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SOLVING THE PROBLEM OF NEW USES

BENJAMIN N. ROIN*

October 1, 2013

Abstract

One of the most dramatic public-policy failures in biomedical research is the lack of incentives for industry to develop new therapeutic uses ("indications") for existing drugs once generics are available. Policymakers and commentators are well aware of this "problem of new uses," but fail to appreciate its magnitude. Over the past decade, this gap in the incentives for pharmaceutical R&D has become one of the greatest barriers to medical progress. 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 indications for existing drugs is much faster, cheaper, and less risky than developing new drugs, and therefore offers the single most promising avenue for delivering new medical treatments to the public. However, pharmaceutical companies invariably lose interest in developing new uses for existing drugs when patients have access to low-cost generics. This article explores the nature and source of this gap in the incentives for developing new medical treatments, showing that it ultimately stems from a simple information problem. At present, the government encourages drug development by granting firms temporary monopoly rights that block generic manufacturers from making or selling imitations of their drugs. The government also makes available an alternative type of monopoly protection for new indications that applies to the act of taking or administering a drug for a new therapeutic use. The latter monopoly rights could provide the appropriate incentives for developing new uses of existing drugs. However, pharmaceutical companies cannot enforce these rights without knowing when physicians prescribe the drug for the patented indication as opposed to some other use. If the government established an infrastructure for pharmaceutical companies to monitor the prescribed indications when pharmacists fill a prescription, those firms would possess the information necessary to enforce patents on new indications, thereby solving the problem of new uses. This article argues that the government could easily create such an infrastructure through the expanding use of e-prescribing software and electronic medical records.

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I. INTRODUCTION

Society's investments in pharmaceutical R&D are subject to a profound distortion. The pharmaceutical industry spends tens of billions of dollars each year on clinical trials for new drugs.[1] Yet it spends almost nothing on trials to establish new therapeutic uses ("indications") of existing drugs that are off patent.[2] Over the past few years, researchers have uncovered hundreds of potential new indications for older drugs, many of which would be breakthrough medical treatments if they prove effective.[3] But the public needs someone to test these potential new indications in clinical trials to evaluate their safety and efficacy.[4] Although these clinical trials are costly, developing a new use for an existing drug is far less expensive, time-consuming

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

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

[3] *See infra* notes and text accompanying notes 274-286.

[4] *See* JERRY AVORN, POWERFUL MEDICINES: THE BENEFITS, RISKS, AND COSTS OF PRESCRIPTION DRUGS _ (2004) (discussing the crucial importance of evaluating new treatments in clinical trials for medical practice); *infra* notes and text accompanying notes 129-142.

and risky than developing a new drug.[5] Investigating new uses for existing drugs therefore may be the public's best chance at making significant progress in the fight against disease.[6] Unfortunately, the government has proven unwilling or unable to provide the necessary funding to test these new indications in clinical trials,[7] and pharmaceutical companies lack incentives to develop new indications for drugs once generics are available.[8] Consequently, nearly all of these potential new medical treatments remain untested hypothesis. This gap in the incentives for pharmaceutical innovation is known as the "problem of new uses."[9]

The current legal infrastructure of drug patents and regulatory exclusivity periods is designed to promote the development of new drugs, not new uses for existing drugs. The pharmaceutical industry's business model revolves around patent rights and exclusivity periods that prevent generic manufacturers from making or selling their drug. By blocking generics from the market, these rights effectively provide pharmaceutical companies with temporary monopoly protection over all of the drug's indications. Once those rights expire, pharmaceutical companies quickly lose their market share to generics. As a result, their incentive to develop new indications also expires, though many indications may remain untested and often undiscovered. The government cannot encourage the development of these new uses by again granting the power to exclude generic manufacturers. That would deny the public access to low-cost generics for the off-patent indication and unduly reward the pharmaceutical firm, breaking the link between the social value of the new use and the incentives for developing it.

The appropriate incentive for developing a new indication is the right to charge consumers using the drug for the patented indication. The current system actually gives firms this legal right, but not the power to enforce it. The government grants "new use" patents that provide a monopoly over the act of taking or administering a drug for a new indication. This legal right has little meaning, however, unless the pharmaceutical company can detect when patients use a generic drug for the patented indication, and pharmaceutical companies almost never have that information. In short, the government provides firms with the appropriate legal right for incentivizing development of new indications, but no infrastructure to enforce that right.

This gap in the incentives for pharmaceutical innovation is a widely recognized problem. Given the lack of protection for new indications of FDA-approved drugs, pharmaceutical

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[5] *See* Michael J. Barratt & Donald E. Frail, *Introduction*, in DRUG REPOSITIONING: BRINGING NEW LIFE TO SHELVED ASSETS AND EXISTING DRUGS 1 (Michael J. Barratt & Donald E. Frail, Eds. 2012); *infra* notes and text accompanying notes 289-303.

[6] *See* Thomas A. Hemphill, *The NIH Promotes Drug Repurposing and Rescue*, 55 RESEARCH TECHNOLOGY MANAGEMENT 6, 6-7 (2012); *infra* Section V.

[7] *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* notes and text accompanying notes 157-196.

[8] *See* Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL'Y & ETHICS 717, 718 (2005); *see infra* notes and text accompanying notes 197-259.

[9] Eisenberg, *supra* note 8.

companies rarely (if ever) test drugs for new therapeutic uses once generics are on the market. Indeed, they often stop testing drugs for new indications long before the patent term expires because the necessary clinical trials for a new indication take many years to complete and firms need time on the market to recoup their R&D investment.[10] The problem has been written off as essentially unsolvable – an inevitable byproduct of motivating pharmaceutical innovation with a temporary right to exclude generics from the market.[11]

This article shows that the magnitude of the problem is far greater than legal scholars and policymakers have recognized. Over the past decade, this seemingly minor gap in the incentives for pharmaceutical innovation has become one of the greatest impediments to medical progress. Recent scientific advances now permit researchers to rapidly screen existing drugs for potential new therapeutic uses.[12] Although researchers are just beginning to use these new screening tools, they have already uncovered a wealth of potential new treatments for critical unmet medical needs.[13] These discoveries have created tremendous excitement in the biomedical research community about the prospects of "repurposing" (or "repositioning") existing drugs for new uses,[14] with hundreds of research articles and opinion pieces on the new screening technologies and potential new uses for existing drugs published in medical journals over the past five years.[15] There is hope that developing new uses for existing drugs could "convert cancer into a treatable chronic disease."[16] There is also a growing "expectation that a substantial percentage of rare diseases if not all 8000 rare diseases might be treatable with drugs in the current pharmacopeia."[17] However, without private industry to fund clinical trials on the safety and efficacy of a drug for the new indication, the benefits are likely to go untapped.

A less obvious but equally severe consequence of the hole in the incentives for pharmaceutical innovation is the loss of a dramatically less expensive path for developing new medical treatments. The costs of identifying and developing new drugs have escalated to levels

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[10] *See* 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 245-249.

[11] *See* 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); Amy Kapczynski & Talha Syed, *The Continuum of Excludability and the Limits of Patents*, 122 YALE L.J. 1900, _ (2013); Eisenberg, *supra* note 8; Henry Grabowski, et al., *Does Generic Entry Always Increase Consumer Welfare?*, 67 FOOD & DRUG L.J. 373, 382 (2012); Christopher-Paul Milne & Jon B. Bruss, *The Economics of Pediatric Formulation Development for Off-Patent Drugs*, 30 CLINICAL THERAPEUTICS 2133, 2136 (2008).

[12] *See* 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).

[13] *See infra* notes and text accompanying notes 274-286.

[14] *See* Ramaiah Muthyala, *Orphan/Rare Drug Discovery Through Drug Repositioning*, 8 DRUG DISCOV TODAY THER STRATEG. 71 (2011).

[15] *See infra* notes 261-288.

[16] Carlos M. Telleria, *Drug Repurposing for Cancer Therapy*, 4 J. CANCER SCI. THER. ix (2012)

[17] Muthyala, *supra* note 14, at ("Some believe that the more obvious winners have already been found.").

that are now widely viewed as unsustainable.[18] As a result, pharmaceutical companies are scaling back their R&D investments and fewer medical treatments are reaching the market.[19] Developing new indications requires only a fraction of the cost, time and risk required to develop a new drug.[20] If pharmaceutical companies had an incentive to pursue these opportunities, they could take a chance on innovative therapies that have a higher risk of failure but offer hope of genuine medical breakthroughs. They would also be inclined to pursue treatments for smaller markets or poorer populations for which developing new drugs had previously been unprofitable. The inability to enforce patents on new indications once generics enter a market distorts pharmaceutical investment away from these opportunities.

This article analyzes the underlying source of the problem and identifies a simple solution that has been overlooked in the burgeoning literature. The inability to enforce new-use patents once generics are on the market ultimately stems from a simple information problem: pharmaceutical companies do not know when patients are using a drug for a patented indication or some other use. If they had that information, they could require pharmacists to dispense the brand-name drug for the patented indication. The growing utilization of electronic prescribing and computerized medical records provides an infrastructure that could overcome this information problem. Physicians can submit the indication for a drug when they write a prescription, and if insurers and pharmaceutical companies both have limited access to patients' (de-identified) medical records, they can police the accuracy of reported indications in most cases. With a few minor policy changes, the government could transform electronic prescribing into a tool that permits the enforcement of new-use patents, addressing one of the most dramatic public policy failures in pharmaceutical innovation.

Part II of the Article examines the economics of de novo (new) drug development and the legal rights that pharmaceutical companies depend upon to block generic manufacturers from making or selling imitations of their new drugs. Part III discusses the importance to society of testing FDA-approved drugs for new indications and the government's failure to adequately fund those clinical trials. Part IV analyzes the lack of incentives for firms to develop new indications for a drug once generics are on the market. Part V shows that the social costs of this gap in the incentives for pharmaceutical innovation are far greater than previously assumed and are getting worse. Finally, Part VI proposes a solution to this problem of new uses.

II. INCENTIVES TO CREATE NEW MEDICAL TREATMENTS THROUGH THE DEVELOPMENT OF NEW DRUGS

[18] *See* Michael D. Rawlins, *Cutting the Cost of Drug Development*, 3 NAT. REV. DRUG DISCOVERY 360, 360 (2004); *infra* notes and text accompanying notes 310-321.

[19] *See* Christopher M. Holman, *Unpredictability in Patent Law and Its Effect on Pharmaceutical Innovation*, 76 MISSOURI L. REV. 645, 646-47 (2011); *see infra* notes and text accompanying notes 310-328.

[20] *See* SAHOO, *supra* note 10.

The pharmaceutical industry, perhaps more than any other industry, depends on legal barriers to imitation to generate a return on their investment. Nowhere else in our economy will firms spend in excess of $1 billion to bring a single product to market that rivals can imitate for fractions of a cent on the dollar. Recognizing the need for protection to sustain these investments, Congress crafted an industry-specific system of drug patents and regulatory exclusivity periods to incentivize pharmaceutical innovation. It designed the system to provide pharmaceutical companies with temporary monopoly protection over new drugs to encourage their development, while eventually allowing low-cost generics onto the market.[21] Although controversial and flawed, the system can fairly take credit for generated immense gains in social welfare by incentivizing the development of new medical treatments.[22]

A. The Extremely High Costs and Uncertainty of Developing New Drugs

Pharmaceutical R&D is an incredibly expensive and time-consuming process with a high risk of failure.[23] The pharmaceutical industry is the most R&D-intensive sector of the global economy.[24] Most large pharmaceutical companies invest several billion dollars in R&D annually.[25] The pharmaceutical industry as a whole now spends over $100 billion a year on R&D – more than any other industry in the world.[26] It also spends a higher percentage of its total sales revenue on R&D than any other industry.[27] These massive investments in R&D produce surprisingly few new products each year. The FDA approves twenty-seven novel drug

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[21] *See* H.R. Rep. 98-857(II), 1984 U.S.C.C.A.N. 2686, 98th Cong., 2nd Sess. 1984 (describing the Hatch-Waxman Act as a "bill [that] allows drug manufacturers to use an abbreviated new drug application (ANDA) when seeking approval to make generic copies of drugs that were approved by the FDA," and that "encourages drug manufacturers to assume the increased costs of research and development of certain products which are subject to premarket clearance by restoring some of the time lost on patent life while the product is awaiting FDA approval"); *see also* Alfred B. Engelberg, *Special Patent Provisions for Pharmaceuticals: Have They Outlived their Usefulness?*, 39 J.L. & TECH. 389, 389 (1999).

[22] *See* Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 507-15 (2009) (reviewing the evidence on the importance of patents for incentivizing pharmaceutical R&D and the social-welfare gains attributable to that innovation).

[23] *See* Christopher P. Adams & Van V. Brantner, *Estimating the Cost of New Drug Development: Is It Really $802 Million?*, 25 HEALTH AFF. 420, 420 (2006); Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 180-83 (2003); Joseph A. DiMasi & Henry G. Grabowski, *R&D Costs and Returns to New Drug Development: A Review of the Evidence*, in THE OXFORD HANDBOOK OF THE ECONOMICS OF THE BIOPHARMACEUTICAL INDUSTRY 21-34 (Patricia M. Danzon & Sean Nicholson eds. 2012).

[24] E.U. JOINT RESEARCH CENTRE, DIRECTORATE-GENERAL FOR RESEARCH AND INNOVATION, EU R&D SCOREBOARD: THE 2012 EU INDUSTRIAL R&D INVESTMENT SCOREBOARD (EU R&D SCOREBOARD) 49 tbl. 5.2 (2012).

[25] *See* Martin Grueber & Tim Studt, *Industrial R&D—Life Sciences*, R&D MAGAZINE, 2012 GLOBAL R&D FUNDING FORECAST 14 (2011).

[26] *See* EU R&D SCOREBOARD, *supra* note 24, at 44 fg. 5.1 (reporting that the global pharmaceutical industry spent approximately €90 billion on R&D in 2011).

[27] *See* STUART O. SCHWEITZER, PHARMACEUTICAL ECONOMICS AND POLICY 21 (2d Ed. 2007).

compounds (i.e., "new molecular entities" or "NMEs") annually on average,[28] along with around twice that number of non-NME drug approvals (i.e., new formulations, new dosages, and new uses of existing drugs).[29] The majority of the industry's R&D spending goes to its de novo drug development programs to produce the handful of novel drug compounds that reach the market every year.[30]

The high cost of de novo drug (i.e., new drug) development is largely attributable to high failure rates, lengthy R&D times, and the sheer costs of clinical trials required for FDA approval.[31] Novel drug compounds must proceed through four main stages of R&D to reach the market: drug discovery, preclinical development, clinical development, and FDA approval.[32] The drug-discovery and preclinical-development stages together take three to seven years to complete on average, and have a stunningly low success rate.[33] For every novel drug compound entering the market, pharmaceutical companies have usually tested between 5,000 and 10,000 compounds in drug discovery and around 250 compounds in preclinical development.[34] The select few drug compounds that emerge from this process advance to the clinical development stage, where firms attempt to establish their drug's safety and efficacy in human trials. Novel

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[28] *See* FDA: Summary of NDA Approvals & Receipts, 1938 to the Present, *at* http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SummaryofNDAApprovalsReceipts1938tothepresent/default.htm; INTERNATIONAL FEDERATION OF PHARMACEUTICAL MANUFACTURERS & ASSOCIATIONS, THE PHARMACEUTICAL INDUSTRY AND GLOBAL HEALTH: FACTS AND FIGURES 7 (2011); Bernard Munos, *A Forensic Analysis of Drug Targets from 2000 through 2012*, _ CLINICAL PHARMACOLOGY & THERAPEUTICS _ (forthcoming 2013) (finding that between 2000 and 2012, the FDA approved 27 New Molecular Entities each year on average (excluding imaging agents)).

[29] *See* Joseph A. DiMasi, *Trends in Post-Approval Pharmaceutical R&D: Dissecting the Data on Line Extensions* (2007) *at* http://www.ifw-kiel.de/konfer/esf-ifw/newtech_1007/dimasi.pdf.

[30] CONGRESSIONAL BUDGET OFFICE (CBO), RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY 2 (2006) (noting that "incremental improvements on existing drugs," or "non-NMEs[,] constitute about two-thirds of the drugs approved by the Food and Drug Administration but account for only about one-third of the industry's R&D spending (by some estimates)"); Bruce Booth & Rodney Zemmel, *Prospects for Productivity*, 3 NATURE REV. DRUG DISCOVERY 451, 451 (2004) ("Although supplemental indications and new formulations of existing products do receive considerable development spending in many companies, the majority of R&D spending today still supports the discovery and development of new molecular entities.").

[31] *See* UNITED STATES GOVERNMENT ACCOUNTABILITY OFFICE (GAO), NEW DRUG DEVELOPMENT: SCIENCE, BUSINESS, REGULATORY, AND INTELLECTUAL PROPERTY ISSUES CITED AS HAMPERING DRUG DEVELOPMENT EFFORTS 6-7 (2006); Benjamin N. Roin, *The Case for Tailoring Patent Awards Based on the Time-to-Market of Inventions*, 61 UCLA L. REV. _ (forthcoming 2014) (noting that R&D times for new drugs are among the longest of any invention).

[32] *See* GAO, *supra* note 31, at 6-7.

[33] *See* GAO, *supra* note 31, at 6; Woodcock, *supra* note 34, at 4.

[34] *See* GAO, *supra* note 31, 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. In general, these two stages typically take a total of 6½ years to successfully complete for a particular compound."); 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).

drug compounds must complete three separate phases of clinical trials for FDA approval.[35] This process is notoriously expensive, takes five to nine years to complete on average,[36] and has a high risk of failure, since 80 to 90 percent of novel drug compounds entering clinical trials fail to reach the market.[37] From start to finish, the entire process of de novo drug development usually takes twelve to sixteen years.[38]

For all these reasons, the cost of de novo drug development is incredibly expensive. A 2007 study estimated that the average capitalized cost of successfully developing a novel drug compound is approximately $1.2 billion – a figure that includes out-of-pocket R&D expenses, the costs of capital, and the sunk costs of failed drug candidates.[39] Roughly half of the total costs were attributable to the drug-discovery and preclinical-development stages, while the other half came from the clinical-development stage necessary to satisfy the FDA's safety and efficacy standards.[40] More recent studies estimate that the average capitalized cost of developing a new drug has risen to between $1.5 and $1.8 billion.[41] Although these estimates of the costs of de novo drug development are controversial,[42] there is little doubt that developing a novel drug compound is extraordinarily costly.[43]

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[35] *See supra* notes 39 & 43.

[36] *See* Kenneth I. Kaitlin, *The Landscape for Pharmaceutical Innovation: Drives of Cost-Effective Clinical Research*, PHARMACEUTICAL OUTSOURCING, May 2010, at 3605.

[37] *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) (finding that between 1993 and 2004, approximately 19% of the drugs that entered clinical trials ultimately made it to the market); Navjot Singh et al., *The Anatomy of Attrition*, in INVENTION REINVENTED: MCKINSEY PERSPECTIVES ON PHARMACEUTICAL R&D 58 (Rodney Zemmel & Mubasher Sheikh, eds. 2010) (reporting that "more than 90 percent of compounds that enter Phase I trials are destined to fall out of the development pipeline").

[38] *See* GAO, *supra* note 31, at 1; Joseph A. DiMasi, *New Drug Development in the United States from 1963 to 1999*, 69 CLINICAL PHARMACOLOGY AND THERAPEUTICS 286, 292 fg. 6 (2001).

[39] Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 469, 469 & 475 (2007); *see also* Christopher P. Adams & Van V. Brantner, *Spending on New Drug Development*, 19 HEALTH ECON. 130, 138 (2010) (estimating that it costs $1.214 billion on average to develop a new drug); Ben Hirschler, *Drug Industry Treading Water on R&D Productivity*, REUTERS, Dec. 3, 2012 (estimating that it costs $1.1 billion on average to develop a new drug).

[40] *See* DiMasi & Grabowski, *supra* note 39, at 469; DiMasi et al., *supra* note 23, at ; Steven M. Paul et al., *How to Improve R&D Productivity: the Pharmaceutical Industry's Grant Challenge*, 9 NAT. REV. DRUG DISCOV. 203, 206 (2010); *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).

[41] *See* Jorge Mestre-Ferrandiz et al., *The R&D Cost of a New Medicine*, Office of Health Economics (2012); Paul et al., *supra* note 40, at 203.

[42] Some cost estimates for pharmaceutical R&D are controversial because they are based on non-public information. *See* Steve Morgan *et al.*, *The Cost of Drug Development: A Systematic Review*, 100 HEALTH POLICY 4, 11 (2011). However, the published studies using publicly available data on pharmaceutical R&D expenditures produce similar (albeit much rougher) estimates of the average capitalized cost of drug development. *See* Adams & Brantner, *supra* note 23, at 420; Adams & Brantner, *supra* note 39, at 138; OFFICE OF TECHNOLOGY ASSESSMENT ("OTA"), PHARMACEUTICAL R&D: COSTS, RISKS, AND REWARDS, OTA-H-522 (1993). A few commentators remain adamant that the published studies of pharmaceutical R&D costs grossly overestimate the true costs of drug

B. The Ease of Imitation by Generics

Pharmaceutical companies' R&D investments are highly susceptible to imitation and free riding by generic manufacturers. This vulnerability is particularly acute for investments in small-molecule drugs,[44] which make up over 90 percent of the drugs on the U.S. market, and roughly 65 percent of the recent drug approvals.[45] Generic manufacturers can quickly imitate these drugs with minimal or no investment in drug discovery, preclinical development or clinical trials.[46] When generic manufacturers enter the market, they typically set steeply discounted prices, which largely eviscerates a pharmaceutical company's revenue streams from a drug.[47]

Generic manufacturers generally skip almost all of the costly R&D involved in de novo drug development. Most small-molecule drugs are relatively easy to reverse engineer and duplicate, [48] and as a result, generic manufacturers can simply copy the drugs that

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development. *See* MARCIA ANGELL, THE TRUTH ABOUT DRUG COMPANIES AND HOW THEY DECEIVE US 37-51 (2004); Donald W. Light & Rebecca Warburton, *Demythologizing the High Costs of Pharmaceutical Research*, 6 BIOSOCIETIES 34 (2011); Public Citizen, *Rx R&D Myths: The Case Against the Drug Industry's R&D 'Scare Card'* (2001). However, many of the criticisms leveled against these studies are difficult to reconcile with basic financial principles. For example, these critics argue that it is inappropriate to consider the costs of capital when calculating the total costs of drug development for private investors. *See* ANGELL, *supra* at 45; Light & Warburton, *supra* at 8.

[43] Reports from academic research centers on the costs of industry-sponsored clinical trials are consistent with the reported high costs of clinical drug development. *See* Kristy Beal et al., *Budget Negotiation for Industry-Sponsored Clinical Trials*, 99 ANASTH. ANALG. 173 (2004); Jeanne Erdmann, *Researchers Facing Increasing Costs for Clinical Research, With Few Solutions*, 97 J. NAT. CANCER INST. 1492 (2005).

[44] *See* Janet Woodcock et al., *The FDA's Assessment of Follow-On Protein Products: A Historical Perspective*, 6 NAT. REV. DRUG DISCOVERY 437, 437-38 (2007). At present, the pharmaceutical industry's R&D investments in the newer large-molecule drugs ("biologics") are slightly less vulnerable to free riding than its investments in small-molecule drugs because biologics are harder to imitate. *See* Katherine Bourzac, *The Science of Biosimilars*, 2 CANCER DISCOVERY 295, 295 (2012). However, the barriers to imitating biologics should greatly diminish as technological improvements eventually allow generic manufacturers to satisfy the FDA's "biosimilarity" requirements with minimal or no clinical studies. *See* Steven A. Berkowitz et al., *Analytical Tools for Characterizing Biopharmaceuticals and the Implications for Biosimilars*, 11 NAT. REV. DRUG DISCOVERY 527, 527 (2012); Woodcock, *supra* at 442. In the long run, therefore, pharmaceutical companies' vulnerability to free-riding imitation in the biologics market should more closely resemble their vulnerability to such competition in the small-molecule markets. *See* Craig Wheeler, *Momenta Pharmaceuticals' Management Presents at 38th Annual dbAccess Health Care Conference (Transcript)*, Seeking Alpha, May 29, 2013; KARSTEN DALGAARD ET AL., BIOSIMILARS SEVEN YEARS ON: WHERE ARE WE AND WHAT'S NEXT? 5-7 (2013); BAIN & COMPANY, BIOSIMILARS: A MARATHON, NOT A SPRINT 2 (2008).

[45] *See* Bernard Munos, *Lessons from 60 Years of Pharmaceutical Innovation*, 8 NAT. REV. DRUG DISCOVERY 959 (2009) ("Of the 1,222 NMEs that have been approved since 1950, 1,103 are small molecules and 119 are biologics."); Munos, *supra* note 28, at _ (finding that between 2000 and 2012, 65% of the NMEs approved by the FDA were small-molecule drugs).

[46] *See* MARTIN A. VOET, THE GENERIC CHALLENGE: UNDERSTANDING PATENTS, FDA & PHARMACEUTICAL LIFECYCLE MANAGEMENT *xxii* (2005) ("Generic companies have no expense for discovery or development or marketing of drugs.").

[47] *See* Richard G. Frank & Erica Seiguer, *Generic Drug Competition in the U.S.*, *in* BUSINESS BRIEFING: PHARMATECH 56, 56–58 (2003).

[48] *See* Arvind K. Bansal & Vishal Koradia, *The Role of Reverse Engineering in the Development of Generic Formulations*, PHARMATECH.COM (2005); Bourzac, *supra* note 44, at 295 ("Conventional drugs are small molecules with defined

pharmaceutical companies identify as therapeutically valuable. This allows generic manufacturers to avoid the difficult and expensive drug-discovery and preclinical-development stages of de novo drug development. Moreover, generic manufacturers avoid the cost and uncertainty of the clinical development stage, because the FDA approves generic drugs based on the clinical-trial data submitted in support of the brand-name drug. Generics still need FDA approval to enter the market, but Congress established an abbreviated regulatory pathway for these products in the Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman Act").[49] Under Hatch-Waxman, generic manufacturers can enter the market based on the clinical-trial data submitted in support of the brand-name drug[50] if they can show (1) that their drug contains the same active ingredient as the brand-name drug,[51] (2) that it is "bioequivalent" to that brand-name drug,[52] and (3) that it will have the same label as the brand-name drug.[53] So long as generic manufacturers can copy the brand-name drug and its label, they can avoid the costly clinical development stage.

As a result, generic drugs are much faster and cheaper to develop than novel drug compounds. 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.[54] 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 about two to three years.[55]

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chemical structures," and once their structure is known, chemists "can reliably make a generic chemical drug whose structure and behavior will be identical to the original"). Reverse engineering controlled-release drugs can be much more challenging than reverse engineering immediate-release drugs, although much of the challenge stems from the difficulty of designing around the pharmaceutical companies' patents on the precise formulations of those drug-delivery systems. *See* Salah U. Ahmed & Venkatesh Naini, *Generic Oral Controlled Release Product Development: Formulation and Process Considerations*, in ORAL CONTROLLED RELEASE FORMULATION DESIGN AND DRUG DELIVERY: THEORY AND PRACTICE 321-22 & 332 (Hong Wen & Kinam Park eds. 2010).

[49] 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*, 540 U.S. _ (2013).

[50] *See* 21 U.S.C. § 355(j)(2)(A)(iv), (j)(8)(B).

[51] *See* 21 U.S.C. §355(j)(2)(A)(ii).

[52] *See* 21 U.S.C. §§355(j)(2)(A)(iii)-(iv). The FDA defines "bioequivalence" as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." 21 CFR § 320.1. As an alternative to showing of bioequivalence, the generic manufacturer can "show that the route of administration, the dosage form, and the strength of [its] drug are the same as those of the listed [branded] drug." 21 U.S.C. §§355(j)(2)(A)(iii).

[53] *See* 21 U.S.C. §355(j)(2)(A)(v). *But see infra* text accompanying note _ (explaining that generic manufacturers are permitted to exclude any patented indications from their drug label so long as it still contains at least one of the FDA-approved indications for the drug).

[54] *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).

[55] *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

Once generics drugs become available, they quickly drive down prices and capture most of the market for the brand-name drug.[56] The typical retail price for a generic drug is between 15 and 25 percent of the brand-name drug price.[57] Pharmaceutical companies have trouble competing at these prices.[58] By some estimates, they usually lose about 80 percent of their sales to generic manufacturers within the first four to six weeks of generic entry.[59] This switch to generic drugs usually occur fastest for top selling drugs,[60] where insurers have more to gain by implementing policies that will encourage patients to switch to the low-cost generics for drugs with higher sales volume.

C. The Need to Delay Generic Entry to Encourage Firms to Develop New Drugs

Given the high costs of de novo drug development and rapid loss of their market share following generic entry, pharmaceutical companies normally require a lengthy period of market exclusivity to recoup their R&D investments.[61] Some new drugs generate very high returns,[62]

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small-molecule generic, … development may be completed in 2-3 years, at a cost of USD 2-3 million."); *cf.* Jean O. Lanjouw, *The Introduction of Pharmaceutical Product Patents in India: 'Heartless Exploitation of the Poor and Suffering?'*, NBER Working Paper 6366, 21 & 39 tbl.4 (1998) (finding that throughout the 1980s and 90s in India, when patent protection for pharmaceuticals in India was extremely weak, "the introduction lag [for generics] was typically four or five years," and "since executives of Indian firms stated in interviews that they usually waited to see the extent of a new drug's acceptance internationally before investing heavily in process development, this implies very quick imitation by Indian firms.").

[56] *See* CBO, *supra* note 30, at 16.

[57] *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; GAO, *supra* note 31, at 1.

[58] *Cf.* Prabir Basu et al., *Analysis of Manufacturing Costs in Pharmaceutical Companies*, 3 J. PHARM. INNOVATION 30, 36 (2008) (reporting that the average costs of goods sold for brand-name drugs is approximately 27 percent).

[59] *See* Rich Silver, *A Wall Street Perspective on Generics*, 2007 GPhA Annual Meeting, at 6 (2007) *available at* http://www.gphaonline.org/AM/CM/ContentDisplay.cfm?ContentFileID=593. Some estimates point to a slightly more gradual erosion of brand-name drug sales to generics, such as a 70 percent drop in market share within six months of generic entry. *See* Datamonitor, *US Most Susceptible to Brand Erosion Post Patent Expiry*, Jan. 13, 2011, at http://about.datamonitor.com/media/archives/5293. On the other hand, one study found that in states that did not require patient consent for generic substitution between 2006 and 2007, Merck lost over 98% of its Zocor (simvastatin) sales for Medicaid patients to generic competitors within six months of its patent expiration. *See* William H. Shrank et al., *State Generic Substitution Laws Can Lower Drug Outlays Under Medicaid*, 29 HEALTH AFFAIRS 1383, 1387 (2010).

[60] *See* CBO, *supra* note 30, at 16.

[61] *See* Henry G. Grabowski, *Patents and New Product Development in the Pharmaceutical and Biotechnology Industries*, in SCIENCE & CENTS: EXPLORING THE ECONOMICS OF BIOTECHNOLOGY 99 (John V. Duca & Mine K. Yücel eds. 2003); Henry G. Grabowski & John Vernon, *The Distribution of Sales Revenues from Pharmaceutical Innovation*, 18 PHARMACOECONOMICS Suppl. 1, 21 (2000); United States Department of Health and Human Services, *Expanding the Use of Generic Drugs*, ASPE Issue Brief, 12-13 (2010), *at* http://aspe.hhs.gov/sp/reports/2010/GenericDrugs/ib.shtml.

[62] *See* Eric David et al., *Pharmaceutical R&D: the Road to Positive Returns*, 8 NAT. REV. DRUG DISCOVERY 609, 610 (2009); Henry Grabowski et al., *Returns on Research and Development for 1990s New Drug Introductions*, 20S PHARMACOECONOMICS 11, 22-23 (2002); THOMSON REUTERS, THE ECONOMIC POWER OF ORPHAN DRUGS 10

but the majority generate returns that are less than the average total development costs for novel drug compounds.[63] Consequently, for pharmaceutical companies to break even on their R&D investments, the market exclusivity period must be long enough for the profits from the commercial winners to offset the losers.

The optimal length of market exclusivity for encouraging de novo drug development is subject to controversy.[64] Nevertheless, a few scholars have produced estimates of the optimal market-exclusivity length for new drugs by comparing the average total R&D costs for novel drug compounds to the average net returns. Their studies suggest that the average novel drug compound needs between 9 to 16 years of market exclusivity for pharmaceutical companies to reach the breakeven point on their R&D investment.[65] Qualitative evidence – i.e., statements from industry insiders and accounts from the trade literature – suggest that pharmaceutical companies generally do not develop a new drug unless they expect at least 10 years of market exclusivity over the product.[66]

D. Promoting New Drug Development with Temporary Monopoly Rights to Delay Generic Entry

Since generic manufacturers only need a few years to develop and mass-produce low-cost imitations of brand-name small-molecule drugs,[67] pharmaceutical companies would have trouble

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(2012). Pharmaceutical companies obviously have trouble predicting which drugs will be successful, or else they would avoid the commercial failures. *See* David et al., *supra* at 610 ("Perhaps no one can consistently identify top-quartile drugs. Indeed, our analysis shows that, in any given small-molecule portfolio, only ~2% of drugs will be top-quartile sellers, whereas ~54% will be fourth-quartile sellers.").

[63] RODNEY ZEMMEL & MUBASHER SHEIKH, INVENTION REINVENTED: MCKINSEY PERSPECTIVES ON PHARMACEUTICAL R&D (2010); *see also* David et al., *supra* note 62, at 610; VALENTINA SARTORI ET AL., VALUE-DRIVEN DRUG DEVELOPMENT—UNLOCKING THE VALUE OF YOUR PIPELINE 3 exh.1 (2011); Grabowski & Vernon, *supra* note 61, at 24; Grabowski *et al.*, *supra* note 62, at 22-23.

[64] *See* Josh Bloom & Els Torreele, *Should Patents on Pharmaceuticals Be Extended to Encourage Innovation?*, WALL ST. J., Jan. 23, 2012.

[65] 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.tevadc.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). The author of this study used the same economic model as the other studies, but assumed lower costs of capital (10% instead of 11.5%-12.5%) and higher contribution margins (60% instead of 50%). *Id.*

[66] *See* Roin, *supra* note 22, 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).

[67] *See supra* notes and text accompanying notes 54-55.

recouping their R&D investments in these products without legal barriers to imitation. Pharmaceuticals is one of the few industries where patent scholars widely agree that firms rely heavily on such legal barriers to appropriate the returns from their R&D investments.[68] Recognizing this need for protection, Congress devised an elaborate system of drug patents and regulatory exclusivity periods to promote the development of new drugs.[69]

Pharmaceutical companies typically rely on product patents covering their drugs' active ingredient and formulation as their primary legal barrier for protection against generic competition.[70] The patent system will protect any newly discovered drug that is novel, nonobvious and useful,[71] giving firms a monopoly over the drug that expires 20 years after they file the patent application.[72] Product patents on the active ingredient in a drug are usually the strongest form of patent protection.[73] 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.[74] Pharmaceutical companies can

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[68] *See, e.g.*, JAMES BESSEN & MICHAEL J. MEURER, PATENT FAILURE: HOW JUDGES, BUREAUCRATS, AND LAWYERS PUT INNOVATORS AT RISK 88-89 (2008) (noting the great importance of patents in the pharmaceutical industry in comparison to most other industries); FEDERAL TRADE COMMISSION (FTC), TO PROMOTE INNOVATION: THE PROPER BALANCE OF COMPETITION AND PATENT LAW AND POLICY 14 (2003) (concluding that patents are "critical" to innovation in the pharmaceutical industry); 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) (noting that patents provide incentives for costly drug development that would not otherwise occur).

[69] *See supra* note 21.

[70] *See* Roin, *supra* note 22, at 545-56; William T. Comer, *Introduction*, *in* 8 COMPREHENSIVE MEDICINAL CHEMISTRY 4 (John B. Taylor & David J. Triggle eds. 2007) ("[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."). 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, _ (Fed. Cir. 2004) (*quoting* 21 C.F.R. § 314.108(a)). 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* Furrow, *supra* note , at 294-96; THOMAS, *supra* note 75, at 39.

[71] *Id.* at 516 & n.56 (discussing the threshold requirements for patenting drugs). Following the Supreme Court's 2013 decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.* , there might be a fourth eligibility requirement when patenting a new drug: does it exist anywhere in nature? 569 U.S. __ (2013). In *Myriad Genetics*, the Supreme Court invalidated a set of patents claiming certain isolated DNA strands because the "location and order of the nucleotides existed in nature before [the patentee] found them." *Id.* at. It is unclear whether this rule applies to non-DNA product patents, but if it does, any compound found in nature may be unpatentable, even if the existence of the natural compound was unknown prior to its patenting.

[72] 35 U.S.C. § 154(a)(2).

[73] *See* VOET, *supra* note 46, at 35 ("The best pharmaceutical patent is a compound patent.").

[74] *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 68, 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.").

also use product patents on their drug's formulation for protection to block generics from the market.[75] However, these formulation patents are only effective if 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.[76] Enforcing a product patent is also easy because the FDA requires generic manufacturers to disclose their drug's chemical composition to the pharmaceutical company, allowing for the automatic detection of infringement.[77]

Pharmaceutical companies can also block generic entry with process patents that cover a method of using their drug under some circumstances.[78] Federal law expressly allows for the patenting of "any new and useful process" that involves "a new use of a known … composition of matter."[79] These new-use patents give firms a legal monopoly over the act of taking or administering a particular drug for a particular indication.[80] Since generic manufacturers are neither taking nor administering them to patients, they do not directly infringe these patents.[81] However, generic manufacturers will indirectly infringe a new-use patent if they "actively induce infringement" by patients, pharmacists or physicians.[82] The FDA requires generic manufacturers to list on their label at least one of the approved indications for the brand-name drug.[83] Since the label instructs physicians and patients in how to use the drug, courts hold the generic manufacturer liable for inducing infringement if their label covers a patented indication.[84] Consequently, if pharmaceutical companies have protection over every FDA-approved indication for their drug, they can effectively exclude generics from the market with new-use

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[75] *See* JOHN R. THOMAS, PHARMACEUTICAL PATENT LAW 39 (2005).

[76] *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).

[77] *See* 35 U.S.C. 271(e)_.

[78] *See supra* notes and text accompanying notes _-_.

[79] 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).

[80] *See* THOMAS, *supra* note 75, at 44-46.

[81] *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, _ n.7 (Fed. Cir. 2003) (noting that "there is no evidence in the record that [the generic manufacturer] has directly practiced or will ever practice any of the methods claimed in the [new use] patent, … [which] is hardly surprising — pharmaceutical companies do not generally treat diseases; rather, they sell drugs to wholesalers or pharmacists, who in turn sell the drugs to patients possessing prescriptions from physicians.").

[82] *See Warner-Lambert Co.*, 316 F.3d at ; 35 U.S.C. § 271(b) (2012) ("Whoever actively induces infringement of a patent shall be liable as an infringer.").

[83] *See* 21 C.F.R. 314.127(a)(7).

[84] *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").

patents.[85]

Although product patents and method-of-use patents provide strong legal barriers against generic competition for many new drugs, many others fall through the cracks.[86] Some new drugs are unpatentable because a prior disclosure – usually in a journal article or older patent application – renders them non-novel or obvious.[87] Over the years, academic researchers and pharmaceutical companies have disclosed millions of distinct compounds with potential therapeutic value, and the vast majority of these compounds have never been tested in humans.[88] Later scientific advances or chance discoveries sometimes reveal that these known compounds are promising drug candidates, but because of the prior disclosures, they can be difficult or impossible patent effectively.[89] Other drugs receive insufficient patent protection to motivate their development because the patent term is too short.[90] Pharmaceutical companies file their patents relatively early in R&D,[91] and thus lose a significant portion of the 20-year term while developing their drugs.[92] The government gives pharmaceutical companies patent-term extensions to partially compensate for this loss of patent life.[93] Even with these extensions, some

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

[86] *See* Roin, *supra* note 22, at 515-45 (discussing how countless potentially valuable new drugs are no longer novel or nonobvious, and thus are unpatentable, due to prior disclosures of the compound in the academic literature or older patent filings); Benjamin N. Roin, *Drug Patent Length* (2009), *at* http://www.law.harvard.edu/faculty/faculty-workshops/faculty-workshop- secure/roin.workshop.paper.summer.2009.pdf (arguing that the current patent term is insufficient for drugs that require lengthy clinical trials to demonstrate efficacy, including treatments for early-stage cancer and cancer prevention); Eric Budish et al., *Do Fixed Patent Terms Distort Innovation? Evidence from Cancer Clinical Trials*, NBER Working Paper No. 19430 (2013), *at* http://www.nber.org/papers/w19430 (finding that the fixed patent term distorts R&D investments away from treatments for early-stage cancer and cancer prevention because they require lengthy clinical trials which erode a substantial portion of the firm's patent life).

[87] *See* Roin, *supra* note 22, at 515-45.

[88] *Cf.* 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).

[89] *See* Roin, *supra* note 22, at 515-45.

[90] *See* Roin, *supra* note 86; Budish et al., *supra* note 86.

[91] GRAHAM L. PATRICK, AN INTRODUCTION TO MEDICINAL CHEMISTRY 257 (3d Ed., 2005); *see also* 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).

[92] *See* Michael K. Dunn, *Timing of Patent Filings and Market Exclusivity*, 10 NATURE REV. DRUG DISCOVERY 487, 488 (2011).

[93] *See* Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187, 187-90 (1999) (discussing the legislative history of the patent-term extensions provided in Hatch-Waxman for drug patents). 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.

drugs take so long to develop that they would have little or no patent life remaining when they finally reach the market,[94] including many drugs for disease prevention or for treating early-stage disease.[95]

Since the patent system does not adequately protect all new drugs, Congress also grants firms regulatory exclusivity periods that run concurrently with their patent rights (if any) over those products.[96] These regulatory exclusivity periods operate as a guaranteed minimum term of protection against generics,[97] but different types of drugs receive different lengths of regulatory 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.[98] This five-year term of "data exclusivity" prevents generic manufacturers from entering the market unless they can produce all of the necessary preclinical and clinical data to support a new drug application, effectively defeating the purpose of being a generic.[99] Drugs approved for so-called "orphan" indications – i.e., diseases with small markets – automatically receive a seven-year term of market exclusivity.[100] When

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[94] *See* Roin, *supra* note 86; Budish et al., *supra* note 86.

[95] *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, Head of Translational Research in the Neurodegeneratives Diseases Group at Sanofi S.A., *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).

[96] *See* Engelberg, *supra* note 21, at 406 (noting that during the negotiations leading to the passage of the Hatch-Waxman Act, pharmaceutical companies were concerned the threat of generic competition would discourage the development of unpatentable drugs, and, "[b]eyond question, the five-year non-patent exclusivity, which effectively guaranteed that every new drug would have an exclusive marketing period of about seven years … whether or not it enjoyed any patent protection was the key to the compromise").

[97] *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).

[98] *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).

[99] *See* THOMAS, *supra* note 75, at .

[100] *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)). Some commentators argue that these exclusivity periods have proven too short to incentivize the development of most new drugs. *See* Roin, *supra* note 22, at 545-55 (showing that despite the guaranteed minimum term of protection through data exclusivity, pharmaceutical companies systematically screen through their pipeline to exclude drugs lacking strong patent protection, revealing that five years is generally insufficient to motivate the development of a new drug); _ . A broad coalition of patient-advocacy groups is currently lobbying to provide for longer exclusivity terms. *See MODDERN Cures Act Reintroduced*, DRUG DISCOVERY & DEVELOPMENT, Sept. 13, 2013, *at* http://www.dddmag.com/news/2013/09/moddern-cures-act-reintroduced; Marc Boutin,

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.[101]

In addition to their established exclusivity periods, pharmaceutical companies sometimes use creative litigation tactics or regulatory maneuvering to delay generic entry for as long as possible.[102] These tactics are known as "evergreening."[103] Most of these tactics have proven unsuccessful,[104] although they attract a great deal of attention from courts and commentators.[105]

In the end, pharmaceutical companies usually manage to keep generics off the market for somewhere between 10 and 15 years following the initial FDA approval of their drug.[106] The average effective patent life for new drugs – the time from FDA approval to generic entry – has remained unchanged at 11 to 12 years for much of the past three decades.[107] With an increasing number of drugs going off-patent, generic manufacturers have gradually come to dominate the overall market for prescription drugs. In 1984, when Congress formally established the regulatory pathway for generic drugs, roughly 19% of the prescriptions filled in the U.S. were for

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MODDERN Cures Act – H.R. 3497 Modernizing Our Drug and Diagnostics, *at* http://www.nationalhealthcouncil.org/NHC_Files/Pdf_Files/2013_VHLC_MODDERN.pdf.

[101] *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).

[102] *See* C. Scott Hemphill & Mark A. Lemley, *Earning Exclusivity: Generic Drug Incentives and the Hatch-Waxman Act*, 77 ANTITRUST L.J. 947, 948 (2011).

[103] *See* Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 348-49 (2007).

[104] *See id.* These evergreening strategies often involve relying on peripheral patents filed late in a drug's R&D or following its initial FDA-approval. *See* Kate S. Gaudry, *Evergreening: A Common Practice to Protect New Drugs*, 29 NATURE: BIOTECHNOLOGY 876 (2011); Lisa Larrimore Ouellette, *How Many Patents Does It Take To Make A Drug? Follow-On Pharmaceutical Patents and University Licensing*, 17 MICH. TELECOMM. TECH. L. REV. 299 (2010). However, these later-filed patents tend to be quite narrow, and generic manufacturers can often design around them easily. *See* C. Scott Hemphill & Bhaven N. Sampat, *When Do Generics Challenge Drug Patents*, 8 J. EMPIRICAL L. STUD. 613 (2011). A recent study by Hemphill and Sampat finds little evidence that these patents affect the date of generic entry. *See* C. Scott Hemphill & Bhaven N. Sampat, *Weak Patents Are a Weak Deterrent: Patent Portfolios, the Orange Book Listing* (2011), at http://conference.nber.org/confer/2012/IPKE/sampat.pdf.

[105] *See, e.g.*, Michael A. Carrier, *A Real-World Analysis of Pharmaceutical Settlements: The Missing Dimension of Product Hopping*, 62 FLA. L. REV. 1009 (2010); Gregory Dolin, *Reverse Settlements as Patent Invalidity Signals*, 24 HARV. J.L. & TECH. 281 (2011); Einer Elhauge & Alex Krueger, *Solving the Patent Settlement Puzzle*, 91 TEX. L. REV. 283 (2013); FEDERAL TRADE COMMISSION (FTC), GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY (2002); Michael Enzo Furrow, *Pharmaceutical Patent Life-Cycle Management after KSR v. Teleflex*, 63 FOOD & DRUG L.J. 275 (2008); Daniel I. Gordin, *Staving Off Death: A Case Study of the Pharmaceutical Industry's Strategies to Protect Blockbuster Franchises*, FOOD & DRUG L.J. 823 (2008); Hemphill & Lemley, *supra* note 102, at 948; C. Scott Hemphill & Baven N. Sampat, *Evergreening, Patent Challenges, and Effective Market Life in Pharmaceuticals*, 31 J. HEALTH ECON. 327 (2012); David E. Korn, *A New History of 180-Day Exclusivity*, 64 FOOD & DRUG L.J. 335 (2009); David W. Opderbeck, *Rational Antitrust Policy and Reverse Payment Settlements in Hatch-Waxman Patent Litigation*, 98 GEO. L.J. 1303 (2010); Arti K. Rai, *Use Patents, Carve-Outs, and Incentives – a New Battle in the Drug-Patent Wars*, 367 N. ENG. J. MED. 491 (2012).

[106] *See* Henry Grabowski & Margaret Kyle, *Generic Competition and Market Exclusivity Periods in Pharmaceuticals*, 27 MANAGERIAL & DECISION ECON. 491, 497 fg. 4 (2007); Hemphill & Sampat, *supra* note 105, at 328.

[107] *See* Grabowski & Kyle, *supra* note 106, at 497 fg. 4; Hemphill & Sampat, *supra* note 105, at 328.

generics.[108] That figure was up to 49% by the year 2000, and reached 80% in 2011.[109]

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

Most of the academic and policy literature regarding pharmaceutical innovation focuses on de novo drug development.[110] Indeed, scholars have often assumed that the discovery and development of novel drug compounds (*i.e.*, NMEs) is the only important form of pharmaceutical innovation.[111] This perception is wrong. The initial FDA-approval of a new drug is only the first milestone in its development. New drugs invariably have other potential therapeutic uses (i.e., indications), and the subsequent development of these new indications often provides the public with immense social value.[112] The testing necessary to establish the safety and efficacy of new indications is very expensive. Government funding for these clinical trials is available, but extremely limited and becoming even scarcer. Consequently, the public primarily relies on industry for the development of new indications.

A. FDA-Approved Drugs and their Potential New Uses

The drug-development process does not end when the FDA approves a new drug for marketing. The FDA's initial approval of a drug generally covers only one specific therapeutic

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[108] *See* CONGRESSIONAL BUDGET OFFICE (CBO), HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES IN THE PHARMACEUTICAL INDUSTRY 27 (1998).

[109] *See* CBO, *supra* note 108, at 27; PhRMA, PHARMACEUTICAL INDUSTRY PROFILE (2012).

[110] *See generally* Dana Goldman & Darius Lakdawalla, *Intellectual Property, Information Technology, Biomedical Research, and Marketing of Patented Products*, *in* 2 HANDBOOK OF HEALTH ECONOMICS 825 (__ eds. 2012) (surveying the economic literature); *add survey for legal literature*.

[111] *See* Ernst R. Berndt, et al., *The Impact of Incremental Innovation in Biopharmaceuticals: Drug Utilisation in Original and Supplemental Indication*, 24 Suppl. 2 PHARMACOECONOMICS 69, 70 (2005) (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. *See* MICHELE BOLDRIN & DAVID K. LEVINE, AGAINST INTELLECTUAL MONOPOLY 231 (2007).

[112] *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). Several studies have found that the efforts by pharmaceutical companies to develop new indications for their drugs typically generate large social returns. *See* Berndt et al., *supra* note 111, at 69; Joshua Cohen et al., *Role of Follow-On Drugs and Indications on the WHO Essential Drug List*, 31 J. CLINICAL PHARMACY & THERAPEUTICS 585 (2006); Joseph A. DiMasi, *Innovating by Developing New Uses of Already-Approved Drugs: Trends in the Marketing Approval of Supplemental Indications*, 35 CLINICAL THERAPEUTICS 808, 809 (2013); Henry Grabowski, et al., *Does Generic Entry Always Increase Consumer Welfare?*, 67 FOOD & DRUG L.J. 373, 377-78 (2012) (noting that many researchers "have documented the significant benefits to patients from supplemental indications").

use.[113] New drugs inevitably have other potential indications for which they might be safe and effective beyond the one initially listed on their label.[114] Although some of these new indications are closely related to the original FDA-approved use,[115] others involve the treatment of unrelated diseases.

Most FDA-approved drugs will have potential new indications for the treatment of entirely different diseases from their established uses.[116] Although pharmaceutical companies specifically engineer and test new drugs to treat a particular condition, their biological effects are inevitably complex and multidimensional.[117] The vast majority of drug compounds operate by targeting biological pathways that may affect the progress or symptoms of a range of diseases,[118] and almost all drugs have "off-target" activity on other biological pathways that may affect a different set of diseases.[119] Consequently, it is common that a drug designed to treat one disease

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[113] *Cf.* Gordon D. Schiff, et al., *Principles of Conservative Prescribing*, 171 ARCHIVES OF INTERNAL MED. 1433, 1436 (2011) ("Even indications for drugs approved by the US Food and Drug Administration must be viewed with caution: while the drug was shown to be effective for the specific indication studied, those patients or situations might not match your patient. Prescribers need to better understand the precise niche for each drug.").

[114] *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).

[115] *See* 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). 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.

[116] SAHOO, *supra* note 115, at 66-85;

[117] *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."); Michael J. Keiser et al., *Predicting New Molecular Targets for Known Drugs*, 462 NATURE 175 (2009) (reporting that "several lines of evidence suggest that drugs may have many physiological targets.").

[118] *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).

[119] *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.").

will have potential new indications for treating one or more entirely different conditions.[120]

There are many examples of drugs that were originally developed for one indication and later "repurposed" (or "repositioned") as treatments for one or more entirely different diseases. The drug Tarceva (erlotinib) is illustrative of how the drug-development process continues following the initial regulatory approval. It was originally developed to treat non-small-cell lung cancer[121] but subsequently approved for pancreatic cancer,[122] and is currently being tested for breast and ovarian cancers.[123] There is also growing interest in the potential to use Tarceva as treatment for psoriasis, type-1 diabetes, Hepatitis C, and a several other non-cancer diseases.[124] Similarly, the antiepileptic lamotrigine later received FDA approval as a maintenance therapy for Bipolar I Disorder,[125] and has been investigated as a treatment for a variety of other neuropsychological conditions.[126] The drug interferon-alpha was originally approved to treat hairy cell leukemia, but its label now includes indications for Non-Hodgkin's Lymphoma, metastatic melanoma, hepatitis C, and several other diseases.[127] As these examples suggest the continuing expansion and refinement of therapeutic uses for FDA-approved drugs is of critical importance to the practice of medicine.[128]

B. The Need for Clinical Trials to Determine the Safety and Efficacy of New Uses

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[120] *See* Joseph A. DiMasi, *supra* note 112, at 808; 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.

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

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

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

[124] *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).

[125] *See* FDA, *Lamictal Labeling Changes Overview* 2 (2010), *available at* http://www.fda.gov.

[126] *See* Meir Bialer, *Why are Antiepileptic Drugs Used for Nonepileptic Conditions?*, 53(Suppl. 7) EPILEPSIA 26, 28-29 (2012); Leslie Citrome, *Adjunctive Lithium and Anticonvulsants for the Treatment of Schizophrenia: What is the Evidence?*, 9 EXPERT REV. OF NEUROTHERAPEUTICS 55 (2009).

[127] *See* Product Information, Intron A, Interferon alfa-2b, Recombinant, *at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103132s5161lbl.pdf.

[128] *See* Ratner & Gura, *supra* note 114, at 869; Bernard Ravina, et al., *Funding Evidence: The National Institute of Neurological Disorders and Stroke Clinical Trials Program*, 1 NEURORX 317, 321-22 (2004).

Although not legally required,[129] clinical trials are generally necessary to demonstrate the safety and therapeutic efficacy of an existing drug for a new indication. Without such clinical data for a new indication, physicians generally are much less likely to prescribe the drug for that new use, particularly if it involves an entirely different disease.[130] Although the FDA does not prohibit off-label prescribing for these types of new indications, it does prohibit pharmaceutical companies from marketing their drugs for any off-label uses.[131] 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.[132] Assuming physicians are aware of the new indication, the principles of evidence-based medicine – which caution against prescribing treatments without sound evidence to support that use[133] – have become an increasingly important part of physician culture over the past two decades.[134] Moreover, almost all insurers now limit their coverage of prescription drugs to indications that are either approved by the FDA or listed in one of the pharmaceutical compendium.[135] Insurers possess a number of highly effective tools to enforce their indication-based restrictions on prescribing.[136]

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[129] 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. *See* William B. Schultz, Deputy Commissioner for Policy, Food and Drug Administration, *Promotion of Unapproved Drugs and Medical Devices*, Statement before the Senate Committee of Labor and Human Resources, Feb. 22, 1996, *available at* http://www.fda.gov/NewsEvents/Testimony/ucm115098.htm.

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

[131] *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).

[132] *See* Grabowski, et al., *supra* note 112, 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, *supra* note 22, 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.").

[133] *See* Gordon Guyatt, et al., *Evidence Based Medicine: A New Approach to Teaching the Practice of Medicine*, 268 JAMA 2420 (1992).

[134] *See* Bradley F. Marple, *Evidence-Based Medicine: Adjusting to a Culture Shift in Health Care*, ENT TODAY, Oct. 2008.

[135] *See* Cohen, et al., *supra* note 114, at 393-97;

[136] *See infra* notes and text accompanying notes _-_; Casali, *supra* note 130, at 1924 ("At the very least, physicians may be facing more red tape in order to prescribe off-label drugs. … More simply, third party payers … might just refuse to reimburse some off-label drugs, at their discretion."). In certain fields, such as psychiatry, insurers are often prohibited from using some of these tools for discouraging off-label prescribing. *See* Stuart Wright, *Memorandum*

Some new indications work their way into medical practice without any supporting evidence from clinical trials,[137] but this type of prescribing is generally thought to be problematic.[138] Off-label prescribing for untested indications is most worrisome when the indication is for an entirely different disease, since there may be little or no sound clinical evidence supporting that use of the drug.[139] Some of these untested indications are probably beneficial to patients, but others are probably ineffective and even harmful.[140] Many commentators suspect that this type of off-label prescribing causes more harm than good,[141] and there are constant calls for investments in clinical trials to test these indications.[142]

C. The High Cost of Clinical Trials

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.[143] At the very least, these development programs involve running phase III studies on the new indication.[144] Completing these clinical trials usually takes

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Report: Ensuring that Medicare Part D Reimbursement is Limited to Drugs Provided for Medically Accepted Indications, OEI-07-08-00152, Department of Health & Humans Services, at 2-3 & 5 (2011).

[137] 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).

[138] *See* JERRY AVORN, POWERFUL MEDICINES: THE BENEFITS, RISKS, AND COSTS OF PRESCRIPTION DRUGS _ (2004); Casali, *supra* note 135; 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); Schiff et al., *supra* note 113; Walton et al., *supra* note 120, 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.").

[139] *See* Schiff et al., *supra* note 113, at 1436.

[140] *See* Rosoff & Coleman, *supra* note 138, at 653.

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

[142] *See* Casali, *supra* note 135; 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 120. 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 113, at 1436.

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

[144] *See* Tudor I. Oprea & J. Mestres, *Drug Repurposing: Far Beyond New Targets for Old Drugs*, 14 AAPS J. 759, 762 (2012) (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

several years or longer, and depending on their size, can cost tens or even hundreds of millions of dollars.[145] In some cases, firms may also be required to complete phase I and II trials as well.[146] Although this process is much less expensive and risky than developing a new drug,[147] total costs can still run in the hundreds of millions of dollars.[148]

In each instance, the cost of clinical trials for new indications depends in part on whether the sponsor is planning to seek FDA approval for that new use. FDA regulations for clinical trials significantly increase the administrative costs of those studies with requirements for additional testing, recordkeeping and reporting.[149] Putting together an application for FDA approval of a new indication is also very costly.[150] The filing fee alone for these applications is over $1 million.[151] 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.[152] The FDA forces sponsors to conduct more rigorous trials,[153] and it (mostly)

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indication. *See* John King, *Can a Drug Live Forever?*, 9 R&D DIRECTIONS _ (2003) ("Modifying indications or doing other novel clinical uses with the product take the longest'" to develop, especially "[a]s one moves farther away from [the original indication], where we have most of our information").

[145] *See* ELLERY & HANSEN, *supra* note 115, at 124; SAHOO, *supra* note 115, 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.").

[146] *See* Curtis R. Chong & David J. Sullivan, *New Uses for Old Drugs*, 448 NATURE 645, 646 (2007).

[147] *See supra* notes and text accompanying notes 31-43.

[148] *See supra* note 145; SAHOO, *supra* note 115, 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.").

[149] *See* IOM, CANCER CLINICAL TRIALS, *supra* note 153, 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'L CANCER INST. 1492 (2005) (commenting on the "tremendous regulatory requirements" associated with conducting clinical trials that hopefully will be submitted to the FDA to support the approval of a new indication for an FDA-approved drug).

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

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

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

[153] *See* INSTITUTE OF MEDICINE (IOM), IMPROVING THE QUALITY OF CANCER CLINICAL TRIALS: WORKSHOP SUMMARY 78-79 (2008) (hereinafter "CANCER CLINICAL TRIALS").

prevents sponsors from distorting their study results with biased trial designs and selective reporting, which is thought to be a serious problem in the peer-review literature.[154] Consequently, most experts express a strong preference for sponsors to complete the FDA-approval process for new indications of drugs,[155] although the costs make it impractical for indications with very small markets.[156]

D. Inadequate Government Funding for Clinical Trials on New Uses

The NIH certainly has the capacity to run clinical trials testing new indications. However, it does not have nearly enough funding to pursue clinical trials for all the promising indications. Following a decade of budget cuts forcing the agency to scale back funding for clinical trials, the public is increasingly reliant on private industry to establish new indications for drugs.

The NIH is very well situated to develop new indications for existing drugs, where there is no need to create a novel drug compound and put it through the costly and scientifically challenging process of preclinical development. When researchers identify a potential new indication for a drug that is already on the market, the NIH can move directly into clinical trials. It has access to a wealth of highly qualified clinical researchers at NIH and university hospitals that can carry out this research without industry support[157] – particularly if they do not need to comply with the FDA's administrative requirements or put together an application for FDA approval of the new indication. As a result, many scholars have argued that the NIH should become much more active in funding clinical trials for new uses of drugs.[158]

The NIH has a relatively limited budget for clinical research, but it has always used some of that funding for clinical trials on new indications.[159] Given the high costs of those trials, the agency understandably is quite cautious in funding them, and strongly prefers pharmaceutical companies to pay for the clinical trials establishing new indications for existing drugs.[160] However,

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

[155] *See* Ratner & Gura, *supra* note 114.

[156] *See* Ratner & Gura, *supra* note 114, 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").

[157] *See* IOM, CANCER CLINICAL TRIALS, *supra* note 153.

[158] *See, e.g.,* Rai*, supra* note 105.

[159] *See* IOM, CANCER CLINICAL TRIALS, *supra* note 153, at 75 (noting that the National Cancer Institute (NCI) tends to fund clinical trials "to extend the indications of already approved drugs"); Ravina, et al., *supra* note 128, at 321-22 (explaining that because "[t]he pharmaceutical industry, which profits from developing new agents, cannot always be expected to be the sole sponsor of postmarketing studies for new indications," the "NINDS is currently supporting trials in several diseases for new uses of an FDA-approved intervention," although the examples given were all comparative-efficacy trials).

[160] *See* Michael Privitera, *Large Clinical Trials in Epilepsy: Funding by the NIH versus Pharmaceutical Industry*, 68 REVIEWS/EPILEPSY RES. 19-94 (2006); John C. Reed, et al., *The NIH's Role in Accelerating Translational Sciences*, 30

the NIH recognizes that industry is often unwilling to test potential new indications that are worthwhile investments from the public's perspective,[161] and does its best to provide the necessary funding.[162]

Unfortunately, the government either does not or cannot offer adequate financial support for this research.[163] Despite the evidence that publicly funded clinical trials generate large social returns on average,[164] the government spends only about one tenth of what the pharmaceutical industry spends on drug trials.[165] This small pool of funding must cover a variety of clinical-research areas that private industry often shuns, ranging from proof-of-concept trials for novel drug targets to comparative-efficacy studies.[166] Since the NIH funding environment is largely

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NATURE BIOTECHNOLGY 16, 18 (2012) ("Clearly, resources must be deployed cautiously when projects reach the clinic due to the high costs associated with clinical trials."); Salim Yusuf, et al., *Sensible Guidelines for the Conduct of Large Randomized Trials*, 5 CLINICAL TRIALS 38, 38 (2008) (noting that randomized and controlled clinical trials are "extremely expensive," and their high costs can "prevent the conduct of important trials of generic questions, especially those that are not supported by industry"). The NIH makes it more difficult to receive grants for large or complex clinical trials (or any grant request exceeding $1.5 million) by imposing additional layers of administrative review on those applications. *See* Francis S. Collins, *National Institute of Health Fiscal Year 2013 Budget Request*, Testimony before the Senate Subcommittee on Labor, Health and Human Services, and Education Appropriations, March 28, 2012.

[161] *See supra* text accompanying notes _-_ & *infra* text accompanying notes 243-259 (describing some of the market failures that lead pharmaceutical companies to underinvest in clinical trials for new indications on their patented drugs).

[162] *See* IOM, TRANSFORMING CLINICAL RESEARCH IN THE UNITED STATES: CHALLENGES AND OPPORTUNITIES: WORKSHOP SUMMARY 21 & 48 (2010) (hereinafter "TRANSFORMING CLINICAL RESEARCH").

[163] *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) ("Current and future trainees are challenged by enormous clinical demands, a highly competitive funding climate and an administrative bureaucracy that can delay activation of a research study for months and sometimes years while the science moves on."); Roxanne Nelson, *Funding Cuts Threaten Modernization of Cancer Research*, MEDSCAPE TODAY NEWS, Jun. 1, 2013, *at* http://www.medscape.com/viewarticle/805163.

[164] *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) (reviewing a series of eight clinical trials carried out by the US National Institute of Neurological Disorders and Strokes, and finding that they "generated major health benefits," "with an overall net benefit of the programme of $15.2 billion at 10 years," equating to a "yearly return on investment [of] 46%"); 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).

[165] Kristy Beal et al., *Budget Negotiation for Industry-Sponsored Clinical Trials*, 99 ANASTHESIA & ANALGESIA 173, 173 (2004); Kenneth A. Getz, *Sizing Up the Clinical Research Market*, CenterWatch 3 (2010) (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); 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 (noting that "Big Pharma" spends approximately $26 billion on clinical trials annually, compared to approximately $2.9 billion spent by the U.S. government).

[166] Charlie Schmidt, *Cooperative Groups Say NCI Trials Funding Inadequate; Some Turn to Industry*, 99 J. NAT'L CANCER INST. 830 (2007) ("While industry-sponsored trials focus chiefly on new-drug development, NCI's trials tackle a broader social agenda, fueled by cancer prevention, quality-of-life issues for patients, and the competing benefits of

zero-sum, proposals to increase funding for certain types of clinical research inevitably meet with resistance from the other areas of clinical research.[167] The demand for NIH funding is continually increasing relative to the supply in all of these fields,[168] since advances in medical science open up new avenues of research faster than they close old ones. Consequently, the NIH appears to fund only a small fraction of the socially valuable clinical trials in need of public support.[169]

There have been countless calls for the government to increase the NIH's funding for clinical research,[170] but the trend runs sharply in the other direction.[171] The NIH's budget fell by 20 percent in real dollars since 2003,[172] resulting in drastic cuts in the number of research projects it funds.[173] These budget cuts have been particularly detrimental to the public sector's

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different treatments or treatment combinations."); *see also* IOM, TRANSFORMING CLINICAL RESEARCH, *supra* note 159, at 21 (2010) (explaining that while industry funds clinical trials "largely to gain … (FDA) approval to market a new drug or a previously approved drug for a new indication, … the federal government conducts large clinical trials to answer medical questions unrelated to gaining regulatory approval for a new drug or therapy"); Nelson, *supra* note 163 (explaining that while industry funds clinical trials to "obtain FDA approval to market a new drug or extend the label of an existing agent," firms ignore a variety of other crucial areas of clinical research that the public must 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"); Janet Woodcock, *Today's Biomedical Innovation: 'Lost in Translation'?*, QB3 Entrepreneurs' Discussion, University of California, San Francisco, Apr. 26, 2012, at 11.

[167] *See* IOM, TRANSFORMING CLINICAL RESEARCH, *supra* note 159, 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).

[168] *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).

[169] *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) (noting that "[b]ased on the large returns for positive [clinical] trials, even if only 10% are positive, we are doing too few trials," and since "trials have other important impacts," "we almost certainly do too few trials").

[170] *See supra* notes _ & _.

[171] *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.

[172] *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 ("Meanwhile, the U.S. economy is stagnant, which … means there's little chance that funding for biomedical research will return tothe rapid growth it enjoyed in decades past. When adjusted for inflation, NIH funding is back to where it was a decade ago.").

[173] *See* Wadman, *supra* note 172. These cutbacks have had a devastating effect on the academic biomedical research community. *Id*. at 10 ("[A]cross the country people are closing labs, retiring early. This is a crisis."); Jones, *supra* note 171 (describing how the "slowly tightening fiscal belts" are causing "historically low success rates [in NIH grants]

capacity to carry out large phase III drug trials,[174] since clinical-trial costs have skyrocketed as the NIH's funding for that research fell.[175] As a result, the NIH has dramatically cut back on the number of phase III drug trials it funds,[176] and many of the established grant programs now cover less than half of trial costs, leaving academic research centers to make up the difference.[177] 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."[178] NIH funding for clinical research fell significantly in the five years following that conference, and the NIH is scheduled to lose another 8.2 percent of its budget over the next five years.[179] Given the federal government's large budget deficit and long-run fiscal troubles, most experts anticipate that NIH funding levels will stay flat or decline for at least another decade, and probably longer.[180]

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build to a crescendo with the enacting of the sequestration," such that many "people [are] essentially shutting their labs down, or shutting down particular areas of research").

[174] *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'").

[175] *See* Roger Collier, *Rapidly Rising Clinical Trial Costs Worry Researchers*, 180 CANADIAN MED. ASS'N J. 277 (2009); Schmidt, *supra* note 166, at 831-33; Yusuf et al., *supra* note 160, at 38.

[176] *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*, 6 CLINICAL ONCOLOGY _ (2011) (explaining that "continued lower funding levels—a consequence of the economic and political climate … means fewer clinical trials," mostly through a "drop in the number of Phase III trials"); IOM, A NATIONAL CANCER CLINICAL TRIALS SYSTEM FOR THE 21ST CENTURY: REINVIGORATING THE NCI COOPERATIVE GROUP PROGRAM 165 (2010) (hereinafter "NCI COOPERATIVE GROUP PROGRAM") (recommending that in response to the funding shortages from public sources, "the total number of trials undertaken by the Cooperative Groups should be reduced to a quantity that can be adequately supported"); Schmidt, *supra* note 166, at 832 ("Buckling under financial pressure, the cooperative groups have begun to eliminate some trials while making other painful cuts. Studies directed toward rare cancers— including sarcoma, some childhood tumors, and head-and-neck cancers—are particularly vulnerable."); Spector, *supra* note 173, at 9 (describing the increasing difficulty of receiving public grants to fund clinical research). 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 174, at 41.

[177] Schmidt, *supra* note , at 830; *see also* Jeanne Erdmann, *Researchers Facing Increasing Costs for Clinical Research, With Few Solutions*, 97 J. NAT'L CANCER INST. 1492, 1492 (2005); 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);

[178] Duley et al., *supra* note 174, 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).

[179] *See* OMB REPORT PURSUANT TO THE SEQUESTRATION TRANSPARENCY ACT OF 2012 (P. L. 112–155), *available at* http://www.whitehouse.gov/sites/default/files/omb/assets/legislative_reports/stareport.pdf.

[180] 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

The biomedical research community is trying to generate public support for increased funding,[181] but it may be an uphill battle. There appears to be a fundamental problem in the political economy of biomedical research funding, which may prevent the government from ever adequately supporting that research. Indeed, the recent NIH budget cuts have merely accelerated a trend dating back to the mid-1960s of declining government support for R&D (as a percentage of GDP) and the concomitant shift to industry funding.[182] Although there are compelling public policy reasons to support the NIH and its clinical research programs,[183] the political incentives to fund this research are relatively weak.[184] The benefits from government-funded R&D take many years to arrive, which is well beyond the relevant political time-horizon for most elected officials.[185] Inadequate government support for R&D can cause significant harm, but those harms are largely invisible to voters, since they cannot observe innovations that do not exist because of inadequate government funding. In a world where legislators are under pressure to reduce the budget deficit without increasing taxes or cutting entitlement programs, cuts to

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flat funding"); *see also* Spector, *supra* note 173, at 10-11 ("The widespread assumption is that U.S. federal spending for medical research will stay flat, or maybe continue to drop. … 'Institutions across the nation are coming to grips with the new normal.'").

[181] *See, e.g.*, Jocelyn Kaiser, *Researchers and Advocates Gather in Washington, D.C., to Protest Cuts to Medical Research*, Science Insider, Apr. 8, 2013, at http://news.sciencemag.org/health/2013/04/researchers-and-advocates-gather-washington-d.c.-protest-cuts-biomedical-research ("Thousands of scientists and patient advocates poured into a square in downtown Washington, D.C., today to hold what organizers billed as the largest-ever rally to call for more funding for biomedical research.").

[182] The past ten years greatly accelerated this trend in the field of clinical research, but did not change its trajectory. *See* Linda Bressler, *Industry Collaboration in Cancer Clinical Trials*, in ONCOLOGY CLINICAL TRIALS: SUCCESSFUL DESIGN, CONDUCT, AND ANALYSIS 315 (WM. Kevin Kelly & Susan Halabi, eds., 2010) ("In the 1950s and 1960s, the majority of research funding to universities came from the government, with private industry providing less than 5% of research funding. The sources of funding have shifted considerably, and by the early 2000s, for-profit companies were providing financial support for 70% of clinical drug trials conducted at academic medical centers."). The same basic pattern holds true for government R&D spending more generally. *See* CONGRESSIONAL BUDGET OFFICE (CBO), FEDERAL SUPPORT FOR RESEARCH AND DEVELOPMENT vii-viii, 3-7 (2007) (noting that "[s]ince [1964], with the exception of a period in the 1980s—when an expansion of national defense activities prompted more funding for research and development—federal R&D spending has generally declined as a share of GDP").

[183] *See supra* note 164.

[184] *See* LINDA R. COHEN & ROGER G. NOLL, THE TECHNOLOGY PORK BARREL 55-63 (1991)

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

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

COHEN & NOLL, *supra* note 184, at 61.

"discretionary" R&D spending may be inevitable.[186] This dynamic helps explain why Congressional leaders consistently express strong, bipartisan support for biomedical research funding at the same time as they slash the NIH's budget.[187]

This political economy problem may be particularly severe in the government's support for the discovery and development of new treatments for unmet medical needs. As the U.S. government takes on a greater share of the nation's health care costs, there is growing political resistance to public support for this type of biomedical research,[188] since it gives rise to new treatments that tend to be expensive.[189] In the 2010 Affordable Care Act, Congress authorized (and encouraged) the NIH to redirect a significant portion of its budget to research cost-savings strategies in health care, comparative efficacy trials, and cost-effectiveness studies.[190] And as a recent article in JAMA explains, this "conflict over research goals … is certain to increase as the nation struggles with aging, cost, deficits, and taxation."[191]

There is a growing consensus within the academic clinical research community that the public must find alternative funding sources for public sector research, including clinical trials for new indications.[192] At present, private industry is one of the few viable options,[193] and university

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[186] *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.").

[187] *See* Jones, *supra* note 170; Brad Plumer, *The Coming R&D Crash*, WASHINGTON POST WONKBLOG, Feb. 26, 2013, *at* http://www.washingtonpost.com/blogs/wonkblog/wp/2013/02/26/the-coming-rd-crash/.

[188] *See* E. Ray Dorsey et al., *Funding of US Biomedical Research, 2003-2008*, 303 JAMA 137, 137 (2010) ("Debate in the United States about the role of the federal government in providing health insurance has cast attention on the allocation of research support, especially between discovery of new clinical interventions and evaluation of their effect, value, and cost.").

[189] *See, e.g.*, Johnston, et al., *supra* note 164, at 1324 (finding that a program of NIH-funded clinical trials "led to increased expenditures on health, [but] the resultant health benefits have a much greater value than these costs, even when valued conservatively").

[190] *See* NIH, HEALTH ECONOMICS: NIH RESEARCH PRIORITIES FOR HEALTH CARE REFORM: MEETING SUMMARY (2010), *at* http://commonfund.nih.gov/pdf/2010May10_11_Health_Econ_Meeting_Summary.pdf.

[191] Moses & Dorsey, *supra* note 172, at 2341.

See IOM, TRANSFORMING CLINICAL RESEARCH, *supra* note 159, at 21 ("The beginnings of a coordinated prioritization of research needs can be seen in the recent increased interest in comparative effectiveness research (CER). … Several speakers and workshop participants raised questions about the ability of the current clinical trials system, which is already showing signs of strain, to absorb a substantial amount of the anticipated CER studies.").

[192] *See* 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, given Congress's inability to maintain a steady level of funding, "it would be preferable for academic medical centers to cease relying so heavily on the NIH for research funding"); Spector, *supra* note 173, 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.").

[193] Moses & Dorsey, *supra* note 172, 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."); *see also* Eastman, *supra* note 194, at ("NCI cooperative groups are going to be turning more and more to industry for research funding."); Jennifer L. Kellen, 3*Clinical Trials Budgeting Methods & Best Practices*, University of California San

researchers are already turning to the pharmaceutical industry.[194] Of course, industry acts with a profit motive, so relying on it for clinical trials can come at the expense of carrying out socially valuable research that would not be profitable for pharmaceutical companies.[195] To maximize the portion of the NIH budget that can go to socially valuable but unprofitable research, NIH officials and academic research centers increasingly emphasize the need to hand-off projects to industry at the earliest possible stage to conserve scarce NIH resources for the research that industry will not fund.[196]

IV. THE FAILURE TO INCENTIVIZE THE DEVELOPMENT OF NEW USES FOR EXISTING DRUGS

Pharmaceutical companies are unlikely to invest in developing a new indication without some form of monopoly protection.[197] As discussed in Section III, it can cost tens or even hundreds of millions of dollars to generate the knowledge that a particular drug is a safe and effective treatment for a specific condition in a certain subset of patients.[198] To recover that investment, pharmaceutical companies must sell the drug for its new indication at a price far above their marginal production costs.[199] This pricing strategy is impractical when other firms

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Francisco, 52 (2010) *at* http://or.ucsf.edu/cg/7893-DSY/version/default/part/4/data/ ("[P]artnerships with industry … are expected to increase").

[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 (describing how academic clinical researchers have increasingly turned to industry for funding, "which the NCI maintains have been highly valuable even if they cannot always compensate for lack of adequate public funding"); 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 176, at (explaining that as the NIH's budget constraints continue, the NCI cooperative groups have starting conducting phase III trials in partnership with pharmaceutical companies, but only "with great reluctance," since '[a] network of publicly funded clinical trials that's not motivated by profit, like the NCI cooperative groups, represents the kind of independent research most dear to our society,'" and the 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) ("Public-private partnerships permit the leveraging of the NIH's clinical and scientific resources with a wide variety of private entities, … [which] we think will hasten the translation of basic discovery to medicine for the public."); Reed et al., *supra* note 160, 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* SAHOO, *supra* note 115, at 41-42.

[198] *See supra* text accompanying notes 143-148.

[199] *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).

can sell the exact same drug to patients for the identical indication.[200] Indeed, clinical trials are the textbook example of an R&D investment firms do not make without monopoly protection, given their high costs and vulnerability to free riding.[201] Since the public largely relies on pharmaceutical companies to fund the clinical development of new indications,[202] it must provide firms with some form of protection to motivate these investments.

The government encourages firms to develop new drugs by offering them the power to exclude generic manufacturers from making or selling the patented drug. This form of monopoly protection is clearly inappropriate for encouraging the development of new indications since it would cover all the drug's uses, including the ones already available to the public. To provide firms with an appropriate incentive for developing new indications, the government would need to offer monopoly protection that attaches to the act of taking or administering the drug for the new indication.

Although the patent system currently provides firms with monopoly rights over new indications, those legal rights are difficult or impossible to enforce without knowing which patients are using the drug for the patented indication as opposed to some other use. Physicians and often insurers have this information, but pharmaceutical companies rarely have access to this type of data. As a result, pharmaceutical companies only invest in developing new indications during the narrow window of time before generics enter the market. This gap in the patent protection for drugs is the single most widely recognized distortion in the incentives for pharmaceutical innovation[203] – "the problem of new uses."[204]

A. Ineligible for the Standard Monopoly Protection Offered to New Drugs

When Congress established the existing legal infrastructure of drug patents and regulatory exclusivity periods, it designed the system to promote the discovery and development of new drugs, not new indications.[205] The pharmaceutical industry's entire business model hinges

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[200] *See* Eisenberg, *supra* note , at 717; Grabowski et al., *supra* note 112, at .

[201] *See* PEDRO BARROS & XAVIER MARTINEZ-GIRALT, HEALTH ECONOMICS: AN INDUSTRIAL ORGANIZATION PERSPECTIVE § 17.1 (2012); BESSEN & MEURER, *supra* note 68, at 88-89 (2008); BOLDRIN & LEVINE, *supra* note 111, at 237; JAFFE & LERNER, *supra* note 68, at 39-41.

[202] *See supra* text accompanying notes _-_.

[203] *See, e.g.*, Grabowski et al., *supra* note 112, at 382 ("[M]anufacturers have no incentive to conduct R&D and seek approval for new indications for a brand after it experiences generic entry because the large majority of prescriptions for such new indications will be filled with the generic."); Thomas A. Hemphill, *The NIH Promotes Drug Repurposing and Rescue*, 55 RES. TECH. MANAGEMENT 6, 8 (2012) ("Off-patent or near patent expired drugs will remain unattractive to the pharmaceutical industry, as the long-term financial returns for the product may be limited."); Philip Walson, *Generic and Therapeutic Orphans*, 1 GENERICS & BIOSIMILARS INITIATIVE J. 39 (2012) ("Neither the brand name nor generic drug industries have done much to improve the testing, formulation and labelling of non-profitable off-patent drugs for either new indications or new, small patient populations.").

[204] Eisenberg, *supra* note , at 717.

[205] *See supra* note 21.

upon acquiring temporary monopoly rights that block generic manufacturers from making and selling their drug.[206] However, the government generally does not provide this form of monopoly protection for new indications of a drug, and for good reason. Monopoly rights that block generic entry give pharmaceutical companies control over the entire market for a drug. This would allow firms to charge consumers supra-competitive prices for the drug's old indications as well as the new.

In the pharmaceutical industry, the standard form of monopoly protection for promoting drug development is the power to exclude generic manufacturers from making or selling that drug compound. As discussed in Section II, 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 for them 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 regulatory exclusivity periods. Although each one offers a different set of legal rights, pharmaceutical companies use them for the same purpose. The objective is always to achieve to delay the introduction of generic drugs onto the market. One or more of these rights will almost always be available to pharmaceutical companies for a new drug. Between their product or process patents and regulatory exclusivity periods, pharmaceutical companies usually enjoy between 10 and 15 years of standard monopoly protection over their new drugs before generics enter and usurp the market.[209]

The government does not provide this standard form of monopoly protection for new indications developed after a drug's initial approval.[210] Pharmaceutical companies can only patent a drug's active ingredient and formulation once, and they invariably file these patents while developing the drug for its first indication.[211] The government generally allows

[206] *See supra* text accompanying notes 61-66.

[207] *See supra* notes and text accompanying notes 23-43.

[208] *See supra* notes and text accompanying notes 56-59.

[209] *See supra* notes and text accompanying notes 106-107.

[210] The U.S. has at least one exception to this rule. 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. 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 in many cases. *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) ("many critics of the pediatric exclusivity provision complain that the benefit to companies of six months of exclusivity dwarfs the cost of conducting the requisite clinical trials"); Barbara A. Noah, *Just a Spoonful of Sugar: Drug Safety for Pediatric Populations*, 37 J.L. MED. & ETHICS 280, 282 (2009) (noting that the pediatric exclusivity provision has "created controversy because it has delayed the market entry of generic versions of blockbuster and/or highly priced drugs, some of which physicians rarely prescribe to children").

[211] *See supra* note 91

pharmaceutical companies to obtain patents on newly discovered indications for drugs.[212] However, as long as a drug has at least one FDA-approved indication that is off-patent, generic manufacturers can easily design around (*i.e.*, ignore) these new-use patents by excluding the patented indications from their label[213] – a practice known as "skinny labeling."[214] Generic manufacturers use this same tactic to design around the regulatory exclusivity periods that are awarded for new indications.[215] Pharmaceutical companies receive a three-year data exclusivity period for any newly approved indication of a drug,[216] and a seven-year data exclusivity period for any new orphan indications,[217] but generic manufacturers can still enter the market if they only list the off-patent indications on their label.[218]

The government's unwillingness to offer firms that develop new indications for older drugs the standard monopoly protection is not an accident.[219] Congress intentionally designed

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[212] Newly discovered indications are eligible for patent protection so long as those indications have not been disclosed in a prior publication or previously used by the public. *Warner-Lambert Co.*, 316 F.3d at . Unfortunately, many potentially valuable new indications have already been disclosed in printed publications, which may render them unpatentable. *See* Ted T. Ashburn & Karl B. Thor, *Drug Repositioning: Identifying and Developing New Uses for Existing Drugs*, 3 NATURE REVIEWS DRUG DISCOVERY 673 (2004) (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 144 (noting that the "[r]ecent academic enthusiasm in this field [of drug repurposing] has resulted in the publication of relatively long lists of drugs that could potentially be repurposed for a variety of indications," but "[a]s this information is now public domain, even if experimentally confirmed, it still constitutes 'prior art.'"). Moreover, some new indications may be unpatentable under the inherent anticipation rules because patients using the drug for its original indication unwittingly benefited from its new (previously unknown) indication. *See* Roin, *supra* note 22, at 525-26.

[213] 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*, 540 U.S. _, _ (2013). 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) ("FDA will refuse to approve an abbreviated application for a new drug [if] … Information submitted in the abbreviated new drug application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the abbreviated new drug application except for changes required … because aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use."). The Federal Circuit has blessed these regulations as consistent with Congressional intent.

[214] *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).

[215] *See* Eisenberg, *supra* note , at 728-30.

[216] *See* 35 U.S.C. § 355(j)(5)(F)(iii).

[217] *See* 21 U.S.C. § 360cc.

[218] *See* SAHOO, *supra* note 115, at 42 ("Innovator companies are still awarded three years of data exclusivity for a change to a product's label that requires clinical trials to be conducted, but in the case of indication extensions though, generics companies can frequently get around this exclusivity by excluding the additional indication from their application. Because of the high levels of off-label prescribing in the US, the generic product is often used for the new indication even though its label does not reflect the new usage.").

[219] *See Warner-Lambert*, 316 F.3d at _ ("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.").

the existing legal infrastructure to provide temporary monopoly protection so consumers would eventually have access to low-cost generic versions of a drug.[220] If pharmaceutical companies received the standard form of monopoly protection for developing new indications, they could delay the entry of generics for much longer than Congress intended, perhaps indefinitely in some cases.[221] Although delaying generic entry may increase the incentives for pharmaceutical innovation, it would significantly increase the nation's health care costs.[222] Growing use of generic drugs has generated tremendous cost savings for consumers and the U.S. health care system.[223] By one estimate, generic drugs saved the U.S. health care system more than a $1 trillion over the past decade, and currently produce about $1 billion in savings every two days.[224] They also increase consumers' access to valuable medications.[225] Even for patients with prescription drug insurance, the high prices of patented drugs can restrict patients' access to those treatments because of the various cost-sharing and coverage restrictions imposed by insurers.[226]

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[220] *See supra* note 205.

[221] *Warner-Lambert*, 316 F.3d at _ (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.").

[222] The average retail price of generic drugs is 15 to 25 percent of the brand-name price, and the percentage of prescriptions filled with generic drugs rose from 19% to almost 80% between 1984 and 2012. 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; United States Government Accountability Office (GAO), *Drug Pricing: Research on Savings from Generic Drug Use*, GAO-12-371R, at 1-2 (2012); CBO, *supra* note 223, at 27; Murray Aitken et al., *Prescription Drug Spending Trends in the United States: Looking Beyond the Turning Point*, 28 HEALTH AFFAIRS w151 (2008).

[223] *See* Steven K. Dobscha et al., *Reducing Drug Costs at a Veterans Affairs Hospital by Increasing Market-share of Generic Fluoxetine*, 43 COMMUNITY MENTAL HEALTH J. 75 (2007); Amy B. Scott et al., *Effects of a Physician Office Generic Drug Sampling System on Generic Dispensing Ratios and Drug Costs in a Large Managed Care Organization*, 13 J. MANAGED CARE PHARMACY 412 (2007); Shrank et al., *supra* note 59.

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

[225] The widespread use of prescription-drug insurance avoids much of the deadweight loss that might otherwise result from drug patents. *See* Benjamin N. Roin, *Intellectual Property versus Prizes: Reframing the Debate*, 81 U. CHI. L. REV. _ (forthcoming 2014); Darius Lakdawalla & Neeraj Sood, *The Welfare Effects of Public Drug Insurance* 93 J. Public Econ. 541 (2007). Moreover, the gains to consumers from generic drug prices may be partially (or even entirely) offset by the reduction in the pharmaceutical company's marketing activities and clinical research (e.g., testing their drugs for new indications) following 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 112; Darius Lakdawalla & Tomas Philipson, *Does Intellectual Property Restrict Output? An Analysis of Pharmaceutical Markets*, 55 J.L. & ECON. 151, 178-79 (2012). Of course, some of the marketing activities responsible for this effect are probably wasteful, which makes the data harder to evaluate.

[226] 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

Standard monopoly rights, which block generic entry from the market entirely, are unsuitable as an incentive for new indications because they allow a firm to charge supra-competitive prices for the drug's old uses as well as the new. The 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.[227] 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."[228] 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. Granting the standard monopoly rights to encourage the development of new indications would break the link between the incentive for those R&D investments and their social value by giving firms control over a drug's entire market.[229]

B. The Enforcement Problem with Monopoly Rights over New Uses

The appropriate incentive for firms to develop a new indication for drugs is monopoly protection over the new indication only, thereby encouraging development of new uses without denying the public access to generics for old uses. The patent system already offers monopoly rights suitable for encouraging the development of new indications – a right to the new use itself. However, firms cannot enforce these rights without knowing when a drug is being used for the patented use. Since that information is rarely available to pharmaceutical companies, these patent rights typically have little or no economic value once generics are on the market.

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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).

[227] *See* Anup Malani & Jonathan S. Masur, *Raising the Stakes in Patent Cases*, 101 GEO. L.J. (forthcoming 2013); Peter S. Menell & Suzanne Scotchmer, *Intellectual Property*, *in* 2 HANDBOOK OF LAW AND ECONOMICS 1477 (A. Mitchell Polinsky & Stenven Shavell eds. 2007) (explaining that "[s]ince the private value of the invention generally reflects the social value, inventors should be willing to bear higher costs for inventions of higher value," and "inventors [will] weed out their bad ideas"); Steven Shavell & Tanquy van Ypersele, *Rewards Versus Intellectual Property Rights*, 44 J.L. & ECON. 525, 530 (2001) ("Under the patent system, … the incentive to invest is linked to actual social surplus because the innovator knows the demand for the potential innovation.").

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

[229] In theory, the government could correct this problem by tailoring the length of exclusivity to the social value of the new indication, granting longer periods for more valuable indications and shorter periods for less valuable indications. *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).

To provide firms with the appropriate incentives for developing new indications, the government must offer them monopoly protection that does not involve blocking generic manufacturers from the entire market for a drug. When a firm delivers a new indication to the public, and the public already had access to the drug's older indications, the appropriate reward is a temporary monopoly right over the new use, not the drug itself. These rights require entirely different enforcement mechanisms. Unlike the standard form of monopoly protection, which attaches to the act of manufacturing and selling the drug compound, monopoly protection for new uses must attach to the act of taking or administering the drug for the new indication.

The patent system seemingly provides this protection already by allowing firms to patent newly discovered indications of drugs.[230] As discussed above, the researchers who discover a new indication can usually patent it, giving them a monopoly right over the act of taking or administering a drug for that specific indication.[231] These new-use patents cannot keep generics off the market if there are any other off-patent FDA-approved uses for the drug.[232] However, they do give firms a legal right to charge patients – probably through their insurer – when they the drug for the patented indication.[233] 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 patients (or their insurers) to pay them directly when they use a low-cost generic for a patented indication.

However, enforcement of a new-use patent is only possible when the relevant parties

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[230] *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).

[231] Of course, not all new indications will be patentable. *See supra* note 212. Normally, the government uses (or could use) regulatory exclusivity periods to fill in where the patent system fails to provide adequate protection to encourage the development of new drugs. *See supra* notes and text accompanying notes 96-101. However, these regulatory exclusivity periods are only meant to block generic manufacturers from the market. They do not provide an enforceable right against patients, insurers, pharmacists, or generic manufacturers that knowingly sell their drug to patients who will use it for a patented indication (so long as the patented indication is not listed on the generic's label). If the government wants to protect unpatentable new indications with regulatory exclusivity periods, it might need to change the nature of those monopoly rights to make them enforceable against these other parties.

[232] *See supra* notes and text accompanying notes 78-85.

[233] Patients (and physicians) could be held directly liable for infringing a new-use patent if they (self-)administer a low-cost generic for the patented indication. *See* Eisenberg, *supra* note _, 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 ("[F]ew 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."). 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 ("[I]t is less efficient to sue numerous patients and physicians than it is to sue a single manufacturer."); *see also* ROBERT MERGES & JOHN DUFFY, PATENT LAW & POLICY: CASES AND MATERIALS 400 (5th Ed. 2011). Insurance companies, pharmacists and generic manufacturers would be a much more sensible target for these suits. Under current law, pharmacists could probably be held liable for indirect infringement if they knowingly dispense a generic drug for a patented indication. <*case*> Establishing liability against the insurer or generic manufacturer might be more difficult, although pharmacists might require insurers to indemnify them from this potential liability as part of their reimbursement agreement.

know that a patient is using the drug for the patented indication. Pharmacists, insurers and generic manufacturers will not be culpable for indirect infringement of a new-use patent without knowledge that a patient is using the drug for a patented indication.[234] Moreover, pharmaceutical companies cannot hold patients or these other parties liable unless they can detect their infringing acts.

Pharmaceutical companies almost never have access to the information they need to enforce a new-use patent.[235] When physicians prescribe a drug to a patient to treat a particular indication, the patient's medical condition is confidential information.[236] Physicians sometimes disclose the prescribed indication to pharmacists and insurers, especially when required as a condition for insurance coverage.[237] However, they almost never share that information with pharmaceutical companies. Without access to patient-level information, pharmaceutical companies cannot enforce their new-use patents to charge insurers when physicians prescribe an off-patent drug for a patented indication.

C. *The Problem of New Uses*

Without a viable enforcement mechanism for new-use patents, the current system fails to provide incentives for the development of new indications separate from the standard monopoly protection awarded to new drugs. Because that monopoly protection is temporary, pharmaceutical companies' interest in testing their drugs for new indications is also temporary.

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[234] *See Global-Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. _ (2011).

[235] Pharmaceutical companies can sometimes purchase patients' de-identified health records. *See* Jordan Robertson, *States' Hospital Data for Sale Puts Privacy in Jeopardy*, BLOOMBERG NEWS, Jun. 5, 2013, at http://www.bloomberg.com/news/2013-06-05/states-hospital-data-for-sale-puts-privacy-in-jeopardy.html (""); Jim Avila & Serena Marshall, *Your Medical Records May Not Be Private: ABC News Investigation*, Sept. 13, 2012, at http://abcnews.go.com/Health/medical-records-private-abc-news-investigation/story?id=17228986&singlePage=true; Carol Eisenberg, *Drugmakers Mine Data for Trial Patients*, BLOOMBERG BUSINESSWEEK MAGAZINE, Nov. 3 2011, *at* http://www.businessweek.com/magazine/drugmakers-mine-data-for-trial-patients-11032011.html. However, they cannot target the records of patients taking a particular drug.

[236] *See* 67 Fed. Reg. 53182.

[237] *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). As noted in Section III, insurers generally limit their coverage for expensive, patented drugs to a specific set of indications. *See supra* note 135. Insurers enforce these coverage restrictions primarily with prior authorization requirements, under which the insurer will not cover the costs of a patient's prescription unless the physician first submits a form to the insurer specifying the indication for the prescription and that it is covered by the plan. *See* Bergeson et al., *supra* note 226, at 376 ("Members within the health plan who request prescriptions for medications requiring PA [Prior Authorization] must go through a specific process to receive approval. Typically, the member's health care provider must submit a form, which is faxed to the health plan and evaluated by a staff pharmacist. The pharmacist then reviews this information in combination with the member's pharmacy claims data to determine whether the member meets the criteria for the medication."). Prior authorization requirements have become "nearly universal" in pharmacy benefit plans for expensive patented drugs. *See* Ha T. Tu & Divya R. Samuel, *Limited Options to Manage Specialty Drug Spending*, Center for Studying Health System Change, Research Brief 22, at 8-9 (2012).

Initially, pharmaceutical companies usually have a strong interest in expanding their drugs' indications, since these "line extensions" can expand their sales.[238] Consequently, they usually continue testing their drugs in clinical trials following the initial FDA approval.[239] These investments are treated as part of the broader lifecycle management of their drugs,[240] and provide a critical source of revenue for the industry[241] as well as important treatments for unmet medical needs.[242]

However, because of the all-or-nothing system of monopoly protection for drugs, the incentives for developing the various different indications of 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.[243] 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 regulatory exclusivity periods for a drug expire and it "goes generic," firms lose control over sales of the drug 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

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[238] *See* ELLERY & HANSEN, *supra* note 115, at 123 (2012) 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").

[239] *See* GIPSTEIN ET AL., *supra* note 238, at 3 ("Most clinical strategies include plans to invest in new indications, phase 4 studies, and other trials.").

[240] ELLERY & HANSEN, *supra* note 115, at xx (describing "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").

[241] GIPSTEIN ET AL., *supra* note 238, at 2 (reporting that expanding drug indications "has become critical to [the] commercial success" of new drugs).

[242] *See supra* note 112. Of course, the incentives for pharmaceutical companies to develop new indications for their drugs do not align perfectly with the public's interest in maximizing the social value of those drugs. Pharmaceutical companies typically capture only a small portion of the social value generated by their drugs. *See* Dana P. Goldman, et al., *The Value of Specialty Oncology Drugs*, 45 HEALTH SERVICE RESEARCH 115 (2010) (finding that the manufacturers of specialty oncology drugs – which are thought to be among the most "overpriced" of all drugs – capture approximately 25 percent of the total value of the drug to patients on average); Tomas J. Philipson & Anupam B. Jena, *Who Benefits from New Medical Technologies? Estimates of Consumer and Producer Surpluses for HIV/AIDS Drugs*, Forum Health Econ. & Pol'y, vol. 9, art. 3 (2006) (finding that the innovators that developed and introduced HIV drugs "captured only 5% of the [U.S. domestic] social surplus arising from these new technologies"). Consequently, they limit their investments to new indications with a lower risk of failure, larger market size, and higher reimbursement rate relative to what the public would prefer. Moreover, because pharmaceutical companies do not capture the social value of information about adverse drug effects or inefficacy, they may be reluctant to test a new indication for one of their drugs if those trials might uncover harmful side effects, or if the trial outcome might be negative and physicians are already prescribing the drug off-label for that use. *See* Eisenberg, *supra* note , at 718; Amy Kapczynski & Talha Syed, *The Continuum of Excludability and the Limits of Patents*, 122 YALE L.J. 1900, _ (2013).

[243] *See supra* notes and text accompanying notes 61-66.

the patented new use, pharmaceutical companies will lack enforceable monopoly rights.[244]

Given the limited term of protection, pharmaceutical companies' willingness to develop new indications for a drug quickly fades following their initial approval. The clinical trials necessary to establish the safety and efficacy of a new indication usually take at least a few years to complete, and often longer.[245] 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 is ticking, and their regulatory exclusivity periods started running when the FDA first approved the drug.[246] 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.[247] After a drug has been on the market for four or five years, pharmaceutical companies tend to be very reluctant to invest in further clinical trials for new indications.[248] 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.[249]

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[244] In some cases, pharmaceutical companies must reformulate the existing drug to provide an effective treatment for the new indication. In other cases, the new indication of the drug may require a much higher dose than currently available for the drug's original indication, or 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 regulatory exclusivity over the new formulation or dosage, while remaining insulated from price competition from generics sold for the old indication. *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.'"); 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'"); Smith, *supra* note 85, at 131 ("Regardless of the patent and regulatory exclusivities, success in this case will depend on an effective generic substitution barrier to prevent off-label use of the existing generic products. As long as inexpensively available generics can be prescribed in a manner that achieves the same clinical result as the more expensive repositioned product, the repositioned product will probably fail. The best barriers include those repositioned products having a formulation required for treatment of a new indication, and where existing generics cannot be substituted for the new formulation.").

[245] *See supra* note 145.

[246] *See* ELLERY & HANSEN, *supra* note 115, 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 115, at 59.

[247] *See* ELLERY & HANSEN, *supra* note 115, at 120 & 124.

[248] *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 238, 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.").

[249] *See* Grabowski, et al., *supra* note 112, 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).

This gap in the incentives for drug development would not be a problem except that clinicians and researchers frequently uncover potential new uses for drugs long after their initial FDA approval. In the past, clinicians were the most likely to discover these new indications,[250] oftentimes through pure serendipity, such as when patients reported that a drug helped resolve an entirely unrelated condition.[251] In recent years, researchers have also become adept at identifying potential new indications for drugs through laboratory work.[252] 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.[253] These insights often reveal a drug's propensity to hit distinct biological targets that may affect other diseases.[254] Moreover, scientific advances are continually revealing previously unknown commonalities in the underlying

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[250] *See* Harold J. Demonaco, et al., *The Major Role of Clinicians in the Discovery of Off-Label Drug Therapies*, 26 PHARMACOTHERAPY 323 (2006); Jack W. Scannell et al., *Diagnosing the Decline in Pharmaceutical R&D Efficiency*, 11 NAT. REV. DRUG DISCOVERY 191, 197 (2012) ("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.").

[251] *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); 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) ("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."). Some clinicians also experiment with untested indications while treating patients for conditions with no established therapy. *See, e.g.*, Tewodros Eguale et al., *Drug, Patient, and Physician Characteristics Associated with Off-Label Prescribing in Primary Care*, 172 ARCH. INTERNAL MED. 781 (2012) ("The reasons for the association of older drugs with off-label use include that these medications have been on the market longer, thereby creating the opportunity for experimentation and discovery of new uses by clinicians.").

[252] *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); Sean Ekins et al., *In Silico Repositioning of Approved Drugs for Rare and Neglected Diseases*, 16 DRUG DISCOVERY TODAY 298 (2011) ("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.").

[253] *Cf.* Oprea & Mestres, *supra* note 144 ("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.").

[254] *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) ("Recent work on large scale mapping of polypharmacology interactions by Paolini et al. revealed the extent of promiscuity of drugs and leads across the proteome," showing that "around 35% of 276,122 active compounds in their database had observed activity for more than one target," and "a significant number (around 25%) had recorded activity across different gene families"); Mizushima, *supra* note 251, at 499 ("[W]e still do not understand the underlying mechanisms of action of many existing medicines, and as such the cellular responses that give rise to their main effects and side effects are yet to be elucidated. To this extent, identification of the mechanisms … [can] be used for developing existing drugs for use as medicines for the treatment of other diseases."); Oprea & Mestres, *supra* note 144, 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.").

pathways for seemingly unrelated diseases, suggesting that treatments effective for one might work for the other.[255]

Commentators now take for granted that pharmaceutical companies will never invest in clinical trials for new indications once generics are on the market.[256] The information produced in clinical trials can have immense social value, but pharmaceutical companies earn their profits by selling drugs, not the information about whether to use a drug for a particular indication.[257] Firms pay for clinical trials to convince regulators to allow their drugs on the market; to convince physicians to prescribe them; and to convince insurers to include the drug on their formularies and pay a high price for it. In short, firms use clinical trials to advertise the drugs they have a monopoly over.[258] Once generics are poised to enter the market, pharmaceutical companies stop making those investments, since any increase in sales would mostly benefit the generic manufacturers.[259] The lack of private sector investment in off-patent drugs is a glaring failure in the current system for promoting pharmaceutical innovation.

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

The lack of incentives for developing new indications of FDA-approved drugs is a longstanding and well-known problem. However, it received very little attention until recently. Over the past decade, this seemingly minor gap has become one of the greatest impediments to the development of valuable new medical treatments. Recent technological advances suggest that the existing pharmacopeia could provide effective treatments for many – and perhaps most – unmet medical needs. Moreover, developing new indications for existing drugs is by far the most efficient route of drug development. As a result, it could allow pharmaceutical firms to develop medical treatments for smaller markets and more challenging pathologies, which industry typically neglects in its de novo drug development programs. Creating a viable business model for the development of new indications would also help overcome the ongoing productivity crisis in the pharmaceutical industry, by providing an alternative to the increasingly unsustainable de novo model. At the same time, it would offer the NIH an invaluable bridge across the "valley of death" which, for the past several decades, has largely prevented the NIH from translating

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[255] *See, e.g.*, Csermely et al., *supra* note 118, 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.)").

[256] *See* Grabowski, et al., *supra* note 112, at 382; Rai, *supra* note 105, at 492.

[257] *See* Eisenberg, *supra* note , at 718.

[258] *See* Joe Collier & Ike Iheanacho, *The Pharmaceutical Industry as an Informant*, 360 LANCET 1405 (2002); Lars Noah, *Authors, Publishers, and Products Liability: Remedies for Defective Information in Books*, 77 OR. L. REV. 1195, 1212 (1998).

[259] *See* Eisenberg, *supra* note .

breakthroughs from basic research into actual medical treatments. Without effective patent protection for new therapeutic uses, all of these benefits are lost.

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 2356 distinct FDA-approved drug compounds,[260] the vast majority of which are off patent.[261] Using new screening technologies, researchers have identified hundreds of potential new uses for these off-patent drugs to treat unmet medical needs.[262] Unfortunately, without private industry to finance the clinical development of these potential new medical treatments, the vast majority of them likely will never be tested.

The recent discovery that the drug bexarotene, an FDA-approved therapy for cutaneous T-cell lymphoma, might also provide an effective treatment for Alzheimer's disease highlights the potential social costs of this policy failure.[263] Paige Cramer and co-authors reported in *Science* that bexarotene is remarkably effective against Alzheimer's in several important preclinical models.[264] Although this discovery attracted a great deal of attention, it remains uncertain whether the treatment will work in humans.[265] The clinical trials needed to test bexarotene for this indication would take 5 to 7 years and hundreds of millions of dollars.[266] With only a few years of patent life remaining on bexarotene, finding industry sponsors for these trials will be difficult, if not impossible.[267]

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[260] *See* 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).

[261] *Cf.* Express Scripts/Medco, *Estimated Dates of Possible First-Time Generics/Rx-to-OTC Market Entry* (2012), *at* https://host1.medcohealth.com/art/corporate/anticipatedfirsttime_generics.pdf (listing the few hundred FDA-approved prescription drugs on the market as of June 2012 that lack generic competition because of patent protection or regulatory exclusivity periods).

[262] *See infra* notes and text accompanying notes _-_.

[263] *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).

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

[265] *See* Strittmatter, *supra* note 263, at 1448; LaFerla, *supra* note 263, at 571-72.

[266] *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").

[267] *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.").

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.[268] However, recent advances in drug-screening technology show that Cramer's discovery is the tip of the iceberg. Historically, most new uses for existing drugs were discovered by serendipity, or by selectively testing individual drugs in cell-based or animal disease models.[269] Over the past decade, researchers have developed a variety of new computational tools to screen known-drug compounds in silico for new indications.[270] 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.[271] These screening tools have shown that existing drugs are much more likely than

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[268] *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).

[269] *See* Chong & Sullivan, *supra* note 146, at 645 ("[M]ost successful crossovers have been the result of chance observations or educated guesses," and "individual labs were limited to screening perhaps hundreds of compounds"); Hee Sook Lee et al., *Rational Drug Repositioning Guided by an Integrated Pharmacological Network of Protein, Disease and Drug*, 6 BMC SYSTEMS BIOLOGY 80 (2012) ("To date most repositioned drugs have been the consequence of serendipitous observations of unexpected efficacy and side effects of drugs in development or on the market."); 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 (same); Qu et al., *supra* note 251, at S4-S5 (same).

[270] *See* Chong & Sullivan, *supra* note 146, at 645; Ekins et al., *supra* note 252, at _ ("To date, there are fewer such examples where in silico [computer simulation] approaches have derived new uses for approved drugs. However, with current technologies and databases, as well as a close integration with in vitro screening, this will change."); Oprea & Mestres, *supra* note 144, 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."); Prashant Nair, *Drug Repurposing Gets a Boost as Academic Researchers Join the Search for Novel Uses of Existing Drugs*, 110 PNAS 2430, 2431 (2013) ("Advances in genomics technologies have helped basic researchers make strides in addressing some of th[e] challenges" of "nuanced understanding and intricate dissection of the often-interwoven genetic pathways underlying human disease."); 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.").

[271] *See* Sivanesan Dakshanamurthy et al., *Predicting New Indications for Approved Drugs Using Proteochemometric Method*, 55 J. MED. CHEM. 6832 (2012); Keiser et al., *supra* note 117; *Predicting New Molecular Targets for Known Drugs*, 462 NATURE 175 (2009); Wermuth, *supra* note 119; Kinnings et al., *supra* note 254; Monica Campillos et al., *Drug Target Identification Using Side-Effect Similarity*, 321 SCIENCE 263 (2008); Zhichao Liu et al., *In Silico Drug Repositioning – What We Need To Know*, 18 DRUG DISCOV TODAY 110 (2013); 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

the average novel drug candidate to be active in multiple targets, pathways and cellular phenotypes – factors indicative of greater potential for multiple uses.[272] Moreover, many of the most promising tools only work for existing drugs because they function by screening databases of published information about drugs' observed clinical effects and known mechanisms of action.[273]

Although researchers are just beginning to use these screening tools, they have already identified hundreds of potential new uses for drugs in the existing arsenal.[274] These include

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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).

[272] In fact, screening of the NIH's collection of all approved and investigational drugs (the "NPC") has shown that in 200 tests for activity in different targets, pathways or cellular phenotypes, drugs within the NPC were more than twice as likely as molecular entities overall to show activity in any given test. Huang et al., *supra* note 260; *see also* Kinnings et al., *supra* note 254.

[273] This is the case, for example, with literature mining and side effect-similarity screening. *See supra* Andronis et al., *supra* note 271, at 358 ("Much of the knowledge covering modern biology and medicine is often buried in various forms of free-text documents."); Campillos et al., *supra* note 271, at 263-64 ("Although unexpected activities derived from off-targets are usually unwanted and harmful, they can sometimes be beneficial and have led to new therapeutic indications for drugs. … Therefore, we explored side-effect information generated from the use of marketed drugs to infer molecular activities of drugs that are not implicit by their chemical similarity or the sequence similarity of their known targets."); Li et al., *supra* note 271, at 1 ("[W]e developed a computational framework to build disease-specific drug-protein connectivity maps, by mining molecular interaction networks and PubMed abstracts," and show "how drug-protein molecular connectivity maps can be constructed to overcome data coverage and noise issues inherent in automatically extracted results."); Liu et al., *supra* note 271, at ; Wermuth, *supra* note 119; Yang & Agarwal, *supra* note 271, at 1 (noting that many drug repositioning "strategies focus primarily on using preclinical information. Unfortunately, clinical therapeutic effects are not always consistent with preclinical outcomes. Recently, a systematic analysis observed that phenotypic screening exceeded target-based approaches in discovering first-in-class small-molecule drugs. 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.").

[274] *See* Keiser et al., *supra* note 117, at 175 ("[A] statistics-based chemoinformatics approach [has been used] to predict new off-targets for 878 purchasable FDA-approved small-molecule drugs and 2,787 pharmaceutical compounds."); Ekins et al., *supra* note 252 (identifying a long list of new uses for existing drugs that have been identified but largely unconfirmed); Sean Ekins & Antony J. Williams, *Finding Promiscuous Old Drugs for New Uses*, 28 PHARM RES. 1785 (2011) (reviewing studies from the prior six years on the screening of FDA-approved drug libraries and reporting "a conservative estimate indicates at least 109 previously approved drugs have shown activity in vitro against additional diseases different than those for which the drugs were originally approved."); Huang et al. *supra* note 260; Oprea & Mestres, *supra* note 144, at ("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.").

possible treatments for cancer,[275] Alzheimer's disease,[276] diabetes,[277] stroke,[278] tuberculosis,[279] maliaria,[280] and a host of other unmet medical needs.[281] Indeed, every recorded effort to screen

[275] *See* Carlos M. Telleria, *Drug Repurposing for Cancer Therapy*, 4 J. CANCER SCI. THER. ix (2012); 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 252, 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 274 (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); 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).

[276] *See* Paige E. Cramer et al., *ApoE-Directed Therapeutics Rapidly Clear β-amyloid and Reverse Deficits in AD Mouse Models*, 335 SCIENCE 1503 (2012); Anne Corbett et al., *Drug Repositioning for Alzheimer's Disease*, 11 NAT REV DRUG DISCOV. 833 (2012) (reporting on "the outcomes of a comprehensive assessment of the published literature, systematic evaluation and a formal consensus process by an expert panel to identify licensed drugs with the most robust breadth of evidence to be considered as potential candidatesfor repositioning in Alzheimer's disease. Fifteen licensed drug candidates were identified by consensus based on candidate therapies proposed by the expert panel.").

[277] *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 252.

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

[279] *See* Kinnings et al., *supra* note 254; Juan Carlos Palomino & Anandi Martin, *Is Repositioning of Drugs a Viable Alternative in the Treatment of Tuberculosis?*, 68 J. ANTIMICROB. CHEMOTHER. 275 (2013).

[280] *See* Ekins et al., *supra* note 252; 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).

[281] *See* Ramaiah Muthyala, *Orphan/Rare Drug Discovery Through Drug Repositioning*, 8 DRUG DISCOV TODAY THER STRATEG. 71 (2011) (multidrug-resistant parasites, progressive multifocal leukoencephalopathy, bacterial pathogens, drug-resistant infections and a range of neurological disorders); Ekins & Williams, *supra* note 274 (malaria and C. parvum); Ekins et al., *supra* note 252 (trypanosomal and Chagas disease); Plane et al., *supra* note 278 (spinal cord injuries and Parkinsons, Alzheimer's and Huntington's disease); Qu et al., *supra* note 251 (systemic lupus erythematosus); Dakshanamurthy et al., *supra* note 271 (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

libraries of FDA-approved drugs for activity against a particular disease uncovered one or more potential new treatments for the condition.[282] Many researchers now suspect that our current arsenal of drugs could provide effective medical treatments for most of the major remaining diseases,[283] including cancer[284] and Alzheimer's disease.[285] There is also hope that repurposing old drugs for new indications will allow researchers to identify effective treatments for most or all of the 8000 rare diseases, which together afflict 15 to 20 percent of the global population.[286]

Unfortunately, because the new screening tools were unavailable when pharmaceutical companies first developed these existing drugs, they were not tested for other indications.[287] 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.[288] As a result, the social costs of this failure in the incentives for pharmaceutical R&D will continue to increase.

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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); Sidharth Chopra et al., *Repurposing FDA-Approved Drugs to Combat Drug-Resistant Acinetobacter Baumannii*, 65 J. ANTIMICROB CHEMOTHER. 2598 (2010) (antibiotic-resistant bacterial infections); 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).

[282] *See* Ekins et al., *supra* note 252 ("From research published in the last six years we have identified 34 studies that have screened libraries of FDA-approved drugs against various whole cell or target assays. These studies have each identified one or more compounds with a suggested new bioactivity that had not been described previously."); Chong & Sullivan, *supra* note 146; Mark S. Boguski et al., *Repurposing with a Difference*, 324 SCIENCE 1394 (2009); Muthyala, *supra* note 281; Ekins & Williams, *supra* note 274; Telleria, *supra* note 275.

[283] *Cf.* Wermuth, *supra* note 119, 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").

[284] *See* Telleria, *supra* note 275 (noting that many researchers are now hoping that repurposing old drugs for new indications will soon "convert cancer into a treatable chronic disease").

[285] *See* Corbett et al., *supra* note 276, at 835-44 (discussing a variety of promising candidates for repurposing for the treatment of Alzheimer's disease).

[286] *See* Muthyala, *supra* note 281, at 71 & 75 ("Some believe that the more obvious winners have already been found.").

[287] Ironically, we know less about the underlying mechanisms of action – and, therefore, the other therapeutic uses – of the drugs that have been on the market the longest. *See* Mizushima, *supra* note 251, at 499 (explaining "when such [older] medicines were developed, it was difficult, if not impossible to investigate the molecular mechanisms of action that give rise to their main effects and side effects, due to a lack of analytical technology" and, as a result, "the mechanisms underlying how these drugs achieve their clinical effect have not been examined.").

[288] *See* Bernard Munos, *A Forensic Analysis of Drug Targets from 2000 to 2012*, CLINICAL PHARMACOLOGY & THERAPEUTICS (2013) ("[D]rug repurposing opportunities continue to appear in the literature, and increasingly in the clinic … . This suggests that we are getting better at designing our drugs rationally, but perhaps the increasing focus on this approach is causing us to miss important therapeutic innovations that happen to lie within our knowledge gaps.").

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

Developing new uses for FDA-approved drugs is far-and-away the most efficient route for producing new medical treatments.[289] New indications take only a fraction of the time, cost and risk involved in developing new drugs. This makes it possible to deliver new medical treatments to the public faster, to pursue treatments for smaller populations that otherwise would be unprofitable, and to pursue treatments for more challenging pathologies or novel drug targets that involve a higher risk of failure.

Developing new uses for existing drugs is generally much faster and cheaper than developing a novel drug compound.[290] It allows firms to skip the drug discovery and preclinical development stages,[291] which typically constitutes between one third and one half of the cost and time of developing a drug.[292] In some cases, firms can also skip the early clinical development stages.[293] This dramatically reduces the cost of bringing a new medical treatment to market.[294]

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[289] *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); Dakshanamurthy et al., *supra* note 271 ("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)."); Asher Mullard, *Could Pharma Open Its Drug Freezers?*, 10 NAT. REV. DRUG DISCOVERY 399, 400 (2011) (referring to the development of new indications as "a route to cost-effective drug development").

[290] *See, e.g.,* Boguski et al., *supra* note 282, at 1394 ("New uses of existing drugs cost much less to develop compared with de novo drug discovery and development."); Corbett et al., *supra* note 276 ("The established safety of the candidate compounds provides several advantages compared with the development of novel therapeutic compounds. The time and cost required to advance a 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 thereforebe bypassed."); Spyros N. Deftereos et al., *Drug Repositioning and Adverse Event Prediction Using High-Throughput Literature Analysis*, 3 WIREs SYSTEM BIOLOGY & MED. 323 (2011) ("New uses of existing drugs, on the other hand, cost much less to develop compared with de novo drug discovery, mainly due to the accumulated data on their preclinical properties and their established safety profiles."); Patricia Fitzpatrick Diamond, *Drug Repositioning Gains in Popularity*, 30 GENETIC ENGINEERING & BIOTECHNOLOGY NEWS (2010) (noting that compared to de novo drug development, developing new indications has the benefit of "entailing lower costs and taking less time"); Qu et al., *supra* note 251 ("Drug repositioning – the use of established drugs for new indications – represents a promising avenue for the development of therapeutics based on its relatively low cost and ready availability of extensive data and knowledge from prior research and development efforts.").

[291] *See* Mullard, *supra* note 119, 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").

[292] *See supra* note 40.

[293] *See supra* notes and text accompanying notes 143-148; *see also* Chong & Sullivan, *supra* note 146, 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 144 ("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.").

[294] *See* Chong & Sullivan, *supra* note 146, 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.").

Whereas de novo drug development typically costs in excess of $1.2 billion per drug,[295] the development of a new indication for an existing drug costs on average $300 million or less.[296] Moreover, while de novo drug development takes an average of 12 to 16 years, [297] pharmaceutical companies can almost always develop a new indication within 12 years, and it often take as little as three.[298]

Developing new uses for an existing drug is also much less risky than de novo drug development.[299] High failure rate in developing new drugs is one of the largest hurdles in pharmaceutical innovation.[300] Much of this risk stems from the difficulty predicting the pharmacological properties of untested drug compounds, including how patients will absorb the active ingredient and whether it has an acceptable toxicity profile.[301] The risk of failure is much lower when developing new indications for established drugs, since pharmaceutical companies

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[295] *See supra* notes and text accompanying notes 39-43.

[296] *See* Sahoo, *supra* note 115, at 28.

[297] *See supra* notes and text accompanying notes 38.

[298] *See* Ashburn & Thor, *supra* note , at 673 ("The advantage of the indication-focused approach, by contrast, is that it has the potential to move the compounds very quickly through clinical trials on the basis of previously collected data."); Dudley et al., *supra* note 251, at 303 ("The drug development cycle for a repositioned drug can be as short as 3–12 years compared to the traditional 10–17 years required to bring a new chemical entity to market."); Elvidge, *supra* note , at 8; THOMSON REUTERS, *supra* note 270, at 1 ("drug repositioning has a number of R&D advantages including a reduction of R&D timelines by up to 3-5 years").

[299] *See* Diamond, *supra* note 290 (noting that "because the drug is already known, it entails less risk that studies will fail"); Liu et al., *supra* note 271, at ("Because the safety profiles of these drugs are known, clinical trials for alternative indications … carry less risk than de novo drug development."); Oprea & Mestres, *supra* note 144, 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. In general, a large literature corpus for a particular drug is regarded as beneficial since, despite potential shortcomings, the clinical observation and monitoring required (in particular in high-risk situations) is manageable. When repurposing an older drug, it is generally anticipated that costs associated with its synthesis (including potential hazardous waste) have already been addressed, which turn the therapeutic management of the new indications economically attractive."). *Cf.* François Chast, *A History of Drug Discovery*, in THE PRACTICE OF MEDICINAL CHEMISTRY 53 (Camille G. Wermuth ed. 3d Ed. 2008) ("Drug discovery remains an uncertain, hazardous, and unpredictable adventure! This is probably why most of drug 'hunters' largely share the opinion of Nobel laureate James Black who famously declared: 'The most fruitful basis for the discovery of a new drug is to start with an old drug.'").

[300] *See* Scannell et al., *supra* note 250, at 199 ("R&D costs are dominated by the cost of failure. Most molecules fail. Most research scientists spend most of their time on products that fail.").

[301] *See* 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. Striking the right therapeutic window, with a safe profile is often a challenge in discovery settings. Much research is being applied to bring value from the toxicology standpoint … . [However,] the field is still plagued by clinical idiosyncratic toxicities."); Matteo Colombo & Ilaria Peretto, *Chemistry Strategies in Early Drug Discovery: An Overview of Recent Trends*, 13 DRUG DISCOVERY TODAY 677, 677 (2008) ("Currently, the fundamental issue in the drug discovery process is the high failure rate in clinical trials, mainly due to liabilities related to poor pharmacokinetics, poor efficacy and high toxicity.").

start with a chemical compound known to be safe and therapeutically effective in humans.[302] 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.[303]

The time, cost and risk advantages of developing new therapeutic uses for existing drugs (as opposed to new drugs) could allow pharmaceutical companies to pursue critical areas of medical research that they currently neglect.[304] Pharmaceutical companies are frequently criticized for ignoring diseases that affect smaller or poorer populations, where they would have greater difficulty recovering the substantial costs of de novo drug development.[305] They are also criticized for not pursuing potential breakthrough drugs aimed at novel disease targets because they have a higher risk of failure. The lower cost and risk involved in developing new indication makes treatment of diseases that are especially challenging, or affect smaller or poorer populations, more attractive to pharmaceutical companies.[306] This is a boon to diseases like Alzheimer's for which no treatment is known and the risk of failure is otherwise astronomical and cost-prohibitive.[307] It would also be beneficial for rare cancers and other serious but uncommon conditions.[308] At the same time, the faster development period offers hope to patients with

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[302] *See supra* note 299; THOMSON REUTERS, *supra* note 270, 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"); 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 for approved products that have been in the marketplace," and because "[w]ith the tested dosages and formulations, approved products have demonstrated their pharmacological activity, have known toxicity profiles both in animals and in humans and have well-studied pharmacokinetics and pharmacodynamics.").

[303] *See* Joseph A. DiMasi et al., *Clinical Approval Success Rates for Investigational Cancer Drugs*, _ CLINICAL PHARMACOLOGY & THERAPEUTICS _ (2013 forthcoming) ("If a second indication is pursued and the first indication is a success, then marketing approval of a second indication is more likely than not."); 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.

[304] *See* Hemphill, *supra* note 203, at 6-7 ("This innovative approach to developing cost-effective, timely new pharmaceutical therapies is necessary to eliminate the backlog of untreated diseases—biomedical researchers have successfully identified the causes of nearly 4,500 diseases but have created new therapies for only 250 of them. This situation is exacerbated by the time and money required to develop a new drug compound—up to 14 years and upwards of $1 billion to move a drug from discovery to commercialization.").

[305] *See, e.g.*, Erdmann, *supra* note 149, at 1492 ("But even when clinical researchers seek pharmaceutical sponsorship, they can find support difficult to secure. If a company has a promising drug to treat lung cancer but an academic researcher wants to test that drug for a rare leukemia, the company may fund only data management and ask the institution to pay for imaging and patient monitoring and to hold the IND.").

[306] *Cf.* Oprea & Mestres, *supra* note 144 ("When repurposing an older drug, it is generally anticipated that costs associated with its synthesis (including potential hazardous waste) have already been addressed, which turn the therapeutic management of the new indications economically attractive.").

[307] *See* Corbett et al., *supra* note 276.

rapidly advancing conditions that may not survive the duration of a de novo drug development project.[309] The hole in the incentives for developing new indications of FDA-approved drugs delays or forecloses these opportunities to improve the odds for these populations.

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

For much of the past decade, the pharmaceutical industry has faced a productivity crisis. After years of increased R&D spending with no commensurate increase in drugs reaching the market, and a persistently high failure rate in expensive late-stage trials, many industry executives have concluded that their current business model of de novo drug development is unsustainable.[310] If pharmaceutical companies were given a viable drug development strategy based on establishing new indications for FDA-approved drugs, it would help revitalize a struggling industry that the public depends on to produce life saving medications.[311]

Tremendous advances in the scientific fields underlying drug discovery and development over the past half century created the hope of a new golden age of pharmaceutical innovation,

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[308] *Cf.* Xu & Coté, *supra* note 308 ("Repurposing FDA-approved products has practical advantages over novel compounds …. [P]revious knowledge and experience can save costs and development time for the new indication…. This can be good news for both patients with rare diseases and for orphan drug developers.").

[309] *See* Francis S. Collins, *Mining for Therapeutic Gold*, 10 NATURE REVIEWS DRUG DISCOVERY 397 (2011) ("Approved drugs and many abandoned compounds have already been tested in humans, and so detailed information is available on their pharmacology, formulation, dosing and potential toxicity. This can enable the rapid testing of new clinical hypotheses, leading to remarkable health outcomes."); 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) ("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.").

[310] *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); Fabio Pammolli et al., *The Productivity Crisis in Pharmaceutical R&D*, 10 NAT REV DRUG DISCOV. 428 (2011); AJAY DHANKHAR ET AL., ESCAPING THE SWORD OF DAMOCLES: TOWARD A NEW FUTURE FOR PHARMACEUTICAL R&D 3 (2012) ("Recent years have seen a collapse in the industry's R&D productivity and a loss of faith in its innovation model. … A recent McKinsey analysis calculates that the average economic return on R&D has dropped from between 13 and 15 percent in the 1990s to between 4 and 9 percent in the past decade. This suggests that much of the current investment in R&D is not creating value. We estimate that cumulative success rates have fallen by as much as 50 percent as the number of drug development programs and the cost per program have doubled."); Steven M. Paul et al., *How to Improve R&D Productivity: the Pharmaceutical Industry's Grand Challenge*, 9 NAT REV DRUG DISCOV. 203 (2010) ("The pharmaceutical industry is facing unprecedented challenges to its business model. Experienced observers and industry analysts have even predicted its imminent demise."); ANDY PASTERNAK ET AL., BRIDGING THE SHAREHOLDER RETURN GAP IN BIG PHARMA: MEANINGFUL COST TRANSFORMATION CAN DELIVER RESULTS 1 (2012).

[311] *See* Boguski et al., *supra* note 282, at 1394 ("One response to the productivity gap is drug "repurposing" or "repositioning"—terms that refer to the identification and development of new uses for existing or abandoned pharmacotherapies."); Nair, *supra* note 270, at 2431 ("The benefits of drug repurposing to pharmaceutical companies facing drying pipelines and expiring patents, to nonprofit organizations seeking cures for rare and neglected diseases, and to patients battling intractable conditions need no overstatement."). *Cf.* Baratt & Frail, *supra* note 289, at 1 ("Against this backdrop of escalating costs associated with increased development timelines and requirements, along with growing regulatory and reimbursement pressures, drug repositioning has emerged as a lower cost and potentially faster approach than de novo drug discovery and development.").

but the reality has been a disappointment.[312] While the pharmaceutical industry invested heavily in R&D to take advantage of new scientific opportunities, their increased R&D spending did not yield commensurate increases in new drugs reaching the market.[313] Indeed, a recent study found that, since the 1950's, the number of FDA-approvals for new drugs per inflation-adjusted dollar of R&D spending has fallen by half approximately every nine years.[314] The market capitalization of pharmaceutical companies has declined in concert (by $550 billion between 2000 and 2010),[315] with the inevitable result of facility closures,[316] job cuts[317] and reductions in R&D investment as firms become more risk averse.[318]

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[312] *See* C.M. Colvis et al., *Partnering for Therapeutics Discovery*, 93 CLINICAL PHARMACOLOGY & THERAPEUTICS 24, 25 (2013) ("[D]espite the recent technology and knowledge advances in biomedical research, the number of drugs that make it to the market every year remains roughly the same."); Kenneth I. Kaitin, *Deconstructing the Drug Development Process: the New Face of Innovation*, 87 CLIN. PHARMACOLOGY THERAPEUTICS. 356 (2010) ("In the area of drug discovery, new technologies such as high-throughput screening, combinatorial chemistry, and a host of "omics" tools (including pharmacogenomics, proteomics, and metabolomics) were supposed to usher in a new era of innovative drug discovery, leading to newer and better medicines for many diseases for which treatment was inadequate or lacking…. Despite the industry's concerted efforts over the past two decades to effect substantive improvements in performance and efficiency in the area of drug development, the metrics suggest that few or no gains have been made.").

[313] *See* Bennani, *supra* note 301, at S33 ("It is now undeniable that increased investments in R&D have not resulted in increased numbers of new molecular entities."); UNITED STATES GOVERNMENT ACCOUNTABILITY OFFICE (GAO), NEW DRUG DEVELOPMENT: SCIENCE, BUSINESS, REGULATORY, AND INTELLECTUAL PROPERTY ISSUES CITED AS HAMPERING DRUG DEVELOPMENT EFFORTS 2 (2006) ("Significant scientific advances have raised new hope for the prevention, treatment, and cure of serious illnesses … . However, over the past several years it has become widely recognized throughout the industry that the productivity of its research and development expenditures has been declining; that is, the number of new drugs being produced has generally declined while research and development expenses have been steadily increasing. Similarly, FDA and analysts reported that pharmaceutical research and development investments were not producing the expected results and that innovation in the pharmaceutical industry had become stagnant.").

[314] *See* Scannell et al., *supra* note 250, at 191 ("R&D efficiency, measured simply in terms of the number of new drugs brought to market by the global biotechnology and pharmaceutical industries per billion US dollars of R&D spending, has declined fairly steadily. We call this trend 'Eroom's Law', in contrast to the more familiar Moore's Law ('Eroom's Law' is 'Moore's Law' backwards). Moore's Law is a term … used more generally for technologies that improve exponentially over time. The data [reported herein] show that the number of new US Food and Drug Administration (FDA)-approved drugs per billion US dollars of R&D spending in the drug industry has halved approximately every 9 years since 1950, in inflation-adjusted terms."). There is some evidence of recent turn-around in the industry. *See* Munos, *supra* note ("A review of the drugs approved since the turn of the millennium suggests that pharmaceutical innovation may be recovering from the slump that brought us patent cliffs and declining sales. The last couple of years have seen an encouraging rise in new drug approvals, including many based on novel modes of action.").

[315] *See* DHANKHAR ET AL., *supra* note 310, at 3 ("In the past 25 years the industry has created in excess of $1 trillion of shareholder value, but destroyed around $550 billion of value during the "decade of doubt" from 2000 to 2010. That value destruction coincided with a 60 percent increase in the R&D spending rate from 10 to 16 percent of sales, and with an even higher increase in absolute spend as worldwide sales grew from $200 billion in 1995 to $800 billion in 2009."); Jean-Pierre Garnier, *Rebuilding the R&D Engine in Pharma*, HARV. BUS. REV., May 1, 2008 (noting that the 15 largest pharmaceutical companies lost approximately $850 billion dollars in shareholder value between 2000 and 2008).

[316] *See, e.g.,* Andrew Jack, *Innovation: Pharmaceutical Groups Become Victims of their Own Success*, FINANCIAL TIMES, Jun. 19, 2013 ("In the UK alone, Pfizer has been winding down its historic postwar Sandwich R&D site in Kent and, earlier this year, AstraZeneca announced the closure of its Alderley Edge complex.").

Many commentators and industry-insiders attribute this productivity crisis to a severe – and perhaps irreparable – breakdown in the pharmaceutical industry's primary business model of de novo drug development.[319] Firms spend in excess of one billion dollars on R&D to deliver a single new drug to the market,[320] but their products are not generating that much revenue.[321] Even back in 2004, commentators realized that the industry's current R&D model is unsustainable.

> It could be argued that the prospects for satisfying unmet medical needs, however, have never been brighter. … Yet, despite the promise, it increasingly seems that these hopes will not be realized without dramatic changes in the way that new medicines are discovered and developed. The cost of drug development is so great that new medicines are in danger of becoming unaffordable for … manufacturers to develop.[322]

Much of the pharmaceutical industry's current troubles stem from the scientific hurdles involved in de novo drug discovery.[323] Firms spend hundreds of millions of dollars creating and optimizing novel drug compounds to maximize a drug's chance of success in clinical trials.[324] Nevertheless, the vast majority of the compounds entering clinical trials fail to reach the market,[325] usually because of problems related to their safety and efficacy.[326] Medicinal chemists

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[317] *See, e.g.,* Bennani, *supra* note 301, at S31-32 (reporting "dramatic numbers of job losses over the past three years" as well as "increasing rates of mergers and acquisitions"); Oprea & Mestres, *supra* note 144, at (citing an "overall reduction of in-house workforce").

[318] *See* Ben Hirschler, *Drug R&D Spending Fell in 2010, and Heading Lower*, REUTERS, Jun. 26, 2011 ("The global drug industry cut its research spending for the first time ever in 2010, after decades of relentless increases, and the pace of decline looks set to quicken this year…. The fall reflects a growing disillusionment with poor returns on pharmaceutical R&D. Disappointing research productivity is arguably the biggest single factor behind the declining valuations of the sector over the past decade."); Martin Grueber, *2012 Global R&D Funding Forecast: Stable Growth of U.S. R&D*, R&D MAGAZINE, Dec. 16, 2011 (citing the pharmaceutical industry as an industry reassessing its R&D spending, with "increased scrutiny of R&D spending versus limited productivity and weak pipelines for blockbuster drugs. In response, many pharmaceutical companies are not only dampening their projections for R&D expense, but are announcing annual cuts of $1 billion or more over the next few years"); Jack, *supra* note 316 (stating that "much of the new millennium has been overshadowed by investor skepticism, with pharmaceutical companies collectively valued at little more than the future cash flows of their current drugs. In other words, their pipelines of experimental treatments have been judged to offer few prospects of success. The industry in turn has cut back sharply the size and scope of research."); Reed, *supra* note 310.

[319] Shelley DuBois, *Novartis CEO: We Need to Re-Think the Blockbuster*, CNN MONEY, Mar. 4, 2013 ("Big Pharma is still big, but its business model is dying. For years, the game in pharmaceuticals has been to research, discover and then fiercely defend billion—dollar drugs … . The old concept of a blockbuster has generally been one drug to treat one disease that affects a large population. Because blockbusters are so profitable, companies scramble to squeeze as much money out of them as possible, arguably in a way that detracts from efforts to research and develop novel treatments…. The old blockbuster—finding strategy hasn't been sustainable."); Bennani, *supra* note 301, at S32.

[320] *See supra* notes and text accompanying notes _-_.

[321] *See supra* note 310.

[322] *See* Michael D. Rawlins, *Cutting the Cost of Drug Development*, 3 NAT. REV. DRUG DISCOVERY 360, 360 (2004).

[323] *See supra* notes and text accompanying notes 300-301.

[324] *See supra* note .

[325] *See supra* note .

[326] *See supra* note 301.

now recognize that it is extremely difficult to design a compound that can be safely administered to patients in a therapeutically effective dose.[327] Many believe that the universe of potentially safe and efficacious drug compounds is quite limited, and a significant percentage of those compounds are already known.[328]

An obvious solution to these problems plaguing their industry would be for firms to develop new uses of FDA-approved drugs.[329] As noted in Section V.B. above, developing new indications is cheaper, faster and less risky than de novo development.[330] It also allows firms to take advantage of the extensive body of knowledge from prior research and clinical experience with existing drugs.[331] New indications for existing drugs could offer firms a pipeline of attractive business opportunities that would help revitalize the pharmaceutical industry while providing the public with a wealth of new medical treatments.[332] However, the patent system fails to provide almost any meaningful protection over new indications developed after a drug's initial FDA-approval.[333] As a result, the development of new drugs not previously approved by the FDA remains the dominant business model, with virtually no investment in new indications for off-patent FDA-approved drugs.[334]

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[327] 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 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 301; 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 (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."). Moreover, medicinal chemists still struggle to predict the pharmacological properties of new drugs before costly clinical trials. *See* Colombo & Peretto, *supra* note 301, at 677; Kaitin, *supra* note 312, at ("[T]he greatest challenge confronting the research-based industry involve bringing promising new drug candidates out of discovery and into development. … [I]n the absence of appropriate validation tools that would allow researchers to identify molecules having the greatest likelihood of successful development, [new drug] discovery technologies merely added time and cost to the R&D process without providing any appreciable benefits. Despite the industry's concerted efforts over the past two decades to effect substantive improvements in performance and efficiency in the area of drug development, the metrics suggest that few or no gains have been made.").

[328] *See* Mizushima, *supra* note 251, at 499; Muthyala, *supra* note 281; Wermuth, *supra* note 119.

[329] Nair, *supra* note 270, at 2431 ("The benefits of drug repurposing to pharmaceutical companies facing drying pipelines and expiring patents … need no overstatement.").

[330] *See supra* notes and text accompanying notes _ -_.

[331] *See* Qu et al., *supra* note 251, at S4.

[332] *See* Boguski et al., *supra* note 282, at 1394 ("One response to the productivity gap is drug "repurposing" or "repositioning"—terms that refer to the identification and development of new uses for existing or abandoned pharmacotherapies. New uses of existing drugs cost much less to develop compared with de novo drug discovery and development.").

[333] *See supra* section IV.

[334] The pharmaceutical industry does develop new indications for failed drug compounds that were abandoned before receiving FDA approval and, therefore, never marketed. *See supra* notes, and text accompanying notes, _ to _.

D. Losing an Opportunity to Bridge the Valley of Death in Biomedical Research

For the past decade, the NIH has struggled to overcome a pervasive failure to translate discoveries from basic research into new medical treatments.[335] NIH-funded research has helped to identify hundreds of potential new drug targets for pharmacological intervention.[336] Unfortunately, much of this research languishes in the so-called valley of death between academia and industry,[337] where neither public nor private funding is available to advance the research.[338] These failures to translate breakthroughs in basic science into new medical treatments represent a fundamental challenge to the NIH's core mission of reducing the burdens of illness and disability.[339] The NIH's leadership has made it a top priority to overcome this

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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).

[335] *See* Elias A. Zerhouni, *US Biomedical Research: Basic, Translational, and Clinical Sciences*, 294 JAMA 1352 (2005); Moses & Dorsey, *supra* note , at 1333; Nancy S. Sung et al., *Central Challenges Facing the National Clinical Research Enterprise*, 289 JAMA 1278 (2003).

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

[337] *See, e.g.*, Declan Butler, *Translational Research: Crossing the Valley of Death*, 453 NATURE 840, 841 (2008) ("[T]here is a growing perception that the enormous resources being put into biomedical research, and the huge strides made in understanding disease mechanisms, are not resulting in commensurate gains in new treatments, diagnostics and prevention. … The pharmaceutical industry, which for many years was expected to carry discoveries across the divide, is now hard pushed to do so. The abyss left behind is sometimes labeled the 'valley of death' — and neither basic researchers, busy with discoveries, nor physicians, busy with patients, are keen to venture there."); Mary Carmichael, *Desperately Seeking Cures*, NEWSWEEK, May 14, 2010 ("But frustration is growing with how few seemingly promising discoveries in basic biomedical science lead to something that helps patients, especially in what is supposed to be a golden age of genetics, neuroscience, and biomedical research in general. … [J]udging by the only criterion that matters to patients and taxpayers—not how many interesting discoveries about cells or genes or synapses have been made, but how many treatments for diseases the money has bought—the return on investment to the American taxpayer [from spending on biomedical research] has been approximately as satisfying as the AIG bailout. … More and more policymakers and patients are therefore asking, where are the cures? The answer is that potential cures, or at least treatments, are stuck in the chasm between a scientific discovery and the doctor's office: what's been called the valley of death."); FASTER CURES, CROSSING OVER THE VALLEY OF DEATH (2009) *at* www.fastercures.org.

[338] *See* Muthyala, *supra* note 281 (discussing the "pharmaceutical valley of death between drug discovery and clinical trials"); 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 (describing the "valley of death" in the context of moving academic discoveries about potential therapeutic effects of a molecule or chemical through the preclinical process); Nuala Moran, *Public Sector Seeks to Bridge 'Valley of Death'*, 25 NATURE BIOTECH. 266 (2007); Reed, *supra* note 310.

[339] *See* National Institutes of Health (NIH), *Mission* (2013), *at* http://www.nih.gov/about/mission.htm (last visited on Sept. 25, 2013); *see also* Butler, *supra* note 337, at 840 ("'NIH stands for the National Institutes of Health, not the National Institutes of Biomedical Research, or the National Institutes of Basic Biomedical Research.' This jab, by molecular biologist Alan Schechter at the NIH, is a pointed one. The organization was formally established in the United States more than half a century ago to serve the nation's public health, and its mission now is to pursue

problem,[340] but progress is painfully slow.[341] Testing older FDA-approved drugs against newly discovered drug targets is thought to be one of the most promising solutions to the valley of death in biomedical research.[342] However, the absence of effective monopoly protection for these new indications largely forecloses this strategy.[343]

Historically, when researchers uncovered a new drug target, they could rely on the pharmaceutical industry to invest in discovering and developing novel drug compounds to hit that target.[344] These new drug targets often provide the best opportunity for a true breakthrough in medical treatments because they represent an entirely different avenue for treating a disease.[345] However, since those targets have never been clinically validated, they have a much higher rate of failure.[346] After years of declining productivity and diminishing returns on their R&D investments, pharmaceutical companies are increasingly reluctant to pursue these opportunities for breakthrough medical treatments.[347] At the same time, support from the public sector

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fundamental knowledge and apply it 'to reduce the burdens of illness and disability.' So when employees at the agency have to check their name tag, some soul searching must be taking place.").

[340] *See* Elias Zerhouni, *The NIH Roadmap*, 302 SCIENCE 63 (2003); Francis S. Collins, *Reengineering Translational Science: the Time is Right*, 3 SCI. TRANSLATIONAL MED. 90cm17 (2011).

[341] *See, e.g.*, Shirley S. Wang, *Sanofi's Zerhouni on Translational Research: No Simple Solution*, WSJ HEALTH BLOG, May 20, 2011 ("When former NIH head Elias Zerhouni ran the $30 billion federal research institute, he pushed for so-called translational research in which findings from basic lab research would be used to develop medicines and other applications that would help patients directly. Now the head of R&D at French drug maker Sanofi, Zerhouni says that such 'bench to bedside' research is more difficult than he thought. … 'At the end of the day, there's a gap in translation,' he said."); 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) (reviewing some of the continuing barriers to translational research).

[342] *See* Collins, *supra* note 309 ("Indeed, drug rescue and repurposing research overall offers a key opportunity to learn from our collective past as we shape our future—a future in which translational science is more efficient and effective at delivering therapies and diagnostics to patients."); Elie Dolgin, *Nonprofit Disease Groups Earmark Grants for Drug Repositioning*, 17 NATURE MED. 1027, 1027 (2011) ("With an increasing academic focus on translational medicine, nonprofit research organizations are also looking to encourage new uses for old drugs."); Muthyala, *supra* note 281.

[343] *See* Weir et al., *supra* note 309 (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.").

[344] *See* Butler, *supra* note 337.

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

[346] *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.

[347] *See* Butler, *supra* note 337, at 840; Metcalf & Dillon, *supra* note 345; Patterson, *supra* note 346; Reed, *supra* note 310 ("[P]rivate companies and venture capitalists are increasingly reluctant to fund the crucial early stages of preclinical development—the research necessary to "translate" promising discoveries made in laboratories into optimized candidate therapeutics ready for testing in clinical trials.").

remains insufficient to advance the research to the stage where it is viable candidate for industry development.[348] As a result, there is growing concern that "many 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."[349]

This valley of death is the result of two fundamental limitations on the public sector's drug development capabilities, both of which could be bypassed if industry had adequate incentives to develop new indications for FDA-approved drugs. The first limitation is that the NIH and NIH-funded institutions (which includes universities and other non-profit research centers) are poorly equipped to conduct de novo drug discovery and preclinical development.[350] For example, these institutions generally lack the capacity and funding to carry out the medicinal chemistry necessary to optimize drug compounds, the exploratory pharmacology necessary to evaluate their drug-like properties, and the rigorous preclinical toxicology testing necessary to advance a novel drug compound into clinical trials.[351] The NIH can sidestep its shortcomings in these areas by developing new indications for existing drugs, since those drugs have already progressed through the stages of research and testing outside its capabilities.[352]

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[348] *See supra* note 338; Moran, *supra* note 337; FASTER CURES, *supra* note 337; Roberts et al., *supra* note 341.

[349] FASTERCURES, *supra* note 337, at 3.

[350] *See, e.g.*, Muthyala, *supra* note 281 ("Academic investigators and disease foundations usually do not have the required infrastructure and expertise to develop drugs."); Declan Butler, *Lost In Translation*, 449 NATURE 158, 158-159 (2007) ("Academic institutions are often naive about what it takes to develop a drug, she says, and much basic research is therefore unusable. That's because few 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"); Department of Health & Human Services (DHHS), 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."); Stephen Frye et al., *US Academic Drug Discovery*, 10 NAT REV DRUG DISCOV. 409 (2011) (reporting the results of a survey regarding obstacles to public sector drug development, wherein "68% identified some aspect of funding (such as amount and stability) as an obstacle. A lack of expertise in medicinal chemistry, a lack of understanding of drug discovery in academia or a poor fit between the more individually oriented conventional academic career paths and the team efforts required for drug discovery were also identified as obstacles by 25% of respondents."); George J. Brewer, *Drug Development for Orphan Diseases in the Context of Personalized Medicine*, 154 TRANSLATIONAL RES. 314 (2009); Hann & Keserü, *supra* note 327.

[351] Reed, *supra* note 310 ("This gap [in the NIH's research capacity] includes 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 , at 19-20 (describing the pharmaceutical industry's core competencies as "Rigor; Medicinal chemistry; High throughput screening; Lead optimization; Manufacturing and scale up; Late phase development; [and] Marketing and distribution," while describing academia's strengths as, "Molecular biology of target; pathways; pathogenesis; Animals and in vitro models and testing scenarios; in depth disease understanding; Relationships with relevant patients; [and] Proximity of patients and laboratory").

[352] *See supra* notes and text accompanying notes _-_; Huang et al., *supra* note 260 (noting that the development of new indications for existing drugs "obviate[s] the need for NME development, a long and expensive process.").

The second limitation is the NIH's lack of capital to fund the later, more costly clinical trial phases[353] and the FDA-approval process.[354] With adequate funding, the NIH could establish new indications for FDA-approved drugs without support from private industry.[355] However, as discussed in Section III.E., government funding for these clinical trials is always (and increasingly) in short supply.[356] Consequently, researchers note that "[d]espite the current enthusiasm [for testing old drugs for new indications], there remains an unmet critical need to fund repurposing projects into phase IIb and phase III."[357] The NIH and academic researchers typically must find industry sponsors to run these trials.[358] Pharmaceutical companies only make these investments when the sales revenue from the new indication is expected to cover the cost of those clinical trials and FDA approval. The inability to earn significant revenue from developing a new indication for an off-patent, FDA-approved drug makes it difficult or impossible to attract

[353] *See* Oprea et al., *supra* note 143, at 61 ("Although the number of clinical studies required when repurposing drugs appears smaller, the petitioner must nevertheless conduct clinical trials with respect to efficacy (e.g., for the novel indication), and sometimes for safety as well (e.g., when doses higher than the approved ones are needed). The financial burden placed on the petitioner, whether an academic unit or any other (non-profit) organization, exceeds the million-dollar range."); Oprea & Mestres, *supra* note 144 ("Despite the current enthusiasm, there remains an unmet critical need to fund repurposing projects into phase IIb and phase III. The burden of proof remains with the petitioner, be it academic or industrial, which implies that any claims for clinical effectiveness against disease have to be demonstrated in clinically controlled conditions"); Weir et al., *supra* note 309, at 1056 (explaining that academic drug development still relies on the for-profit sector to take drugs through the more expensive later-stage clinical trials, giving the example of auranofin for chronic lymphocytic leukemia).

[354] *See, e.g.,* Brewer, *supra* note 350 (explaining that government support is often insufficient to cover even the administrative support necessary to meet the FDA's recordkeeping requirements for documenting clinical trial studies).

[355] *See* Rai, *supra* note , at 491-92; Dolgin, *supra* note 342, at 1027.

[356] *See supra* notes and text accompanying notes _-_. Moreover, there might be significant advantages to partnering with pharmaceutical companies even when the NIH does not need private sector funding for the necessary clinical trials. *See* Butler, *supra* note 350, at 158-159 ("translational 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 in San Francisco, California"); Colvis et al., *supra* note 312, at 25 ("The culture of therapeutic development needs to change. We cannot afford to work in silos of academia, government, and industry when the need for new treatments is so pressing. The ultimate stakeholders are the patients who are waiting for treatments."); Muthyala, *supra* note 281 (stating with respect to the NIH and NCATS, "[t]hey are making comprehensive and conscious efforts to identify … potential partners, and mak[e] data and resources available to the pharma industry"); Nair, *supra* note 270, at 2431; Woodcock, *supra* note , at 19 (noting that from the FDA's perspective, studies funded by pharmaceutical companies are superior to academic studies in their "rigor").

[357] Oprea & Mestres, *supra* note 144; Weir et al., *supra* note 309, 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 350.

[358] *See supra* notes and text accompanying notes _-_; Boguski et al., *supra* note 282, at 1394-95 ("Uliana and Barcinski's point about the '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. This is especially true in the case of generic drugs or drugs that cannot otherwise be patented."); *cf.* Oprea et al., *supra* note 143 ("Although the number of clinical studies required when repurposing drugs appears smaller, the petitioner must nevertheless conduct clinical trials with respect to efficacy (e.g., for the novel indication), and sometimes for safety as well (e.g., when doses higher than the approved ones are needed). The financial burden placed on the petitioner, whether an academic unit or any other (non-profit) organization, exceeds the million-dollar range.").

industry sponsors for these R&D investments.[359] This second, critical limitation on the NIH's efforts to translate breakthroughs in basic science into actual medical treatments for the public is similarly addressed if industry had adequate incentives to develop new indications for FDA-approved drugs.

The NIH leadership still believes repurposing known drugs is one of the most promising strategies for bridging the valley of death in biomedical research.[360] Indeed, drug repurposing has become a cornerstone of the NIH's translational research program.[361] Not only is it investing in screening technologies that can identify new indications of known drug compounds.[362] The NIH also 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.[363] However, because pharmaceutical companies will not invest in new indications for drugs once generics are on the market, the NIH largely restricts its repurposing efforts to failed drug candidates that never received FDA approval.[364] It is focusing on these failed drug candidates instead of FDA-approved drugs because the failed drug candidates are still eligible for effective monopoly protection against generic manufacturers,[365] and therefore may attract industry sponsorship.[366] Unfortunately, failed drug candidates are statistically *far* less likely to prove safe and effective for a new indication.[367] The

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[359] *See* Mullard, *supra* note 289, 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.").

[360] *See* Collins, *supra* note 340.

[361] *See* Collins, *supra* note 309 (stating that drug repurposing "will be an important focus of the NIH's proposed National Center for Advancing Translational Sciences (NCATS). Indeed, drug rescue and repurposing research overall offers a key opportunity to learn from our collective past as we shape our future — a future in which translational science is more efficient and effective at delivering therapies and diagnostics to patients."); Cimmino & Aifantis, *supra* note 275, 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."); Muthyala, *supra* note 281 ("[T]he National Institutes of Health (NIH) Chemical Genomics Center (NCGC) is acting as a national resource for the translation of information found in the genome into biological insights and to new therapeutics, particularly for Rare and Neglected Diseases.").

[362] *See* Huang et al., *supra* note 260; Collins, *supra* note 340; Dakshanamurthy et al., *supra* note 271, at 6832.

[363] *See* Nair, *supra* note 270, at 2431; Colvis et al., *supra* note 312, at 24-25; Jocelyn Kaiser, *NIH's Secondhand Shop for Tried-and-Tested Drugs*, 332 SCIENCE 1492 (2011) (explaining the NIH is focusing its translational research on drugs not previously approved by the FDA due to patent protection concerns); Mullard, *supra* note 119.

[364] *See supra* note 363.

[365] *See supra* notes and text accompanying notes _-_ (Section IV.A.)

[366] *See* Diamond, *supra* note 290; Smith, *supra* note 85 ("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.").

[367] DiMasi et al., *supra* note 303 (finding that "success in reaching the marketplace for second indications pursued was highly correlated with whether the first indication pursued reaches the marketplace. If a second indication is pursued and the first indication is a success, then marketing approval of a second indication is more likely than not. However, if the lead indication fails, then the likelihood of success for a second indication is only 2.5%. The results

NIH has been forced to direct its R&D investments toward these much less promising medical treatments because firms have no effective form of monopoly protection over new indications of FDA-approved drugs.

E. Conclusion

Each of the problems discussed above is the direct result of the government's failure to offer enforceable patent protection over new indications of off-patent drugs. In recent years, it has become clear that the social costs of this hole in the incentives for pharmaceutical innovation are immense. There are now thousands of FDA-approved drugs that are off-patent, and screening technologies have allowed researchers to identify hundreds and even thousands of potential new uses for those products. The number of off-patent drugs will continue to grow over time, as will researchers ability to identify potential new uses. As a result, this already severe problem will only get worse.

VI. SOLVING THE PROBLEM OF NEW USES

The problems discussed in Sections V all stem from the same informational barrier in the pricing infrastructure of prescription drugs. When pharmacists fill a prescription for a drug that has more than one indication, pharmaceutical companies do not know which of those indications the drug was prescribed to treat.[368] Without this information, they cannot enforce a new-use patent over a particular indication, and therefore lack the economic incentive to develop new indications for drugs once generics are available.

This section will show that, with the growth of electronic prescribing ("e-prescribing") and electronic health records, we can now overcome this information problem under most circumstances.[369] Physicians can submit the indication for a drug when they write a prescription,

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are qualitatively similar for third indications. If a third indication is pursued, then likelihood of success for that third indication falls from 42% to less than 2% dependent on whether the first indication is a success.").

[368] Tewodros Eguale et al., *Enhancing Pharmacosurveillance with Systematic Collection of Treatment Indication in Electronic Prescribing*, 33 DRUG SAF. 559 (2010) (discussing the absence of information available on the indication for a prescription and consequences thereof).

[369] There is an expansive literature on the potential benefits of e-prescribing, but none of it mentions the use of indication reporting to facilitate the enforcement of new-use patents or differential pricing by indication. *See, e.g.*, Eguale et al., *supra* note 368, at 560 ("Mandatory documentation of treatment indication at the time of prescription has several potential advantages, including the opportunity to generate diagnosis-based reminders for drug selection and follow-up, to incorporate clinical guidelines into the decision process, provide pharmacists with critical information for safe dispensing of drugs and appropriate patient counseling and to create longitudinal drug treatment history (e.g. treatment failures by indication and their reasons). It will also enhance capacity for new automated pharmacosurveillance methods to be developed that assesses safety and effectiveness of drugs by treatment indication. Moreover, using such data will allow evaluation of the magnitude of off-label prescribing and its determinants with the associated safety and economic implications."); Maria A. Friedman et al., *Interoperable*

and pharmaceutical companies could often verify the reported indication (along with insurers) with limited access to patients' (de-identified) medical records. With a few minor policy changes, the government could transform e-prescribing and electronic medical records into the needed infrastructure for enforcing new-use patents, thereby closing a critical gap in the incentives for pharmaceutical innovation.

A. *Reporting Indications Through E-Prescribing Software*

The first step in permitting pharmaceutical companies to enforce patents on new uses for drugs is to establish an infrastructure for physicians to report the indications for their prescriptions with minimal disruption to their practice. In the past, this type of reporting was impractical.[370] However, in a world where physicians write their prescriptions electronically, they can easily record the indications for their prescriptions.[371]

E-prescribing software enables the electronic transmission of prescription information from the prescriber's computer to a pharmacy computer.[372] Most U.S. physicians already use e-

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Electronic Prescribing in the United States: a Progress Report, 28 HEALTH AFF. 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).

[370] *See, e.g.*, 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* 1-2 (OEI-07-08-00152) (2011).

[371] *See* Eguale et al., *supra* note 368 ("Our study shows that physicians can document treatment indication with high accuracy at the time of prescribing using an electronic prescribing system. This process can be integrated into their work-flow."); 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"); Tamblyn et al., *supra* note 369, at 153 (finding that with two-weeks experience, physicians became adept at quickly entering indications with their e-prescriptions).

[372] *See* Electronic Prescribing: Web Definitions, *at* http://en.wikipedia.org/wiki/electronic_prescribing (last accessed Sept. 22, 2013). The U.S. government publications typically define electronic prescribing as "a prescriber's ability to electronically send an accurate, error-free and understandable prescription directly to a pharmacy from the point-of-care." Centers for Medicare & Medicaid Services (CMS), *E-Prescribing*, at www.cms.gov/Medicare/E-Health/Eprescribing/index.html; U.S. Department of Health and Human Services, What electronic prescribing capabilities will I need to implement?, *at* www.hrsa.gov/healthit/toolbox/HealthITAdoptiontoolbox/MeaningfulUse/whaterxcaps.htlml

prescribing, although its adoption is not yet universal.[373] Congress is encouraging the transition with financial incentives for physicians to use e-prescribing instead of handwriting their prescriptions.[374] The Department of Health and Human Services is pushing to achieve its goal of nationwide, universal e-prescribing adoption by the end of 2016.[375]

Many scholars argue that the government should take advantage of e-prescribing's capabilities to record and track the indications for prescriptions for independent reasons.[376] E-prescribing software can – and, in some cases, already does – require physicians to list the indications of prescriptions.[377] It can also transmit that information to pharmacists to use at the point of sale.[378] Commentators note that this information could help pharmacists avoid medication errors and allow insurers to track and discourage inappropriate off-label prescribing.[379] It could also be used to inform physicians of treatment alternatives and guideline recommendations at the time of prescribing.[380]

This literature on e-prescribing overlooks what is almost certainly the greatest potential benefit of such a system: creating incentives for firms to develop new uses for off-patent drugs. If physicians must report the indications for their prescriptions to pharmacists,[381] those pharmacists

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[373] Fotsch, *supra* note 369 at 917 (reporting that, as of November 2011, "more than 50% of community-based providers were using e-prescribing").

[374] *See* 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) (describing the financial incentives provided by the government for physicians to adopt e-prescribing and the impact of that incentive program); Fotsch, *supra* note 369, at 917 (attributing the "record pace" of the adoption of e-prescribing to the "HITECH Act and the tens of billions of dollars in federal payments to health-care providers it offered to encourage adoption of EHRs and utilization of e-prescribing"); Maria A. Friedman et al., *Interoperable Electronic Prescribing in the United States: a Progress Report*, 28 HEALTH AFF. 393 (2009).

[375] *See* 78 FED. REG. 21308, 21311, 42 C.F.R. part 411, Apr. 10, 2013.

[376] *See, e.g.*, Eguale et al., *supra* note 251, at 781 ("Electronic prescribing should document treatment indication to monitor off-label use."); PETER KILBRIDGE, E-PRESCRIBING 32 (2001) (noting that reporting indications to pharmacists through e-prescribing software can enhance patient safety by allowing pharmacists to guard against mistaken dosages or other contraindications).

[377] *See* Eguale et al., *supra* note 368; Tamblyn et al., *supra* note 369, at 149-51; 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); MICHAEL VAN ORNUM, ELECTRONIC PRESCRIBING: A SAFETY AND IMPLEMENTATION GUIDE 63 (2008) ("Some e-prescribing applications allow the prescriber to identify the indication for the prescription during the prescribing process. Others allow entry of problems or diagnosis independent of the prescribing process.").

[378] *See* VAN ORNUM, *supra* note 377, at 155-156.

[379] *See supra* note 376.

[380] *See* VAN ORNUM, *supra* note 377, at 66 ("Driving drug selection by indication is an opportunity for professional organizations to collaborate on specific therapy suggestions that span multiple disease states. Their suggestions could be incorporated into the e-prescribing application to help the prescriber find the right prescription the first time.").

[381] Although mandatory indication reporting would take up physicians' time, U.S. physicians might eagerly embrace such a system because it could replace the burdensome paperwork-based prior-authorization systems now used by many insurers. *See* CENTER FOR HEALTH TRANSFORMATION, ELECTRONIC PRIOR AUTHORIZATION AND ITS

would have a legal obligation not to infringe any new-use patents by dispensing low-cost generics for patented indications.[382] And if pharmaceutical companies had access to this same information about the prescribed indication (minus any personal information about the individual patient to protect his or her privacy), they could enforce their new-use patents against the pharmacists.[383] Pharmacists would be required to dispense the pharmaceutical companies' more expensive, brand-name drug instead of a low-cost generic when physicians prescribe that drug for a patented indication. Alternatively, the pharmacist could dispense the low-cost generic and then report the sale to the patient's insurer and the pharmaceutical company, allowing the pharmaceutical company to bill the insurer directly for the sale.[384] In either case, pharmaceutical companies could charge insurers when physicians prescribe an off-patent drug for a patented indication, thereby providing the financial incentive to develop those new uses.

Although no country has ever implemented a nationwide system of e-prescribing that included the reporting of indications, recent pilot programs suggest such a system is feasible. Tewodros Eguale and co-authors studied the adoption of such a system among primary care physicians in Quebec.[385] They report a high level of accuracy (97%) in the indications submitted by physicians through e-prescribing.[386]

Most e-prescribing software programs lack the functionality to record indications along with each prescription and transmit that information to pharmacists,[387] but the government

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POTENTIAL IMPACT ON HEALTHCARE: HOW PAPER-BASED PRIOR AUTHORIZATION IMPEDES ELECTRONIC PRESCRIBING (2012) (discussing how e-prescribing software that requires indication reporting can also operate as electronic prior authorization, thereby avoiding the time-consuming process of paper-based prior authorization).

[382] *See supra* notes and text accompanying notes _-_ (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. *See Global-Tech Appliances, Inc., v. SEB S.A.*, 563 U.S. __ (2011). Alternatively, the government could require that pharmacists' e-prescribing software notify them when a prescribed indication is covered by a new-use patent. Since pharmaceutical companies generally must list those patents in the FDA's Orange Book, pharmacies' e-prescribing software could link to that information. *See Caraco Pharm. Labs. v. Novo Nordisk*, 566 U.S. ___ (2012).

[383] *See supra* notes and text accompanying notes _-_ (explaining how pharmaceutical companies could enforce their new-use patents if they knew the prescribed indication for each sale). Pharmacists would presumably demand indemnification from insurers for liability under these circumstances. Consequently, the real parties of interest in these disputes would be the pharmaceutical companies and insurers. *See supra* note _.

[384] To protect patients' privacy, pharmacists could transmit information about the prescribed indication to the relevant pharmaceutical company without identifying the individual patient.

[385] *See* Eguale et al., *supra* note 368, at 559.

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

[387] *See* VAN ORNUM, *supra* note 377, at 155-156 ("The practice of including indications on prescriptions is gaining momentum among prescribers, but is less consistent than it could be. The diagnosis or indication could easily be added to prescriptions but many applications have not developed tools for this. Most e-prescribing applications allow the entry of a problem or diagnosis in the patient's profile. Others go so far as to link the drug to the problem

could easily correct this problem.[388] As noted above, the government is already using various incentives to expedite the transition to universal adoption of e-prescribing by physicians.[389] It would only need to alter its specifications for qualifying software to require a feature where physicians report the indication for their prescriptions.[390] Software vendors could easily incorporate this functionality into their systems.[391] Once the nationwide transition to electronic prescribing is complete, pharmaceutical companies and insurers could use this system to link reimbursement rates for drugs to the reported indication on each prescription.

B. *Allowing Firms to Verify Reported Indications with Electronic Medical Records*

The second step in permitting pharmaceutical companies to enforce patents on new uses for drugs is to give them access to patient-level information that will allow them to verify the accuracy of reported indications. Needless to say, pharmaceutical companies would be reluctant to develop a new indication for an older drug if they think physicians will falsely report their prescribed indication to avoid the higher price. Although the Eguale study found a high level of accuracy in the reported indications through e-prescribing,[392] the risk of fraud will be greater if a drug's price depends on the listed indication.[393] To police the accuracy of submitted indications, both insurers and pharmaceutical companies would need access to patients' electronic medical records, although that access could be greatly restricted to protect patients' privacy.

The government already provides insurers with access to patient's health records[394] to use for their coverage determinations.[395] As discussed in Section III, most insurers limit their

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or diagnosis within the application. In a tragic lack of foresight, the crucial piece of information—the reason for which the drug is prescribed—often fails to reach the pharmacy.").

[388] Indeed, the government already requires physicians and pharmacists to report the indication with the prescription under Medicare Part B, though this information is not shared with the pharmaceutical firm. *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) (stating that "CMS [Center for Medicare and Medicaid Services] currently requires prescribers and pharmacies transmitting outpatient prescriptions for Medicare Part B to include a diagnosis code on the face of the prescription and in the National Council for Prescription Drug Programs (NCPDP) standardized claim transmission field.").

[389] *See supra* note and text accompanying note 374.

[390] *See* 21 C.F.R. § 1311.205 (listing the required elements for an e-prescribing software program to qualify for federal incentive benefits).

[391] *See* Eguale et al., *supra* note 251 (noting, with respect to linking a prescribed drug to an indication, "vendors could easily incorporate this feature into EHR [electronic health records] systems").

[392] *See supra* text accompanying note 386.

[393] *Cf.* Shah et al., *supra* note 388, at 508 ("physicians were worried that entering diagnosis codes on prescriptions could lead to denial of claims for "off-label" indications. Some physicians were so convinced that public and private payers might deny coverage for medications written off-label that they proposed writing only the labeled indication on the prescription regardless of the patient's condition.").

[394] *See* 45 C.F.R. § 164.508(a)(2).

coverage for prescription drugs to indications that are approved by the FDA or listed in one or more of the pharmaceutical compendia.[396] Insurers often enforce these coverage restrictions by requiring physicians to submit prior authorization forms listing the indication for their prescription.[397] Although physicians could misreport indications on prior authorization forms to skirt insurers' coverage restrictions, these actions constitute fraud,[398] and insurers can check patients' medical records to verify physicians' reported indications.[399] Insurers report that, in most instances, their prior-authorization requirements are extremely effective at stopping physicians from prescribing expensive drugs for non-covered indications.[400] Their success suggests that insurers can generally deduce the actual indication for a prescription when they have access to patient health records. It also suggests that having access that information effectively deters most fraudulent reporting of indications.

If pharmaceutical companies also had access to patients' medical records, they would be in the same position as insurers to verify reported indications for prescriptions. This information would allow pharmaceutical companies to more reliably enforce their new-use patents, creating an incentive to develop those new indications.

Of course, patients' have legitimate privacy interests in their medical records that should be protected under such a system. The government could limit pharmaceutical companies' access to patients' medical records by requiring de-identification of the records.[401] It could also prohibit pharmaceutical companies from using those medical records for anything other than billing. If government believes these privacy safeguards are inadequate, it could expand its existing HIPAA framework to include pharmaceutical companies as "covered entitities," which would impose strict regulations on pharmaceutical companies' use of patients' confidential medical information.[402]

Admittedly, pharmaceutical companies could not depend on patients' medical records to prevent physicians from misreporting indications under all circumstances. Some diagnoses are hard to distinguish from others based on the information contained in a patient's medical records

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

[396] *See supra* note and text accompanying note 135.

[397] *See supra* note 237.

[398] *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.

[399] *See* CENTER FOR HEALTH TRANSFORMATION, *supra* note 381, at 13.

[400] *See* Wright, *supra* note 136, at 5 ("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," and they have "had great success at preventing payments for drugs not provided for medically accepted indications by using prior authorization when permitted").

[401] Indeed, pharmaceutical companies are already allowed to purchase such de-identified patient-level health records for research purposes. *See supra* note 235.

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

(e.g., many psychiatric conditions),[403] leaving room for fraudulent reporting not susceptible to audit. In these cases, enforcing new-use patents may be cost-prohibitive, and pharmaceutical companies may remain unwilling to develop these new indications.

However, in most circumstances, this system should allow pharmaceutical companies to enforce new-use patents over new indications – as evidenced by the success of insurance companies policing coverage restrictions. Pharmaceutical companies could distinguish many indications based on the prescribing physicians' specialty or records of concomitant and follow-up treatments. When physicians use laboratory and imaging tests to diagnose a condition, those test results are available for review in patients' medical files, clearly signaling the indication in most cases. As diagnostic technology advances, such testing will become increasingly common, making it easier to verify reported indications. When pharmaceutical companies can detect fraud easily through access to patients' medical records, physicians would be reluctant to misreport indications, allowing pharmaceutical companies to enforce their new-use patents.

C. Conclusion

With these two simple changes, we can address one of the most critical problems facing biomedical research. The government only needs to modify the specifications for qualifying e-prescribing software and establish privacy rules allowing pharmaceutical companies restricted access to patients' health records. Pharmaceutical companies would then have the necessary information to enforce new-use patents.

The implementation of this new infrastructure provides the government with an opportunity to reassess the appropriate incentives for investment in new indications. For example, the government may wish to revisit the rules governing when new uses can be rendered unpatentable by prior disclosures, or create regulatory exclusivity periods that could similarly be enforced against pharmacists and insurers.[404] It is also possible that, given differences in the development times for new indications, a uniform 20-year patent term provides too much protection for some and too little protection for others.[405] The government might beneficially clarify the standards for indirect infringement to allow a cleaner line of enforcement against insurers.[406]

Using this approach to providing monopoly protection over new indications would also benefit people in need of these treatments in the developing world. This paper outlines a

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[403] *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).

[404] *See* Roin, *supra* note 22.

[405] *See* Roin, *supra* note 86; Budish et al., *supra* note 86; Roin, *supra* note 31.

[406] *See supra* note and text accompanying note 233. The government may also want to create a mechanism for resolving disputes between third-party payers and pharmaceutical companies. This could be modeled on the dispute resolution mechanism currently used by pharmaceutical companies and generic manufacturers.

proposal that will permit pharmaceutical companies to enforce patents over new indications after a drug has gone generic. However, the proposal can only be implemented in countries that are sufficiently developed to maintain a sophisticated IT structure for the delivery of healthcare. E-prescribing must be nearly universal and pharmaceutical companies as well as insurers need access to electronic health records. In other words, this form of monopoly protection will only be enforceable in wealthier countries. In most developing countries, patients would have the benefit of access to the new indications, while paying only the generic price. Moreover, by encouraging pharmaceutical companies to finance more of the clinical trials for new indications, this approach could also free up NIH funding for research in tropical diseases.

Government funding for clinical trials of new indications will always be critical, but getting industry to contribute is also essential. With an infrastructure that can support enforcement of new-use patents, pharmaceutical companies will have much stronger incentives to develop new uses for existing drugs. E-prescribing was never intended to accomplish these goals, but if implemented properly, this could be its most important legacy.