCER CLINICAL TRIALS, *supra* note 72, at 78-79. 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. 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*

involve running phase III studies on the new indication.¹⁶⁸ 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.¹⁶⁹ In some cases, firms may also be required to complete phase I and II trials.¹⁷⁰ Although developing a new use for an existing drug is much less expensive and risky than developing a new drug,¹⁷¹ total costs often still run in the hundreds of millions of dollars.¹⁷²

E. Inadequate Government Funding for Drug-Repurposing Trials

The NIH 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 private industry.¹⁷³ 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. Opinions differ over the NIH’s competency relative to private industry at identifying the most promising drugs to test in clinical trials and performing that research.¹⁷⁴ But the available

Source and Conclusion Among Nutrition-Related Scientific Articles, 4 PLoS Med. e.5 (2007). Consequently, many medical experts express a strong preference for sponsors to complete the FDA-approval process for new indications of drugs, although the costs can make it impractical for indications with small markets. See Ratner & Gura, *supra* note 130, 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”).

168. See Oprea & Mestres, *supra* note 12, 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).

169. See ELLERY & HANSEN, *supra* note 70, at 124; SAHOO, *supra* note 70, 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.”).

170. See Chong & Sullivan, *supra* note 58, at 646.

171. See *supra* notes 27-36 and accompanying text.

172. See *supra* note 169; SAHOO, *supra* note 70, 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.”).

173. See *supra* note 48, and accompanying text.

174. 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 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.”).

empirical studies still point to large social returns from the agency's past clinical-research programs, suggesting that further NIH efforts to repurpose old drugs would be beneficial.¹⁷⁵

Regardless, Congress does not provide enough clinical-research funding for the NIH to sustain a meaningful drug-repurposing program.¹⁷⁶ The government invests about one-tenth of what the pharmaceutical industry invests in drug trials.¹⁷⁷ 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.¹⁷⁸ 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.¹⁷⁹ Moreover, the demand for NIH funding is continually increasing relative to the supply in all of these fields,¹⁸⁰ since advances in medical science seem to 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.¹⁸¹

175. 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).

176. 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>.

177. 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/crro/files/2010/01/Vragovic-6-17-09.pdf>.

178. See Nelson, *supra* note 176 (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 41, at 11; IOM, TRANSFORMING CLINICAL RESEARCH IN THE UNITED STATES: CHALLENGES AND OPPORTUNITIES: WORKSHOP SUMMARY 21 (2010) (hereinafter “TRANSFORMING CLINICAL RESEARCH”); Charlie Schmidt, *Cooperative Groups Say NCI Trials Funding Inadequate; Some Turn to Industry*, 99 J. NAT'L CANCER INST. 830;

179. See IOM, TRANSFORMING CLINICAL RESEARCH, *supra* note 178, 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).

180. 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).

181. 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).

Despite countless calls for the government to increase the NIH's funding for clinical research, the trend runs sharply in the other direction.¹⁸² The NIH's budget fell by 20% in real dollars between 2003 and 2013,¹⁸³ forcing drastic cuts in the number of NIH-funded research projects.¹⁸⁴ These budget cuts have been particularly detrimental to the public sector's capacity to carry out large phase III drug trials,¹⁸⁵ since clinical-trial costs have skyrocketed while NIH funding levels fell.¹⁸⁶ Consequently, the NIH has had to cut back dramatically on the number of phase III drug trials it supports,¹⁸⁷ and many of the established grant programs now cover less than half of trial costs, leaving academic research centers to make up the difference.¹⁸⁸ 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."¹⁸⁹ NIH

182. 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.

183. 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.

184. See Wadman, *supra* note 183, at 10 ("[A]cross the country people are closing labs, retiring early. This is a crisis."); Jones, *supra* note 182 (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").

185. 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").

186. See Roger Collier, *Rapidly Rising Clinical Trial Costs Worry Researchers*, 180 CANADIAN MED. ASS'N J. 277 (2009); Schmidt, *supra* note 178, at 831-33; Salim Yusuf, et al., *Sensible Guidelines for the Conduct of Large Randomized Trials*, 5 CLINICAL TRIALS 38, 38 (2008).

187. 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"); *Revamping the Clinical Trials System*, 1 CANCER DISCOVERY 194 (2011); Schmidt, *supra* note 178, at 832; Spector, *supra* note 182, 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 185, at 41.

188. Schmidt, *supra* note 178, at 830; see also Erdmann, *supra* note 167, 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).

189. Duley et al., *supra* note 185, 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); Paul Goldberg, *ASCO Says NCTN Budget Cut by 40 Percent, Warns of 'Dangerous Disruption of Cancer Care'*, CANCER LETTER, vol. 40, iss. 14, pg. 1 (2014).

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.¹⁹⁰ 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.¹⁹¹

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.¹⁹² Given the high costs of Phase III clinical trials, private-sector investment is one of the few viable alternatives to government grants.¹⁹³ University clinical researchers are already

190. 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.

191. 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 182, at 10-11 ("The widespread assumption is that U.S. federal spending for medical research will stay flat, or maybe continue to drop."). 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. See CONGRESSIONAL BUDGET OFFICE (CBO), FEDERAL SUPPORT FOR RESEARCH AND DEVELOPMENT vii-viii, 3-7 (2007). The duration of this trend hints that a broader political-economy problem may be stifling public R&D funding levels. It is easy to imagine that the political incentives for politicians to spend taxpayer dollars on R&D programs are far lower than the social returns from those investments. See LINDA R. COHEN & ROGER G. NOLL, THE TECHNOLOGY PORK BARREL 55-63 (1991). The benefits from increased government funding for R&D take many years to arrive, which is well beyond the relevant political time-horizon for most elected officials. See *id.* at 61; Stuart Minor Benjamin & Arti K. Rai, *Fixing Innovation Policy: A Structural Perspective*, 77 GEORGE WASHINGTON L. REV. 1, 13 (2008). Expending government resources on tax cuts, social-service programs, or any other spending project meant to deliver immediate and observable benefits to the public probably generate social returns that are easier for elected officials to capture as political gains. See Moses & Dorsey, *supra* note 183, at 234. 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. See *supra* note 175. 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 a politically expedient strategy. 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.").

192. See Spector, *supra* note 182, 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).

193. Moses & Dorsey, *supra* note 183, 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,¹⁹⁴ but this strategy forces them to work on clinical trials meant to be profitable to the sponsoring company,¹⁹⁵ 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.¹⁹⁶

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

With the NIH struggling to maintain its existing research programs, pharmaceutical companies may be the only actors with pockets deep enough to support wide-scale drug-repurposing investments. But for firms to recover an investment developing a new indication through the market, they would need to sell the drug for its new indication at a price far above their marginal production costs.¹⁹⁷ 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.¹⁹⁸ Consequently, without government intervention in the market, firms should 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 70% to 80% of the market for their drugs within six months of generic entry.¹⁹⁹ However, before entering the market for a new drug, generic manufacturers usually need two to three years to set up their

194. 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”).

195. See Frandzel, *supra* note 187 (explaining that as the NIH’s budget woes worsen, the NCI cooperative groups have started 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”).

196. See Barbara J. Culliton, *Interview: Extracting Knowledge From Science: A Conversation With Elias Zerhouni*, _ HEALTH AFFAIRS W94, W97 (2006); Reed et al., *supra* note 35, 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....”).

197. 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).

198. See Eisenberg, *New Uses*, *supra* note 16, at 717; Grabowski et al., *supra* note 16, at ; PEDRO BARROS & XAVIER MARTINEZ-GIRALT, HEALTH ECONOMICS: AN INDUSTRIAL ORGANIZATION PERSPECTIVE § 17.1 (2012); BESSEN & MEURER, *supra* note 61, at 88-89 (2008); BOLDRIN & LEVINE, *supra* note 121, at 237; JAFFE & LERNER, *supra* note 61, at 39-41.

199. See *supra* note 64, and accompanying text.

production facilities.²⁰⁰ 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 probably insufficient to incentivize the development of most new drugs,²⁰¹ 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.

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.²⁰² Pharmaceutical companies are unlikely to invest in developing a new indication without some form of monopoly protection,²⁰³ 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 finance the clinical trials necessary to establish the drug's safety and efficacy for that new indication.²⁰⁴

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 their R&D investments.²⁰⁵ 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

200. See *supra* note 62, and accompanying text.

201. 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.tevad.com/Brill_Exclusivity_in_Biogenerics.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 61, 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).

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

203. See SAHOO, *supra* note 70, at 41-42.

204. See *infra* notes 272-279, and accompanying text.

205. See *supra* note **Error! Bookmark not defined.** and accompanying text.

government offers firms monopoly rights that only cover the act of taking or administering the drug for the new indication. These rights are better suited than the standard monopoly protection to incentivizing firms to develop new uses for existing drugs. However, pharmaceutical companies generally cannot enforce these rights 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.²⁰⁶

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.²⁰⁷ Since firms quickly lose their market position to generics soon after they enter,²⁰⁸ 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.²⁰⁹ The patent system will protect any newly discovered drug that is novel, nonobvious, and useful,²¹⁰ giving firms a monopoly over the drug that expires twenty years after they file the patent application.²¹¹ Product patents on the active ingredient in a drug are usually the strongest form of patent protection for blocking generic entry.²¹² 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

206. See *supra* note 70.

207. See *supra* notes 28 & 41-42 and accompanying text.

208. See *supra* notes 63-64 and accompanying text.

209. See Roin, *Unpatentable Drugs*, *supra* note 61, at 545-56; Comer, *supra* note **Error! Bookmark not defined.**, 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.”).

210. See 35 U.S.C. §§ 101-103 & 112.

211. See 35 U.S.C. § 154(a)(2).

212. 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)).

drugs.²¹³ Pharmaceutical companies can also use product patents on their drug’s formulation to block generics from the market.²¹⁴ 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.²¹⁵ 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.²¹⁶

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.²¹⁷ Federal law expressly allows for the patenting of “any new and useful process” that involves “a new use of a known . . . composition of matter.”²¹⁸ 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.²¹⁹ Generic manufacturers do not directly infringe these patents, since they only make and sell drugs, and do not take or administer them to patients.²²⁰ But generic manufacturers can be held liable for indirectly infringing a new-use patent if they “actively induce infringement” by patients, pharmacists, or physicians.²²¹ The FDA requires generic manufacturers to list on their label at least one FDA-approved indication for the drug.²²² 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.²²³ Consequently, if pharmaceutical companies have protection

213. 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 61, 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.”).

214. See THOMAS, *supra* note 65, 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).

215. 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).

216. See 21 C.F.R. § 314.95 (2013).

217. See Eisenberg, *New Uses*, *supra* note 16, at 720-25.

218. 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).

219. See THOMAS, *supra* note 65, at 44-46, 235-37.

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

221. See 35 U.S.C. § 271(b) (2012).

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

223. 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).

over every FDA-approved indication for their drug, they can effectively exclude generics from the market.²²⁴

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,²²⁵ 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.²²⁶ 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, which would essentially defeat the purpose of being a generic.²²⁷ New indications for FDA-approved drugs receive three years of data exclusivity.²²⁸ 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.²²⁹ 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.²³⁰

One or more of these exclusionary rights for blocking generic entry will almost always be available to protect new drugs (although not necessarily sufficient to motivate their development). In the end, pharmaceutical companies usually manage to keep generics off the market for somewhere between ten and fifteen years following the initial FDA approval of their drug.²³¹ 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.²³² Once that protection expires, generics quickly enter and take over the market in most cases.²³³

224. 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 DISCOV TODAY THER STRATEG. 131, 131-32 (2011).

225. 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).

226. 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).

227. See THOMAS, *supra* note 65, at 349-52.

228. 21 U.S.C. § 355(c)(3)(E)(iii).

229. 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)).

230. 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).

231. See *supra* note 67.

232. See Grabowski & Kyle, *supra* note 67, at 497 fig. 4; Hemphill & Sampat, *supra* note 67, at 328.

233. See *supra* note 64, and accompanying text.

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

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.²³⁴ 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.”²³⁵ 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.²³⁶ This suggests that the exclusionary rights that temporarily bar generics from the market are poorly suited for encouraging the development of new indications.

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.²³⁷ The public would benefit from the development of these new indications, but it would also have less access to lower-cost generics, which are thought to generate significant value for society.²³⁸ Over the last decade alone, generic drugs reportedly saved the U.S. health care system more than a \$1 trillion.²³⁹ According to one estimate, generics currently produce about \$1 billion

234. 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 105, at 530.

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

236. 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).

237. 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 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.”).

238. See U.S. CONGRESSIONAL BUDGET OFFICE (CBO), EFFECTS OF USING GENERIC DRUGS ON MEDICARE’S PRESCRIPTION DRUG SPENDING (2010).

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

in savings every two days.²⁴⁰ Since the government pays for a significant portion of the nation's prescription-drug spending,²⁴¹ these cost savings may translate into reduced deadweight loss from reduced taxation.²⁴² The lower prices for generics may also increase consumers' access to valuable medical treatments. The widespread use of prescription-drug insurance likely avoids much of the deadweight loss that might otherwise result from the higher prices for patented drugs.²⁴³ 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.²⁴⁴ Given these potential 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.²⁴⁵

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.²⁴⁶ Pharmaceutical

240. See *id.* at 1.

241. See U.S. Government Accountability Office, (GA)-12-371R, *Drug Pricing: Research on Savings from Generic Drug Use* 4-6 (2012).

242. The magnitude of the deadweight loss caused by taxation and its relevance to public policy are controversial. See LOUIS KAPLOW, *THE THEORY OF TAXATION AND PUBLIC ECONOMICS* 222-25 (2010) (arguing that when policymakers are deciding whether to provide a public good, they usually should not consider the labor distortion incidental to financing that public good because there may be corresponding redistributive benefits from that good and because any distortionary effects could be offset by adjusting the income tax).

243. See Roin, *Intellectual Property versus Prizes*, *supra* note 105, at 1047-53; Darius Lakdawalla & Neeraj Sood, *The Welfare Effects of Public Drug Insurance* 93 J. PUBLIC ECON. 541 (2007).

244. See *supra* note 118. 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 16; Darius Lakdawalla & Tomas Philipson, *Does Intellectual Property Restrict Output? An Analysis of Pharmaceutical Markets*, 55 J.L. & ECON. 151, 178-79 (2012).

245. See Mossinghoff, *supra* note 16, 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).

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).

246. 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%2004%2009.pdf>.

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.²⁴⁷ As noted above, pharmaceutical companies can usually obtain process patents on newly discovered indications for drugs.²⁴⁸ 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 label²⁴⁹—a practice known as “skinny labeling.”²⁵⁰ Generic manufacturers use this same tactic to design around any FDA-exclusivity periods awarded for new indications.²⁵¹ Pharmaceutical companies receive a three-year data exclusivity period for any newly approved indication of a drug²⁵² and a seven-year data exclusivity period for any new orphan indications.²⁵³ However, generic manufacturers can still enter the market if they only list the off-patent indications on their label.²⁵⁴ Much like the process patents available for additional indications, these FDA-exclusivity periods for new uses generally fail to block generic competition.²⁵⁵

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.²⁵⁶ However, as explained below, pharmaceutical companies usually have no way to enforce these

247. 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 & 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 Maebius, *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).

248. See *supra* notes 218-219, and accompanying text.

249. 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).

250. 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).

251. See Eisenberg, *New Uses*, *supra* note 16, at 728-30.

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

253. See 21 U.S.C. § 360cc.

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

255. See SAHOO, *supra* note 70, at 42.

256. 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).

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-approved uses for the drug.²⁵⁷ Nonetheless, they do give firms a legal right to charge patients—or their insurer—when the patients use that drug for the patented indication.²⁵⁸ 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.²⁵⁹

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.²⁶⁰ 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

257. See *supra* notes 217-224 and accompanying text.

258. 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 16, 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 MERGES & DUFFY, *supra* note 256, at 400. Insurance companies, pharmacy benefit managers, pharmacy chains and (possibly) generic manufacturers would be more sensible targets 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 250. 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.

259. See Eisenberg, *New Uses*, *supra* note 16.

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

be held liable for indirectly infringing a new-use patent unless they know the prescription is for a patented indication.²⁶¹

Pharmaceutical companies rarely have access to the information they need to enforce a new-use patent against pharmacists or insurers.²⁶² When physicians prescribe a drug to a patient to treat a particular indication, the patient's medical condition is confidential information.²⁶³ Physicians will often disclose the prescribed indication to pharmacists and insurers because the insurer may require that information as a condition for coverage.²⁶⁴ 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.²⁶⁵ 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,

261. 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).

262. See 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).

263. See 67 Fed. Reg. 53182.

264. See *infra* note 422 and accompanying text.

265. 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 261, 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 250. 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 through contractual provisions when they sell the data, or refuse to sell the data in the first place.

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.²⁶⁶

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.²⁶⁷ Consequently, firms often continue testing their drugs for new indications, at least for a short while.²⁶⁸ These investments are treated as part of the broader lifecycle management of their drugs.²⁶⁹ Indication expansion increasingly provides a critical source of revenue for the industry²⁷⁰ as well as important treatments for unmet medical needs.²⁷¹

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.²⁷² 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.²⁷³

266. 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 367, 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).

267. *See* ELLERY & HANSEN, *supra* note 70, 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 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").

268. *See* GIPSTEIN ET AL., *supra* note 267, at 3 ("Most clinical strategies include plans to invest in new indications, phase 4 studies, and other trials.").

269. ELLERY & HANSEN, *supra* note 70, 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").

270. GIPSTEIN ET AL., *supra* note 267, at 2 (reporting that expanding drug indications "has become critical to [the] commercial success" of new drugs).

271. *See supra* note 6.

272. *See* VOET, *supra* note 212, at 35-39.

273. *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 224, at 131 (explaining that drug repurposing is only profitable when firms have "an effective generic substitution barrier to prevent off-label use of

Given the limited term of protection, pharmaceutical companies' willingness to develop new indications for a drug quickly fades following the drug's initial approval.²⁷⁴ 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.²⁷⁵ 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.²⁷⁶ 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.²⁷⁷ 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

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.”); David Cavalla, *David Cavalla – Drug Repositioning Panel Talk Transcript*, Drug Repositioning Conference, San Francisco, CA, Jul. 20, 2011, at <https://www.collaborativedrug.com/buzz/2011/07/20/david-cavalla-drug-repositioning-panel-talk-transcript/> (“[T]he one factor which is most prominent and affects nearly all drug repurposing projects is the issue of differentiation, ... and that is essentially the issue of whether you’re able to control the opportunity of an existing drug, vis-à-vis generic competition, ... which [otherwise] can drastically reduce the value of the project you’re trying to develop.”).

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’”); Cavalla, *supra* note 273 (explaining that if the repurposed drug requires “reformulating or ... slightly changing the active ingredient, ... the risk associated with your projects can be drastically reduced”); Bhupinder Singh Sekhon, *Repositioning Drugs and Biologics: Retargeting Old/Existing Drugs for Potential Therapeutic Applications*, 4 J. PHARM. EDUC. RES. 1, 11 (2013) (“Patent strategies directed to protecting new formulations, indications and methods of use, when combined with strategically repositioned products, can provide effective and long lasting product exclusivity even where the underlying API, and the original formulations, indications and methods of use are off-patent.”).

274. In theory, pharmaceutical companies could negotiate a compensation scheme with insurers or PBMs ex ante for developing a new use for old drug. Negotiating prices ex ante would be costly, however, since firms must negotiate prices for all the indications that ultimately fail in clinical trials in addition to the ones that succeed. Moreover, PBMs would probably be reluctant to negotiate a new indication's price and position on the formulary without clinical-trial data to evaluate its therapeutic value relative to alternative treatments, which is the most important determinant of price. See *infra* note 404.

275. See *supra* note 169.

276. See ELLERY & HANSEN, *supra* note 70, 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 70, at 59.

277. See ELLERY & HANSEN, *supra* note 70, at 120 & 124.

new indications.²⁷⁸ 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.²⁷⁹

IV. 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 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 the most efficient route for drug development. As a result, it could allow pharmaceutical firms to develop medical treatments for smaller markets and more challenging pathologies. 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 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,²⁸⁰ the vast majority of which are off patent.²⁸¹ Using new screening technologies, researchers have identified hundreds of potential new uses for these off-patent drugs to treat unmet medical needs.²⁸² 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

278. 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 267, 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.”).

279. See Grabowski, et al., *supra* note 16, 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).

280. See Huang et al., *supra* note 21, at 80ps16.

281. See *supra* note 4.

282. See *supra* note 21; *infra* notes 293-296, and accompanying text.

the potential social costs of this policy failure.²⁸³ Paige Cramer and co-authors reported in *Science* that bexarotene is remarkably effective against Alzheimer's in several important preclinical models.²⁸⁴ Although this discovery attracted a great deal of attention, it remains uncertain whether the treatment will work in humans.²⁸⁵ The clinical trials needed to test bexarotene for this indication would take five to seven years and hundreds of millions of dollars.²⁸⁶ With only a few years of patent life remaining on bexarotene, finding industry sponsors for these trials will be difficult, if not impossible.²⁸⁷

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.²⁸⁸ But Cramer et al.'s discovery is just the tip of the iceberg.²⁸⁹ The medical literature contains hundreds of other examples of old drugs with preclinical evidence suggesting valuable new indications.²⁹⁰ The popular press is even starting to carry stories on the opportunities to develop new medical treatments through drug repurposing.²⁹¹

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.²⁹² Over the past decade,

283. 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).

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

285. See Strittmatter, *supra* note 283, at 1448; LaFerla, *supra* note 283, at 571-72.

286. 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").

287. 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.").

288. 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).

289. See Stephen Ornes, *Using Old Drugs in New Ways*, 4 *CANCER TODAY* (2014); Gupta et al., *supra* note 24; Irene Seunghyun Hong et al., *Medication Repurposing: New Uses for Old Drugs*, 27 *J. PHARMACY TECH.* 132 (2011).

290. See *infra* notes 297-308.

291. 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>.

292. See Chong & Sullivan, *supra* note 58, 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*

scientists developed a variety of new computational tools to screen known-drug compounds in silico for new indications.²⁹³ 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.²⁹⁴ These screening tools have shown that existing drugs are much more likely than the average novel drug candidate to be active in multiple targets, pathways, and cellular phenotypes—factors indicative of greater potential for multiple uses.²⁹⁵ Moreover, many of the

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 33, at S4-S5.

293. See Chong & Sullivan, *supra* note 58, at 645; Ekins et al., *supra* note 22; Oprea & Mestres, *supra* note 12, 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 141, 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.”).

294. See Hao Ye et al., *Construction of Drug Network Based on Side Effects and its Application for Drug Repositioning*, 9 PLoS ONE e87864 (2014); Dakshanamurthy et al., *supra* note 27; Keiser et al., *supra* note 22; 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 140; Kinnings et al., *supra* note 151; Monica Campillos et al., *Drug Target Identification Using Side-Effect Similarity*, 321 SCIENCE 263 (2008); Liu et al., *supra* note 33; 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, 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).

295. See Huang et al., *supra* note 21; Kinnings et al., *supra* note 151.

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.²⁹⁶

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.²⁹⁷ These include possible treatments for cancer²⁹⁸ (including cancer prevention²⁹⁹), Alzheimer's disease,³⁰⁰ depression,³⁰¹ diabetes,³⁰² stroke,³⁰³ tuberculosis,³⁰⁴ malaria,³⁰⁵ multi-drug resistant bacteria,³⁰⁶ and

296. This is the case, for example, with literature mining and side effect-similarity screening. See Ye et al., *supra* note 294; Andronis et al., *supra* note 294, at 358; Campillos et al., *supra* note 294, at 263-64; Li et al., *supra* note 294, at 1; Liu et al., *supra* note 33; Wermuth, *supra* note 140; Yang & Agarwal, *supra* note 294, 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.").

297. See *supra* note 22.

298. See Telleria, *supra* note 24, at ix; Bin Li et al., *Repurposing the FDA-Approved Pinworm Drug Pyrvinium as a Novel Chemotherapeutic Agent for Intestinal Polyposis*, 9 PLOS ONE e101969 (2014); 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 149, at 446 (childhood brain tumors, breast cancer, leukemia, and sarcomas); 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 22 (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-1alpha Aynthesis 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); Elizabeth A. Platz et al., *A Novel Two-Stage, Transdisciplinary Study Identifies Digoxin as a Possible Drug for Prostate Cancer Treatment*, 1 CANCER DISCOVERY 68 (2011); 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).

299. See Alejandro Vazques Martin et al., *Repositioning Chloroquine and Metformin to Eliminate Cancer Stem Cell Traits in Pre-Malignant Lesions*, 14 DRUG RESIST. UPDATE 212 (2011); Li et al., *supra* note 298; Gupta et al., *supra* note 24.

300. See Cramer et al., *supra* note 284; Corbett et al., *supra* note 26; Jennifer M. Plane et al., *Prospects for Minocycline Neuroprotection*, 67 ARCH NEUROL. 1442 (2010).

301. Ye et al, *supra* note 294, at 6-8; Butcher, *supra* note 26, at 22.

302. 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 149.

303. 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); Plane et al.,

a host of other unmet medical needs.³⁰⁷ 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.³⁰⁸ Many researchers now suspect that our current arsenal of drugs could provide important treatments for a sizeable portion of the remaining major unmet medical needs.³⁰⁹

supra note 300; Susan C. Fagan, *Drug Repurposing for Drug Development in Stroke*, 30 PHARMACOTHERAPY 51S (2010).

304. See Kinnings et al., *supra* note 151; Juan Carlos Palomino & Anandi Martin, *Is Repositioning of Drugs a Viable Alternative in the Treatment of Tuberculosis?*, 68 J. ANTIMICROB. CHEMOTHER. 275 (2013).

305. See Ekins et al., *supra* note 22; 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); Katherine T. Andrews et al., *Drug Repurposing and Human Parasitic Protozoan Diseases*, 4 INT’L J. PARASITOLOGY: DRUGS & DRUG RESISTANCE 95, 99-103 & 104-05 (2014).

306. 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); Muthyala, *supra* note 25, at 71.

307. 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 35 (Cryptosporidiosis); Muthyala, *supra* note 25, at 71 (multidrug-resistant parasites, progressive multifocal leukoencephalopathy, and a range of neurological disorders); Ekins & Williams, *supra* note 22 (C. parvum); Ekins et al., *supra* note 22 (trypanosomal and Chagas disease); Plane et al., *supra* note 300 (spinal cord injuries, Parkinsons, Huntington’s disease, and others); Eftychia Lekka et al., *Literature Analysis for Systematic Drug Repurposing: a Case Study from Biovista*, 8 DRUG DISCOVERY TODAY: THERAPEUTIC STRATEGIES 103, 103 (2011) (multiple sclerosis); Allen S. Kaplan, *Investigating the Potential of Olanzapine in Anorexia Nervosa Treatment*, 1 IMS MAGAZINE 19 (2013) (anorexia nervosa); Qu et al., *supra* note 33 (systemic lupus erythematosus); Dakshanamurthy et al., *supra* note 27 (rheumatoid arthritis); Autumn S. Downey et al., *Efficacy of Pyrvinium 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); Andrews et al., *supra* note 305, at 104-05 (various parasitic diseases); Ye et al, *supra* note 294, at 6 (rheumatoid arthritis).

308. Ekins et al., *supra* note 22; see also Chong & Sullivan, *supra* note 58; Boguski et al., *supra* note 16; Muthyala, *supra* note 25; Ekins & Williams, *supra* note 22; Telleria, *supra* note 24.

309. See *supra* notes 24-26, and accompanying text. For some, the optimism over drug repurposing refers not just to developing new uses for FDA-approved drugs, but also to developing new treatments by reformulating FDA-approved drugs or modifying their chemical structure. See Wermuth, *supra* note 140, 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”).

Now that these drugs are off patent, firms lack the incentive to fund the necessary clinical research for 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 currently the most efficient route for producing new medical treatments.³¹⁰ Repurposing drugs is generally much faster and cheaper than developing a novel drug compound.³¹¹ It allows firms to skip the drug discovery and preclinical development stages,³¹² which typically constitute between one third and one half of the cost and time of developing a drug.³¹³ In some cases, firms can also skip the early clinical development stages.³¹⁴ This dramatically reduces the cost of bringing a new medical treatment to market.³¹⁵ Whereas de novo drug development typically costs in excess of \$1.2 billion per drug,³¹⁶ developing a new indication costs on average \$300 million or less.³¹⁷ Moreover, while de novo drug development takes an average of twelve to sixteen years,³¹⁸ pharmaceutical companies can almost always develop a new indication within twelve years, and it can take as little as three.³¹⁹

310. See Barratt & Frail, *supra* note 8, at 1; Dakshanamurthy et al., *supra* note 27 (“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 27, at 400 (referring to the development of new indications as “a route to cost-effective drug development”).

311. See *supra* note 27 & 167-172, and accompanying text.

312. See *supra* notes 31 & 169, and accompanying text; Mullard, *supra* note 140, 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”).

313. See *supra* note 30.

314. See *supra* notes 167-172 and accompanying text; see also Chong & Sullivan, *supra* note 58, 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 12 (“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.”).

315. See Chong & Sullivan, *supra* note 58, 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.”).

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

317. See SAHOO, *supra* note 70, at 28.

318. See *supra* note 29 and accompanying text.

319. See Ashburn & Karl B. Thor, *Drug Repositioning: Identifying and Developing New Uses for Existing Drugs*, 3 NATURE REVIEWS DRUG DISCOVERY 673, 673 (2004) (“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 147, 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

Drug repurposing is also much less risky than de novo drug development.³²⁰ The high failure rate in developing new drugs is one of the largest hurdles in pharmaceutical innovation.³²¹ 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.³²² Problems with toxicity and efficacy are the primary reason for failures in clinical trials.³²³ Medicinal chemists now recognize that these problems reflect a fundamental challenge in drug science, since it is extremely difficult to design a compound that can be safely administered to patients in a therapeutically effective dose.³²⁴ 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.³²⁵ The risk of failure is much lower when developing new indications for established drugs because pharmaceutical companies start with a chemical compound known to be safe and therapeutically effective in humans.³²⁶ The extensive body of knowledge from prior research and clinical experience with existing drugs also diminishes failure risks.³²⁷ 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.³²⁸

Because of its time, cost, and risk advantages over de novo drug development, drug repurposing could allow pharmaceutical companies to pursue critical areas of medical research that they currently neglect.³²⁹ 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.³³⁰ Over the past decade, experts have also

to market.”); Elvidge, *supra* note 273, at 8; THOMSON REUTERS, *supra* note 293, at 1 (“drug repositioning has a number of R&D advantages including a reduction of R&D timelines by up to 3-5 years”).

320. See *supra* notes 33 & 37-44, and accompanying text.

321. See Scannell et al., *supra* note 144, at 199.

322. See *supra* notes 37-38 and accompanying text.

323. See *supra* note 43.

324. See *supra* note 40, 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 38; Hann & Keserü, *supra* note 38. Moreover, medicinal chemists still struggle to predict the pharmacological properties of new drugs before costly clinical trials. See Colombo & Peretto, *supra* note 43, at 677; Kaitin, *supra* note 37.

325. See Mizushima, *supra* note 147, at 499; Muthyala, *supra* note 25; Wermuth, *supra* note 140.

326. See *supra* note 33, and accompanying text; THOMSON REUTERS, *supra* note 293, 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”).

327. See Qu et al., *supra* note 33, at S4.

328. 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>.

329. See *supra* note 34, and accompanying text; Hemphill, *supra* note 16, at 6-7.

330. See, e.g., Erdmann, *supra* note 167, at 1492.

become increasingly worried that industry is failing to pursue potential breakthrough treatments aimed at novel disease targets because of the higher failure rate.³³¹ 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),³³² for serious but uncommon conditions (e.g., rare cancers),³³³ and for diseases that primarily afflict the uninsured poor (e.g., multi-drug resistant tuberculosis).³³⁴ At the same time, the faster development period offers hope to patients with rapidly advancing conditions who will not survive the duration of a de novo drug development project.³³⁵ But without an incentive for firms to developing new uses for off-patent drugs, society loses most of these opportunities to spur R&D spending in neglected areas.

C. 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.³³⁶ NIH-funded research has identified underlying molecular causes for thousands of human diseases, revealing new biological targets for pharmacological intervention.³³⁷ “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 defined molecular causes.”³³⁸ The pharmaceutical industry – struggling with productivity problems³³⁹ – has been reluctant to gamble on developing new drugs for these newly identified (and thus unvalidated) molecular targets. The result is “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

331. See *supra* notes 50 & 53-55, and accompanying text; *infra* Part IV.C.

332. See Corbett et al., *supra* note 26.

333. See Xu & Côté, *supra* note 44.

334. 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).

335. See Collins, *Therapeutic Gold*, *supra* note 55, at 397; Weir et al., *supra* note 12, 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.”).

336. See Collins, *Translational Science*, *supra* note 46; Elias A. Zerhouni, *US Biomedical Research: Basic, Translational, and Clinical Sciences*, 294 JAMA 1352 (2005); Moses & Dorsey, *supra* note 183, 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).

337. See *supra* notes 297-308, and accompanying text; see also Meredith Wadman, *The Bridge Between Lab and Clinic: Q&A Francis Collins*, 468 NATURE 877 (2010).

338. Collins, *Translational Science*, *supra* note 46, at 2; *supra* note 54.

339. See Scannell et al., *supra* note 144; SA Morris et al., *The PCAST Report: Impact and Implications for the Pharmaceutical Industry*, 94 CLINICAL PHARMACOLOGY & THERAPEUTICS 300, 300 (2013); 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>; AJAY DHANKHAR ET AL., ESCAPING THE SWORD OF DAMOCLES: TOWARD A NEW FUTURE FOR PHARMACEUTICAL R&D 3 (2012); Michael D. Rawlins, *Cutting the Cost of Drug Development*, 3 NAT. REV. DRUG DISCOVERY 360, 360 (2004).

in clinical trials.”³⁴⁰ The NIH lacks the resources and institutional capacity to fill in this gap directly by advancing novel drug compounds through preclinical R&D.³⁴¹ Consequently, most newly discovered targets languish in the so-called valley of death between academia and industry,³⁴² where neither public nor private funding is available to advance the research to the point of commercial viability.³⁴³ 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.³⁴⁴ Many experts argue that drug repurposing is the NIH’s best opportunity to translate breakthroughs in basic research into commercialized products.³⁴⁵ 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.³⁴⁶ As a result, the NIH has been unable to take advantage of drug repurposing as a solution to its valley-of-death problem.³⁴⁷

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.³⁴⁸ 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.³⁴⁹ However, developing new drugs based on unvalidated targets also involves more uncertainty, and thus a higher failure rate.³⁵⁰ With drug-development costs on the rise,

340. Reed, *supra* note 48.

341. See *infra* note 354 and accompanying text.

342. See, e.g., Butler, *supra* note 51, at 841; Mary Carmichael, *Desperately Seeking Cures*, NEWSWEEK, May 14, 2010; FASTER CURES, *supra* note 53; Collins, *Translational Science*, *supra* note 46.

343. See Muthyala, *supra* note 25; 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 48.

344. See *supra* note 44 and accompanying text.

345. See *supra* note 55; Reed et al., *supra* note 35; Boguski et al., *supra* note 16; O’Connor & Roth, *supra* note 58.

346. See *supra* note 58; Weir et al., *supra* note 12 (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.”).

347. See *infra* notes 366 & 367.

348. See Butler, *supra* note 51.

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

350. *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.

pharmaceutical companies are increasingly reluctant to pursue these higher-risk projects, leaving a crucial funding gap at preclinical R&D.³⁵¹

At the same time, support from the public sector remains insufficient to advance breakthroughs in basic research into viable candidates for industry development.³⁵² In addition to the NIH's budget constraints,³⁵³ 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.³⁵⁴ 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."³⁵⁵

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 IV.A above) to search for any FDA-approved drugs that may be active against that target.³⁵⁶ Since those drugs are already on the market and have established safety and efficacy profiles,³⁵⁷ 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.³⁵⁸ This shortcut across preclinical R&D would drastically reduce the time and expense of moving from target discovery to human trials,³⁵⁹ which, as Francis Collins explains, "can enable the rapid testing of new clinical hypotheses, leading to remarkable health outcomes."³⁶⁰

Unfortunately, the NIH generally cannot utilize this solution to the valley-of-death problem unless there are incentives for private industry to fund clinical trials on the new uses it identifies. 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.³⁶¹ However, as

351. Elias A. Zerhouni, *Turning the Titanic*, 6 SCI. TRANSLATIONAL MED. 221 (2014); Reed, *supra* note 48; see also Butler, *supra* note 51, at 840; Metcalf & Dillon, *supra* note 349; Patterson, *supra* note 350; Collins, *Translational Science*, *supra* note 46; Rai et al., *supra* note 50.

352. See *supra* note 343; Moran, *supra* note 342; FASTER CURES, *supra* note 53; 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).

353. See *supra* Part II.E.

354. See *supra* note 48; Reed, *supra* note 48; Woodcock, *supra* note 41, at 19-20.

355. 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 352, at 268.

356. See Huang et al., *supra* note 21.

357. See *supra* note 33, 326 & 327, and accompanying text.

358. See Huang et al., *supra* note 21 (noting that the development of new indications for existing drugs "obviate[s] the need for NME development, a long and expensive process.").

359. See *supra* notes 311-319, and accompanying text.

360. Collins, *Therapeutic Gold*, *supra* note 55, at 397; see also Hemphill, *supra* note 16, at 6-7; Cimmino & Aifantis, *supra* note 298, 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.").

361. See Rai, *supra* note 16, 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

discussed in Part II.E above, government funding for clinical trials is always (and increasingly) in short supply, particularly for the costly late-stage clinical trials.³⁶² In the medical literature on drug repurposing, researchers describe “an unmet critical need to fund repurposing projects into phase IIb and phase III [trials].”³⁶³ University or NIH researchers generally must find an industry sponsor to pay for these studies.³⁶⁴ Since firms have little or no incentive to invest in drugs once generics are on the market,³⁶⁵ public-private partnerships of this sort are infeasible when repurposing an off-patent drug.³⁶⁶ 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.³⁶⁷

off-patent 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 48, 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 55, at 25; Nair, *supra* note 141, at 2431; Woodcock, *supra* note 41, at 19 (noting that from the FDA’s perspective, studies funded by pharmaceutical companies are superior to academic studies in their “rigor”).

362. See *supra* notes 182-191, and accompanying text.

363. Oprea & Mestres, *supra* note 12; Weir et al., *supra* note 12, 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 48.

364. See *supra* notes 192, 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).

365. See *supra* Part III.D.

366. See Mullard, *supra* note 27, 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.”).

367. See Noel Southall, *Noel Southall – Drug Repositioning Panel Discussion Transcript*, Drug Repositioning Conference, San Francisco, CA, Jul. 20, 2011, at <https://www.collaborativedrug.com/buzz/2011/07/20/noel-southall-drug-repositioning-panel-discussion-transcript/> (“I work at NIH, the opportunities for doing repurposing are not limited necessarily by commercialization requirements. However, the best path to a marketed product is through a commercialization partner, and that is definitely something that we recognize.”). 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 55. 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 141, at 2431; Colvis et al., *supra* note 55, at 24-25; Jocelyn Kaiser, *NIH’s Secondhand Shop for Tried-and-Tested Drugs*, 332 SCIENCE 1492 (2011); Mullard, *supra* note 140. 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 328 (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-

V. THE INFORMATION BARRIERS UNDERLYING THE PROBLEM OF NEW USES

As discussed in Part III.C, the current patent laws would provide incentives for drug repurposing if firms knew when physicians prescribed off-patent drugs for new uses, since firms could use that information to enforce their new-use patents. The existing literature on the problem of new uses pays scant attention to this issue. Most articles on the subject mention the concern only in passing, typically as a brief (one or two sentence) explanation for why new-use patents become unenforceable once generics are on the market.³⁶⁸ The literature instead searches for alternative incentive mechanisms to support drug repurposing, consistent with calls from NIH leaders for a “new funding paradigm” to support drug repurposing,³⁶⁹ preferably through “[n]ew paths to exclusivity and pricing/reimbursement strategies ... to promote private sector engagement.”³⁷⁰ These searches mostly end on a pessimistic note, with scholars concluding that the standard policy options for promoting private sector drug development (including patents, FDA-exclusivity periods, consumer subsidies and prizes) all seem ill suited to promoting drug repurposing.³⁷¹ The pessimism stems from the literature’s failure to recognize that these different systems all face the same underlying problem – the inability to observe utilization rates for new indications. The incentives for developing inventions should be linked to their social value, and since inventions’ social value largely depends on their frequency of use, information about utilization rates is crucial for designing a socially beneficial incentive system.³⁷² Unless the government observes when (or at least how often) physicians prescribe repurposed drugs for their new indications, tractable solutions for the problem of new uses will remain illusive.

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. Most other areas of under-investment in drug development are easily amenable to correction through one or more of the standard, market-based policy levers for incentivizing pharmaceutical R&D—namely, patents or FDA-exclusivity periods to bar generics from the market, and consumer subsidies to boost sales revenue from drugs. Some new drugs receive inadequate monopoly protection through the existing Hatch-Waxman framework, either because they are unpatentable³⁷³ or

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 33; Smith, *supra* note 224 (“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.”).

368. *See supra* note 103.

369. *See* Austin, *supra* note 16, at 19.

370. *See* Weir et al., *supra* note 12, at 1057.

371. *See supra* notes 76-82; Eisenberg, *New Uses*, *supra* note 16, at 739; Hemphill, *Repurposing Pharmaceuticals*, *supra* note 91, at 1250016-4 n.7; Rai, *supra* note 16, at 492; Milne & Bruss, *supra* note 16; Grabowski, et al., *supra* note 16.

372. *See infra* notes and text accompanying notes 379-390.

373. *See* Roin, *Unpatentable Drugs*, *supra* note 61, at 515-45. Over the years, researchers have disclosed millions of compounds with potentially valuable therapeutic properties through journal articles and older patent

because they take too long to develop given the fixed 20-year patent term.³⁷⁴ In these cases, the underlying problem is that the standard monopoly protection (i.e., the right to bar generic entry) 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.³⁷⁵ Other socially valuable drugs may fail to reach the public because market demand for them is too low relative to their social value,³⁷⁶ possibly including treatments for malaria and other tropical diseases.³⁷⁷ 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, guaranteed reimbursement from insurers, or other price supports) to bolster market demand for those products.³⁷⁸

None of these market-based mechanisms for encouraging pharmaceutical innovation offer an appealing solution to the problem of new uses because the market currently fails to differentiate between sales for drugs' old and new indications.³⁷⁹ Granting firms the standard monopoly protection over off-patent drugs through patents or FDA-exclusivity periods would bar generics from the market entirely—allowing those firms to charge consumers for that drug's

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 61, 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 292-296, 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 61, at 545-47 (collecting sources).

374. See Eric Budish et al, *Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials*, 105 AM. ECON. REV. 2044 (2015); Benjamin N. Roin, *Drug Patent Length* (2010) (hereinafter Roin, *Drug Patent Length*), at <http://law.stanford.edu/wp-content/uploads/sites/default/files/event/263873/media/slspublic/Benjamin%20Roin%20-%20Drug%20Patent%20Length.pdf>.

375. See Roin, *Unpatentable Drugs*, *supra* note 61, at 556-569; Budish et al., *supra* note 374, at 2058-2061.

376. 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).

377. 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).

378. See Roin, *Intellectual Property versus Prizes*, *supra* note 105, at 1062-66.

379. See *supra* notes 262-265, and accompanying text.

new and old uses alike.³⁸⁰ Similarly, subsidizing consumer prices for repurposed drugs would transfer money to innovators for each drug sale regardless of whether patients take it for the new or old use. Both approaches tie the incentives to repurpose old drugs to their overall sales instead of sales for the new indications, and thus break the link between new indications' social value and the incentive to develop them.³⁸¹

Using a prize system to promote drug repurposing would encounter essentially the same problem.³⁸² Many scholars have argued that the government should award firms monetary prizes for new drugs instead of patents to avoid the deadweight loss from monopoly pricing and offer better incentives for innovation.³⁸³ A few of them claim that a prize system would also solve the problem of new uses because the government could offer prizes for new indications based on their social value.³⁸⁴ But the government needs a mechanism to calculate these rewards,³⁸⁵ and the proposed drug-prize systems all base their prize payouts in part on drugs' actual or expected sales volume.³⁸⁶ This approach to calculating prize payouts would conflate sales for old and new uses, much like monopoly rights that block generic entry and consumer subsidies for repurposed drugs.³⁸⁷

380. See *supra* Part III.B.

381. See *supra* notes 234-235, and accompanying text.

382. 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”).

383. See Roin, *Intellectual Property versus Prizes*, *supra* note 105, at 1005 n.19 (collecting sources).

384. See HOLLIS & POGGE, *supra* note 376, 14-15 & 17; Fisher & Syed, *supra* note 376, 43 & 46.

385. See Roin, *Intellectual Property versus Prizes*, *supra* note 105, at 1034-38.

386. See *id.* at 160 & n.254-255 (collecting sources). Amy Kapczynski and Talha Syed note that it might be possible to design a prize system “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.” Kapczynski & Syed, *supra* note 382, at 1955. 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.

387. The importance of good information about utilization rates for new indications is evident in Aidan Hollis and Thomas Pogge’s proposed Health Impact Fund (“HIF”). See HOLLIS & POGGE, *supra* note 376, at 17. Hollis and Pogge state that the proposed HIF would incentivize firms to test old drugs for new uses because “firms will be able to make use of patents issued for new uses,” since “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 their proposed mechanism for calculating prize payouts would require information about utilization rates, since it offers innovators “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].” *Id.* at 24. Hollis and Pogge 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 376. 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 (or estimate) a new indication’s utilization rate to calculate its prize. *Id.* at 45-48.

Ultimately, without a way to measure the utilization rates for new indications distinct from drugs' overall sales, designing an efficient incentive system of any type to encourage repurposing off-patent drugs is extremely difficult. Whenever the government offers rewards for incentivizing innovation (whether they be patents, prizes, and any other financial inducement for investing in R&D), those rewards should be linked to the inventions' social value.³⁸⁸ An invention's social value is mostly a function of how often people use it and the value generated by each use.³⁸⁹ Since an invention's utilization rate is a critical component of its social value, a reward-based incentive system for promoting innovation generally requires a mechanism to link the reward for inventions to their utilization rate.³⁹⁰ These incentive mechanisms typically link rewards to inventions' sales volume, which tends to be the most accurate and observable proxy for inventions' utilization rates.³⁹¹ However, if the invention at issue is a new indication for a drug with one or more other uses, the government cannot determine its utilization rates by observing the drug's overall sales. Consequently, unless the government knows when (or how often) physicians are prescribing old drugs for their new uses, it cannot easily tie the incentives for developing new indications to their social value.

Information about utilization rates is important even when the public finances drug-repurposing trials, since the government still needs a way to link its funding for those trials to their social returns. Assuming that the NIH's budget were sufficient for such an initiative,³⁹² it could institute a large-scale grant program to fund drug-repurposing trials without monitoring utilization rates for the new indications it develops. But the program's success would hinge on whether the NIH selects indications to develop that ultimately prove valuable and are prescribed often enough to justify their development costs. Much like private sector firms, the NIH does not have perfect information when deciding whether to develop a new medical treatment. It can only speculate about the treatment's likely therapeutic value and future utilization. Predicting future demand for a new medical treatment is challenging even for pharmaceutical companies,³⁹³ whose predictions are sometimes wildly off the mark.³⁹⁴ Although the public cannot expect perfect decision-making from NIH officials, it wants them to predict utilization honestly, using the best information available, and using methodologies that improve over time as they learn from experience. If the government cannot observe utilization rates for new indications *ex post*, it is hard to devise mechanisms that will discipline NIH predictions to enhance accuracy,

388. See Shavell & van Ypersele, *supra* note 105, at 530.

389. See *supra* notes 234-236, and accompanying text.

390. See *supra* note 105, and accompanying text.

391. See Roin, *Intellectual Property versus Prizes*, *supra* note 105, at 1036, 1058.

392. See *supra* Part II.E (noting the NIH's severe (and worsening) funding shortage for phase III clinical trials—including trials for new uses of existing drugs—because of ongoing budget cuts and rising clinical research costs).

393. See ARTHUR G. COOK, *FORECASTING FOR THE PHARMACEUTICAL INDUSTRY: MODELS FOR NEW PRODUCT AND IN-MARKET FORECASTING AND HOW TO USE THEM* 35-69 (2006) (outlining the standard market forecasting algorithms that pharmaceutical companies use to predict demand for new products under development).

394. See, e.g., John LaMattina, *Challenges in Commercializing Inhaled Insulin*, FORBES, Aug. 22, 2013, at <http://www.forbes.com/sites/johnlamattina/2013/08/22/challenges-in-commercializing-inhaled-insulin/> (recounting Pfizer's gross overestimation of market demand for inhaled insulin, and resulting \$2.6 billion pretax loss, and describing the general difficulty of predicting market demand for new medical treatments).

promote accountability, and enable officials to learn from experience.³⁹⁵ This can lead to poorly informed funding decisions and potentially deter policymakers from financing the program.³⁹⁶

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

Focusing on the information barriers underlying the problem of new uses reveals that it is a much broader problem than currently recognized. Ultimately, industry's unwillingness to develop new uses for off-patent drugs is about barriers to information for sellers that impede price discrimination, preventing drug companies from stopping arbitrage to support differential pricing by indication. Each of the different indications for a drug is essentially a distinct product. They require separate clinical trials to establish,³⁹⁷ benefit a different group of patients, and have different cost-benefit profiles.³⁹⁸ 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.³⁹⁹ Consequently, they have no choice but to charge the

395. 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 program evaluations of large government-funded R&D programs to estimate social returns, explaining that these 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”); K.M. Quinlan et al., *Evaluation of Large Research Initiatives: Outcomes, Challenges, and Methodological Considerations*, in REFORMING THE EVALUATION OF RESEARCH: NEW DIRECTIONS FOR EVALUATION 62 (C.L.S. Coryn & M. Scriven Eds., 2008).

396. Concerns about utilization rates played a decisive role in the National Cancer Institutes' (NCI) controversial 2007 decision not to fund the planned P-4 STELLAR trial, which would have tested the previously approved drug letrozole (Femara®) as a preventive agent for breast cancer. See Editorial, *NCI and the STELLAR Trial*, 369 LANCET 2134 (2007). Although NCI experts were optimistic about the trial's likelihood of success, the review board concluded that “even if [the results are] positive, it is unlikely to change the practice of preventive oncology.” Kirsten Boyd Goldberg, *Three NCAB Members Say They Cannot Offer “Strong Endorsement” of P-4 Trial*, CANCER LETTER, vol. 33, no. 23, at 1 (2007). The review board reasoned that “[f]ew women have been taking the previously tested chemoprevention drugs,” and that “[s]ince Novartis' exclusivity for letrozole would end in 2011, the company wouldn't have an incentive for marketing the agent for prevention.” *Id.* at 2. But the NIH had to make this decision with little information about the other chemoprevention drugs' utilization rates. See Liz Savage, *Researchers Wonder Why High-Risk Women are not Taking Chemoprevention Drugs*, 99 J. NAT'L CANCER INST. 913 (2007) (“A few studies have attempted to quantify women's interest in chemoprevention, but the estimates vary widely. Anecdotally, at least, the number is believed to be low, and this assumption is being used to make funding decisions.”). Even today, government officials and academics have limited (and seemingly inconsistent) information about patient uptake for chemopreventive treatments. See, e.g., LS Donnelly et al., *Uptake of Tamoxifen in Consecutive Premenopausal Women Under Surveillance in a High-Risk Breast Cancer Clinic*, 110 BRITISH J. CANCER 1681, 1685 (2014) (finding that estimates of tamoxifen uptake for breast-cancer prevention among high-risk patients range from 1.1% to 42%). The NCI's decision to cancel the P-4 STELLAR trial remains controversial. See Banu Arun et al., *Breast Cancer Prevention Trials: Large and Small Trials*, 37 SEMINARS IN ONCOLOGY 367, 377 (2010).

397. See *supra* Part II.C.

398. Gregson et al., *supra* note 402, at 123 (“Different indications generally involve distinct customers, value propositions and competing (reference) products, as well as different doses.”).

399. See *supra* notes 262-265, and accompanying text.

same price for these otherwise distinctive goods.⁴⁰⁰ This obstacle to price discrimination 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.⁴⁰¹ But those same information barriers also prevent pharmaceutical companies from efficiently pricing on-patent drugs with multiple indications. This Part offers a brief first look at this price-discrimination problem in the market for prescription drugs. It argues that the inability to price drugs by indication reduces firms' incentive to invest in new indications for their patented drugs because they cannot charge the profit-maximizing price for both the old and new uses. Even an infinite patent term for drugs would not correct this dynamic inefficiency. This Part also argues that the inability to price drugs by indication reduces patients' access to some valuable medical treatments, and possibly reduces total static consumer welfare, since it forces insurers to deny coverage for certain drug indications instead of negotiating lower prices for those treatments.

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.⁴⁰² 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.⁴⁰³ Insurers will have a very different willingness-to-pay for those indications.⁴⁰⁴ As a result, pharmaceutical companies would be unable to market the drug

400. See SAHOO, *supra* note 70, 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 402, 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.”).

401. See *supra* Part III.D.

402. 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.”).

403. 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 8, at 54.

404. 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 402, 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 discussions of the drug's therapeutic value relative to alternative treatments. See Gregson et al., *supra* note 402, 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.

effectively for its lower-value indication without greatly underpricing the high-value indication.⁴⁰⁵ 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 indication by dividing it into multiple treatments to save on the low-dose indication.⁴⁰⁶ 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 reduce patients' access to secondary uses for on-patent drugs. When pharmaceutical companies develop more than one indication for their on-patent drugs, they frequently price drugs with multiple indications to reflect their most valuable uses,⁴⁰⁷ which can make the drugs too expensive for some of their other possible uses, such as indications that are experimental, offer smaller therapeutic benefits, or in markets with more price competition from alternative treatments.⁴⁰⁸ Insurers commonly exclude these lower-value indications from their plan's coverage.⁴⁰⁹ 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,⁴¹⁰ including prior authorization and step therapy.⁴¹¹ These enforcement mechanisms for indication-based coverage restrictions have proven to be quite effective at limiting patients' access to excluded therapies.⁴¹² Although these excluded indications are likely to be less valuable than the drug's primary indication, they may

405. See SAHOO, *supra* note 70, 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 70, 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.”).

406. 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).

407. See ELLERY & HANSEN, *supra* note 70, at 128; PHARMA FUTURES, *supra* note 405, at 15; Gregson et al., *supra* note 402, at 123.

408. See ELLERY & HANSEN, *supra* note 70, at 128.

409. See Neville, *supra* note 404, at 38-39; Cohen et al, *supra* note 130, at 393-397.

410. See James C. Robinson, *Comparative Effectiveness Research: From Clinical Information to Economic Incentives*, 29 HEALTH AFFAIRS 1788, (2010); 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).

411. See *supra* note 118.

412. See Shoemaker et al., *supra* note 118, 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).

still offer significant health benefits to some patients.⁴¹³ 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. This change would likely benefit patients, although the overall impact of differential pricing by indication on static welfare and consumer deadweight loss is beyond the scope of this article.⁴¹⁴

At a basic level, differential pricing by indication is necessary for linking pharmaceutical pricing to the value (or willingness to pay) for those treatments, which is thought to be a core public-policy objective in the pricing of pharmaceuticals.⁴¹⁵ Most of the information about a drug's therapeutic value relevant to its price comes from clinical trials and other empirical studies, which are generally indication-specific. Without differential pricing by indication, pharmaceutical companies and insurers cannot tie the price of a medical treatment to the evidence of its therapeutic value if that treatment is a drug with multiple uses.⁴¹⁶

VII. PRIOR AUTHORIZATION AS A MODEL FOR SOLVING THE PROBLEM OF NEW USES

The various impediments to pharmaceutical innovation discussed in Part IV and VI all stem from the same underlying problem – the inability to observe the utilization rates for a drug's different indications. If pharmaceutical companies and insurers could both observe the intended indication for a drug with each prescription, then they could negotiate separate prices for that drug's different uses, which would correct the distortions discussed in Part VI. Such a

413. Although some experts suspect 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).

414. Price discrimination by monopolists is generally (but not necessarily) associated with increased static efficiency and lower consumer deadweight loss. See Lars A. Stole, *Price Discrimination and Competition*, in III HANDBOOK OF INDUSTRIAL ORGANIZATION (Mark Armstrong & Robert H. Porter, eds. 2007). In this context, allowing differential pricing by indication should lead to lower prices for lower-value indications and higher prices for higher-value indications. These changes would affect consumer access to those medical treatments, but since the vast majority of U.S. consumers have prescription-drug insurance, that effect would be largely mediated through insurance coverage and premiums. Given the pressure on insurers to cover clinically validated indications with high therapeutic value, see Tu & Samuel, *supra* note 410, at 3-5, insurance coverage would presumably lessen the direct impact of higher prices for higher value indications on patients' access to those treatments. Meanwhile, the lower prices for lower-value indications should make insurers more likely to cover them. If insurers increase their coverage for lower-value indications without fully offsetting reductions in their coverage for higher-value indications, then the value and cost of their insurance plans should increase, since the insurer is providing and paying for more care. This increase in price and value of prescription-drug insurance would have conflicting effects on consumer demand for those products. Consequently, allowing differential pricing by indication could impact static efficiency by either increasing or decreasing total enrollment in prescription-drug insurance plans and spending on health care. Government subsidies and regulations for prescription-drug insurance could influence how any price changes affect insurance enrollment numbers and the social welfare implications of that adjustment.

415. See Dyfrig A. Hughes, *Value-Based Pricing: Incentives for Innovation or Zero Net Benefit?*, 29 PHARMACOECONOMICS 731 (2011); Patricia M. Danzon & Erin Taylor, *Drug Pricing and Value in Oncology*, 15 (suppl. 1) ONCOLOGIST 24, 24-25 (2010);

416. See Peter B. Bach, *Indication-Specific Pricing for Cancer Drugs*, 312 J. AM. MED. ASS'N 1629 (2014).

system would also work with our existing patent laws (and possibly our regulatory exclusivity periods)⁴¹⁷ to enable pharmaceutical companies to enforce their new-use patents against pharmacists,⁴¹⁸ insurers, and PBMs,⁴¹⁹ thereby helping to correct the distortions discussed in Part IV. Pharmacists would be required to dispense the pharmaceutical companies' more expensive, brand name drug instead of a low-cost generic when physicians prescribe it for a protected 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 price indications separately for their patented drugs and charge insurers when physicians prescribe an off-patent drug for a patented indication.

Fortunately, an infrastructure through which third parties can observe prescribed indications already exists – prior authorization. As discussed above, most insurers limit their coverage for drugs by the prescribed indication.⁴²⁰ The PBMs administering prescription-drug plans use prior authorization to enforce those coverage restrictions.⁴²¹ When physicians prescribe a drug subject to prior authorization, the PBM requires them to list the indication and provide additional information about the patient's condition and need for treatment to support the listed indication. PBMs use this information to determine whether they will cover the prescribed drug.⁴²² Physicians sometimes misreport indications to skirt insurers' coverage restrictions.⁴²³

417. See *infra* text accompanying notes 488-489 (discussing the additional regulatory changes needed to make FDA-exclusivity periods enforceable monopoly rights over new indications when generics are on the market).

418. See *supra* notes 258 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 used for insurance authorization operate to notify pharmacists when the indication for a prescription is patent protected. 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); Mahn, *supra* note 250 (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.").

419. See *supra* note 258 & 261-263, and accompanying text (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), since pharmacists might demand indemnification from them for any liability owed to the pharmaceutical companies. 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) indirect infringement standards.

420. See *supra* note 409.

421. 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 410, at 8-9.

422. 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 118, at 376.

Such misreporting is fraud,⁴²⁴ however, and PBMs can check patients' medical records to verify physicians' reported indications.⁴²⁵ This threat of detection is not always credible, and therefore is not always sufficient to discourage fraudulent reporting (as discussed below).⁴²⁶ However, PBMs claim they have "had great success at preventing payments for drugs not provided for medically accepted indications by using prior authorization."⁴²⁷ 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. If pharmaceutical companies also had access to reported indications for prescriptions and to patients' medical records to verify those reports, they would be in the same position as insurers to observe prescribed indications.

In this sense, the problem of new uses results from pharmaceutical companies' inability to access an existing information infrastructure developed by third-party payers to enforce indication-based access restrictions to prescription drugs. Insurers and PBMs can require physicians to report indications to them as a condition for covering the drug's costs. Pharmaceutical companies do not have this direct (or contractual) relationship with the prescribing physician to impose these reporting requirements. They might be able to contract with the insurer or pharmacist to disclose reported indications for prescriptions of the company's patented drugs. However, those companies would have no right to demand indication reporting when physicians prescribe a low-cost generic for a new use they patented. The pharmaceutical companies also have no right to review patients' medical records to verify reported indications, unlike insurers and PBMs, who are permitted under federal law to require access to those records as a condition for coverage.⁴²⁸

Solving the problem of new uses is a simple matter of giving pharmaceutical companies the same rights as PBMs to access information about prescribed indications. First, the government needs to ensure that physicians report indications along with their prescriptions – presumably through electronic prescribing ("e-prescribing") software,⁴²⁹ standard prior

423. 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) (reporting on some physician's willingness to misreport indications to deceive insurers into covering the costs of treatment excluded under the patient's prescription-drug plan).

424. 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.

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

426. See *infra* note and text accompanying note 447.

427. Wright, *supra* note 118, 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").

428. See 45 C.F.R. § 164.508(a)(2); Mark A. Rothstein, *Access to Sensitive Information in Segmented Electronic Health Records*, 40 J.L. MED. & ETHICS 394, 396 (2012).

429. 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

authorization tools, or the newer electronic-prior authorization (“e-prior authorization”) – when necessary for enforcing new-use patents or regulatory exclusivity periods.⁴³⁰ Second, the government must grant pharmaceutical companies access that information when they need it to enforce their monopoly right over a new use or to police a differential pricing scheme.⁴³¹ Third, the government needs to give pharmaceutical companies access to patient’s medical records for the purpose of verifying reported indications.⁴³²

pricing by indication. *See, e.g.,* Eguale et al., *supra* note 262, 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).

430. 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. *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 429, at 917. CMS would only need to alter its specifications for qualifying software to require indication reporting or e-prior authorization. *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”).

431. 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. *See* 21 USC §355-1(f)(3)(D). 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). 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 463-467 (discussing this concern).

432. As an alternative or complement to allowing pharmaceutical companies (restricted) access to patient medical records to discourage fraudulent reporting of indications, the government could implement policies meant to eliminate physicians’ incentive to misreport indications. For example, the government could prohibit PBMs from imposing higher co-pays for more expensive indications. However, there would be social costs to such a policy to

Of course, this system must be designed to protect patients legitimate privacy interests in their medical records while still allowing pharmaceutical companies to observe prescribed indications. The federal medical-information privacy laws – known as the Health Insurance Portability and Accountability Act (HIPAA)⁴³³ – provide a framework for structuring these privacy safeguards. HIPAA allows authorized third parties (such as PBMs) to access patients’ otherwise confidential medical information when used for billing and coverage determinations.⁴³⁴ To protect patients’ privacy, HIPAA also imposes strict safeguards to prevent those third parties from using the information for other purposes or from disclosing it to others unless it is de-identified.⁴³⁵ Pharmaceutical companies currently do not qualify under HIPAA as authorized third parties (or “covered entities”) eligible to receive identifiable patient medical information for billing purposes,⁴³⁶ probably because pharmaceutical companies have not been involved in that billing system. But policymakers could amend HIPAA to include pharmaceutical companies in the HIPAA framework, which would permit them restricted access to the reported indications for prescriptions and the patients’ medical records for purposes of verifying those reported indications. Alternatively, the government could give pharmaceutical companies’ access to patients’ medical records without amending HIPAA by requiring that the information be de-identified.⁴³⁷

Perhaps the greatest cost of such a system is the burden on physicians when reporting indications and supporting information for that diagnosis. Indication reporting alone is fairly quick and easy with modern electronic-prescribing software.⁴³⁸ Tewodros Eguale and co-authors

the extent that those higher co-pays reduce unnecessary utilization beyond what the prior authorization accomplishes.

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

434. See Federal Register, vol. 67, No. 157, Aug. 14, 2002, Department of Health and Human Services (HHS), 45 CFR Parts 160 and 164, Standards for Privacy of Individually Identifiable Health Information, at 53208-09, 53216 (discussing the importance of sharing medical information for proper billing of health care services).

435. See 45 CFR 164.502(d)(2).

436. See 45 CFR 164.502 (2007).

437. Under this approach, pharmaceutical companies would have access to reported indications for prescriptions and the patients’ medical records stripped of all identifying information except for 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). Of course, the unique identification code would need to be the same for the reported indication and the patient’s medical records.

438. Most U.S. physicians are already using e-prescribing to send prescriptions directly to pharmacists, and the country is quickly approaching universal adoption. See Meghan Hufstader Gabriel and Matthew Swain, *E-Prescribing Trends in the United States*, ONC DATA BRIEF, no.18, Office of the National Coordinator for Health Information Technology (2014). At present, physicians usually enter little more than the drug’s name and dosage when writing a prescription. See MICHAEL VAN ORNUM, *ELECTRONIC PRESCRIBING: A SAFETY AND IMPLEMENTATION GUIDE* 155-56 (2008). However, some e-prescribing software is designed to require physicians to list the indication for their prescriptions, usually by selecting a diagnosis from a short scroll-down menu. See Eguale et al., *supra* note 262; Tamblyn et al., *supra* note 429, at 149-51; VAN ORNUM, *supra* at 63. The government could make these indication-reporting features mandatory through slight modifications to existing CMS regulations, which

studied the adoption of a system of mandatory indication reporting through e-prescribing for primary care physicians in Quebec.⁴³⁹ They found that physicians reported indications accurately 97% of the time,⁴⁴⁰ and that the process imposed relatively little burden on physicians.⁴⁴¹ But prior authorization involves more than just indication reporting. Physicians must also disclose information supporting the diagnosis. Traditional prior-authorization systems are also largely manual, requiring physicians to telephone PBMs or fill out and fax to them a paper form with the information needed to document the listed indication.⁴⁴² Not surprisingly, physicians often complain that these procedures are costly and burdensome.⁴⁴³ Expanding prior authorization to include new uses for old drugs would increase those costs and burdens on physicians. Fortunately, most PBMs are transitioning to e-prior authorization,⁴⁴⁴ which is meant to streamline the review process by linking e-prescriptions to the patient's e-health records and the PBM's prior authorization requirements.⁴⁴⁵ These programs allow physicians to provide PBMs with any information they need for prior authorization electronically as they write their prescription, and will even auto-complete most of the data fields.⁴⁴⁶ Although e-prior authorization is still more

use a combination of subsidies and penalties to encourage physicians to adopt and use qualifying e-prescribing software. *See* 78 FED. REG. 21308, 21311, 42 C.F.R. part 411, Apr. 10, 2013.

439. *See* Eguale et al., *supra* note 262, at 559.

440. *See id.* at 566.

441. *Id.* at 565; *see also* Tamblyn et al., *supra* note 429, 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).

442. *See* American Medical Association (AMA), *Standardization of Prior Authorization for Medical Services White Paper 2-3* (2011); E-Prior Authorization, *supra* note 444.

443. Wright, *supra* note 118, at 6; *see also* Vann et al., *supra* note 444, at 251-52; AMA, *supra* note 442. 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).

444. *See* The New Standard for Electronic Prior Authorization, Pharmacy Town Hall Series, 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").

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

446. *See* E-Prior Authorization, *supra* note 444, 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).

burdensome than writing a simple prescription, it should significantly lessen the costs to physicians from indication reporting and verification.

Another limitation of the prior-authorization model for observing indications is that it is not always effective. But there are important exceptions. The system will not work well for diagnoses that are hard to distinguish based on the information contained in a patient's medical records, which is true for many closely related indications (e.g., mild versus moderate back pain) and for conditions with highly subjective diagnostic criteria (e.g., many psychiatric disorders).⁴⁴⁷ Physicians could misreport these indications with little fear of being caught. In these cases, enforcing new-use patents may be cost-prohibitive, and pharmaceutical companies would probably 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, PBM's success in using prior authorization to enforce indication-based access restrictions in prescription-drug insurance plans suggests that it is often (and perhaps usually) effective at distinguishing a drug's different indications. The system works when firms can distinguish the indications based on the prescribing physicians' specialty or records of concomitant and follow-up treatments. It also works when diagnostic test results or information clearly signaling the indication are present in the patient's medical files. 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.⁴⁴⁸

Relying on e-prescribing software, e-health records and e-prior authorization to overcome the problem of new uses also benefits people in developing countries. This system 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 (and perhaps FDA-exclusivity periods) only in the wealthier 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.⁴⁴⁹ Moreover, encouraging pharmaceutical companies to finance more clinical

447. 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).

448. 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.”).

449. 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*

trials for new uses will free up NIH funding for drug-repurposing projects aimed at tropical diseases.⁴⁵⁰

The indication-reporting and verification system outlined above is the most obvious approach to observing utilization rates for new indications because it builds on our existing prior authorization system. There are other possible approaches, however, including trying to estimate each indication's utilization rates instead of directly observing indications for each prescription. For example, firms might infer utilization rates for new indications through some combination of physician surveys, test markets, random sampling, and by comparing the drug's total sales before and after the new indications' development.⁴⁵¹ Assuming these estimates are reasonably accurate and difficult to manipulate, firms could use them to link rewards for new indications to their estimated utilization rate.⁴⁵² This Article does not address the feasibility of these alternative systems or, assuming they are feasible, compare them to the prior-authorization model discussed above. Rather, it endeavors to show that the prior-authorization model is a feasible system for allowing pharmaceutical companies to observe the utilization rates for indications, which shows that the problem of new uses is solvable.

VIII. COMPARING NEW-USE PATENTS AND FDA-EXCLUSIVITY PERIODS AS INCENTIVES FOR DEVELOPING NEW USES FOR OLD DRUGS

Once there is a system for firms to observe the utilization rates for new indications, the government could implement a variety of different incentive mechanisms to spur investment in

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).

450. Cf. Muthyala, *supra* note 25; Boguski et al., *supra* note 16. 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.

451. Estimating sales for a new indication based on the change in the drug's overall sales following the new indication's development has at least three drawbacks. First, some physicians would begin prescribing the old drug for its new use long before Phase III clinical trials are complete. See *supra* note 162 (discussing off-label prescribing rates). And the multi-year ramp-up period to peak sales for most new drugs suggests that many physicians would wait years before they begin prescribing the new treatment. See Joseph A. DiMasi et al., *R&D Costs and Returns by Therapeutic Category*, 38 DRUG INFO. J. 211, 219 fg.5 (2004); Henry G. Grabowski & John Vernon, *The Distribution of Sales Revenues from Pharmaceutical Innovation*, 18 PHARMACOECONOMICS Suppl. 1, 21 (2000). Second, any number of unobserved factors might confound this simple before-and-after analysis. Most drugs are prescribed for multiple indications, see *supra* notes 141-142, and physicians might change their prescribing practices for any one of those indications during the relevant time period in response to new information about those treatments or their alternatives. Third, the system might be highly vulnerable to gaming. Innovators could inflate the estimated utilization rate for their new indication by subtly promoting the drugs' older indications, while payers could do the opposite by discouraging physicians from prescribing those older treatments.

452. The government would also need to amend the indirect patent infringement rules to allow pharmaceutical companies to enforce their new-use patents or FDA-exclusivity periods based on these estimated usage figures. Alternatively, it could implement a prize system for new indications that links prize payouts to estimated utilization rates, or use these estimates to guide public sector funding for drug repurposing.

repurposing off-patent drugs for new uses, including new-use patents, FDA-exclusivity periods, prizes, consumer subsidies, and government funding for drug repurposing trials.⁴⁵³ This Article does not attempt to identify the optimal incentive mechanism for drug repurposing. It assumes that the government will use new-use patents and FDA-exclusivity periods because those incentive mechanisms are already in place.⁴⁵⁴ Because enforceable monopoly rights over new indications implicate slightly different policy considerations than they do for new drugs, these issues warrant further discussion. This Part compares new-use patents to FDA-exclusivity periods as tools for promoting drug repurposing, examining their relative strengths and weaknesses, and suggesting a few areas for reform. It frames the comparison in terms of false positives and false negatives, wherein false positives are monopoly rights granted for new uses that patients would have benefited from anyway, and false negatives are failures to protect new uses that will not be developed because they were denied protection.

A. Shortcomings with the Existing Patent Protections for New Uses of Old Drugs

The existing patent laws are not the ideal incentive mechanism for drug repurposing. In addition to the patent system's standard shortcomings (e.g., incomplete value capture, patent racing and consumer deadweight loss), there are several distinct policy failures that will likely arise in the patent protection for new indications if those patents are made enforceable. The system will likely produce many false negatives by denying protection to new indications that will not be developed without that protection. It will also produce some false positives by awarding new-use patents for indications that the public would receive anyway. And the 20-year patent term (which runs from the patent-filing date) will give too little protection to some new indications and too much to others. This section briefly discusses these policy failures and possible corrective measures.

The most obvious and pronounced problem with existing patent laws as applied to new uses of old drugs would be the false negatives – valuable new uses that are ineligible for patent protection and are unlikely to be developed without that protection. The patent laws are designed to reward and protect the creation of new inventions, not their subsequent development or commercialization.⁴⁵⁵ The system will not protect a valuable idea if it is not new or is obvious.⁴⁵⁶ A previously published article or patent application that merely mentions the possibility of using a drug for a particular indication will prevent anyone from later patenting it, even if the indication remains untested and unused in medical practice. As discussed in Part IV.A above, researchers have already disclosed many potentially valuable new uses for existing drugs in published journal articles, albeit without any clinical-trial evidence to support their use in medicine.⁴⁵⁷ All of those new indications are likely ineligible for patent protection now.⁴⁵⁸

453. See *supra* Part V.

454. See *supra* Part III.A.

455. See Roin, *Unpatentable Drugs*, *supra* note 61, at 515-45.

456. See *id.*

457. See *supra* notes 297-307

458. See Ashburn & Thor, *supra* note 319, 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 12 (noting that the “[r]ecent academic enthusiasm in this field [of drug repurposing] has resulted in the

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.⁴⁵⁹ These gaps in the patent coverage for new indications weigh against relying exclusively on the existing patent system to encourage drug repurposing,⁴⁶⁰ and conceivably might warrant granting patents on new uses for old drugs so long as they are not accepted medical treatments, even if the idea for the new use is not novel or is obvious.

False positives in the patent protection for new uses would likely arise in three different circumstances. The first is when firms are willing to finance clinical trials on a new use without monopoly protection over it.⁴⁶¹ For the reasons outlined in Part II, this situation is probably rare for new uses of drugs that are accessible – or are soon to be accessible – as generics.

The second set of false positives would occur when clinical trials are unnecessary for the public to benefit from a new use – that is, when the social benefits from testing the new use in clinical trials are outweighed by the private costs of those trials and social costs of monopoly pricing over the new use. This situation might occur if most or all physicians will reasonably infer that a new indication is safe and effective and are willing to prescribing it without supporting clinical-trial evidence – perhaps because the new use is closely related to the drug’s original indication or because the new use’s therapeutic effects are readily apparent through clinical observation. Awarding enforceable patent rights on these new uses would allow the patentee to charge monopoly prices for the new indication even though patients would have benefited from it anyway. The patentability standards would likely screen out many of these false positives. For example, if a new indication’s safety and efficacy is strongly suggested by the drug’s original use, then the new indication should be obvious and thus ineligible for patent protection.⁴⁶² However, designing a patent system that would prevent all such false positives is probably impossible.

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 61, 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).

459. *See* Roin, *Unpatentable Drugs*, *supra* note 61, 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)).

460. *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).

461. A related version of this type of false positive would occur when firms patent a new use that the public sector otherwise would have developed in a timely manner. The new-use patent crowds out public sector clinical-trial investments. The social welfare implications of this crowding out are unclear, since they depend in part on a comparison of the virtues and vices of public and private R&D investments.

462. 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 61, at 532-33 (*quoting* *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368-69 (Fed. Cir. 2007)).

The third set of false positives would occur when firms acquire and enforce a new-use patent without ever testing that new use in clinical trials. Under the existing patent laws, firms can patent a new use with evidence of its efficacy from preclinical experiments.⁴⁶³ If physicians are willing to prescribe the drug off-label for a patented indication without any supporting clinical-trial evidence, firms might earn significant revenues from a new-use patent without ever investing in clinical trials.⁴⁶⁴ The patentee might choose to invest in clinical trials anyway, since a positive outcome could boost sales for the new indication⁴⁶⁵ and justify fewer formulary restrictions and higher reimbursement rates from PBMs.⁴⁶⁶ However, as more physicians become willing to prescribe a drug off-label for a new indication without supporting clinical-trial evidence, the patentee has less to gain from a positive outcome in the trials and more to lose by risking a negative outcome that would jeopardize the drug's existing sales.⁴⁶⁷ When off-label prescribing without clinical-trial evidence is sufficiently common that patentees are unwilling to invest in clinical trials, the public will suffer the social costs of the patent monopoly without any corresponding benefit. The government could probably avoid these false positives with a rule that requires firms to produce clinical-trial evidence supporting their patented new indication before they could enforce the patent, although it would need to set a standard for the amount and quality of the clinical-trial evidence.

The 20-year patent term generates further—and potentially quite serious—false positives and negatives for new indications. Patents run for 20 years from their filing date.⁴⁶⁸ Since pharmaceutical companies file their patents early in R&D,⁴⁶⁹ they often lose a significant portion of their product's patent life before it reaches the market.⁴⁷⁰ Drug-development projects that take longer to complete generally involve higher total R&D costs, and thus usually need a longer

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

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

465. A positive outcome would lessen any doubts among physicians about the treatments safety and efficacy. See *supra* note 156 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 157 and accompanying text.

466. See *supra* note 404.

467. See ELLERY & HANSEN, *supra* note 70, 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 16, at 718; Kapczynski & Syed, *supra* note 382.

468. See 35 U.S.C. § 154(a)(2).

469. 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 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).

470. See Michael K. Dunn, *Timing of Patent Filings and Market Exclusivity*, 10 NATURE REV. DRUG DISCOVERY 487, 488 (2011); ZANDERS, *supra* note 469, at 322-23.

monopoly period to incentivize their development.⁴⁷¹ But the current patent system does the opposite, offering firms a variable monopoly period of a term inversely related to their product's development time.⁴⁷² 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.⁴⁷³ Patent-term extensions partially offset this distortionary effect for new drugs,⁴⁷⁴ but those extensions are not available for new indications of FDA-approved drugs.⁴⁷⁵ Given the tremendous variance in R&D times for new indications,⁴⁷⁶ the false positives and negatives caused by the fixed patent-term could be substantial. This problem suggests that the government might want to revisit both the length and timing of the 20-year patent term as it applies to new indications.

B. Shortcomings with the Existing FDA-Exclusivity Protections for New Uses of Old Drugs

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.⁴⁷⁷ Unlike patents, which

471. See Roin, *Drug Patent Length*, *supra* note 374, 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 374; cf. Benjamin N. Roin, *The Case for Tailoring Patent Awards Based on Time-to-Market*, 61 UCLA L. REV. 672, 723-46 (2014) (hereinafter *Case for Tailoring*) (arguing that inventions' time-to-market is strongly correlated with their optimal patent strength).

472. See Roin, *Drug Patent Length*, *supra* note 374, at 44-46; Budish et al., *supra* note 374, at .

473. See Roin, *Drug Patent Length*, *supra* note 374, at 46-52; Budish et al., *supra* note 374. 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).

474. See Mossinghoff, *supra* note 16. 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.

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

476. See Dudley et al., *supra* note 147, 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.")

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

protect novel and nonobvious inventions for 20-years from the filing date,⁴⁷⁸ 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.⁴⁷⁹ Since the government grants monopoly protection over new indications (primarily) to motivate investment in clinical trials,⁴⁸⁰ FDA-exclusivity periods offer a tighter link between the criteria for granting monopoly protection and the justification for those awards.⁴⁸¹ That link is not perfect, however, and FDA-exclusivity periods therefore have their own problems with false positives and negatives.

With their closer link between the eligibility criteria for receiving monopoly protection and the economic need for that protection, FDA-exclusivity periods avoid many of the patent system's problems with false positives and negatives 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 problems 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.⁴⁸² 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.⁴⁸³

However, FDA-exclusivity periods have three potentially important drawbacks relative to patent protection for new uses. First, they may exacerbate the patent system's risk of false positives with new indications that do not need clinical trials for the public to benefit from them. Unlike the patent system, FDA-exclusivity periods will protect any new indication that the FDA approves, including ones closely related to the drug's original use that may not need or warrant costly clinical trials.⁴⁸⁴ The government could try to avoid this problem by conditioning FDA-exclusivity periods for new uses on the indications being significantly different from the original indication, although difficult line-drawing problems might arise under such a system.

Second, FDA-exclusivity periods for new uses may generate many false negatives by only protecting 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

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

479. See *supra* notes 225-230, and accompanying text.

480. See *supra* Part II.F.

481. See Roin, *Unpatentable Drugs*, *supra* note 61, 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.”).

482. 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”).

483. See *supra* notes 468-476 and accompanying text.

484. See *supra* text accompanying notes 225-229.

revenue to justify a full clinical-development program compliant with FDA requirements.⁴⁸⁵ 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 the term of protection based on features indicative of the incentive required to motivate the new indication's development (for example, the size and duration of clinical trials).⁴⁸⁶

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 VII. The existing regulatory-exclusivity periods operate against generic manufacturers, preventing them from listing any protected indications on their generic-drug label.⁴⁸⁷ 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.⁴⁸⁸ 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.⁴⁸⁹

IX. CONCLUSION

Repurposing old drugs for new uses is perhaps the single most promising avenue for delivering valuable new medical treatments to the public. Recent technological advances suggest that the existing body of FDA-approved drugs could provide effective treatments for many of today's unmet medical needs. Repurposing old drugs is also much faster and less expensive than developing a new drug, and the odds of success are far greater. Pharmaceutical companies currently have little or no incentive to invest in developing new uses for off-patent

485. See *supra* note 35.

486. See Roin, *Drug Patent Length*, *supra* note 374; Budish et al., *supra* note 374; Roin, *Case for Tailoring*, *supra* note 471, at 751-53.

487. 21 C.F.R. § 314.108; *supra* notes 254-255 and accompanying text.

488. 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)).

489. 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 250.

drugs, and as a result, these opportunities mostly lie fallow. Our failure to incentivize drug repurposing (otherwise known as the problem of new uses) is a significant public policy problem. It is also a misunderstood problem. Our system is not failing because it does not provide appropriate incentive mechanisms to reward investments in repurposing old drugs, as the existing literature often assumes. It fails because pharmaceutical companies do not observe whether physicians are prescribing a drug for an old or new use, and therefore cannot separate the markets for those two products. Without knowing when physicians are prescribing a drug for one use or another, firms cannot set separate prices for the different indications of their patented drugs, and they cannot enforce monopoly rights over new uses for off-patent drugs. It might have been impractical for pharmaceutical companies to observe prescribed indications before the information technology (IT) revolution, but no longer. PBM's successful use of prior authorization to enforce their indication-based coverage restrictions in prescription-drug insurance plans demonstrates that the existing healthcare IT system can allow third parties to observe indications for many (and perhaps most) prescriptions. While the existing IT infrastructure for indication reporting and verification is built for providers and payers to observe indications, it could just as easily provide that information to pharmaceutical companies, thereby correcting the underlying source of the problem of new uses.