Missing Markets for Innovation: Evidence from New Uses for Existing Drugs*

Eric Budish Maya Durvasula Benjamin Roin Heidi Williams

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Abstract

For large classes of potential inventions, it is either not possible or not profitable for firms to enforce intellectual property rights. In this paper, we show that these missing incentives yield quantitatively significant underinvestment in research and development. We develop a simple model that defines large classes of inventions for which intellectual property rights are necessary to incentivize private investment, but are either unavailable or unenforceable in practice. We identify an empirical setting—research into new therapeutic uses for existing drugs—in which there is sharp variation in the enforceability of intellectual property rights on otherwise comparable inventions over time. This variation allows us to test two claims central both to our model and to the design of innovation policy more generally—that intellectual property rights create private incentives for innovation only when they are enforceable, and that incentives are increasing in the duration and enforceability of these rights. We show that when intellectual property rights become unenforceable, research investment and commercialization nearly cease. The welfare consequences of inadequate incentives for the development of new uses are large, in terms of both missed therapeutic opportunities and dollars of forgone social value. Our estimates suggest that 280–800 new uses for existing drugs would have been developed under counterfactual policies. Measures of the value of these uses drawn from existing literature suggest that the social cost of this particular missing market is on the order of several trillion dollars.

Budish: University of Chicago & NBER (eric.budish@chicagobooth.edu); *Durvasula*: Stanford University & Stanford Law School (maya.durvasula@stanford.edu); *Roin*: Charles River Associates (bnroin@gmail.com); *Williams*: Dartmouth College & NBER (heidi.lie.williams@dartmouth.edu). We are grateful to Daron Acemoglu, Daniel Fetter, Amy Finkelstein, Matthew Gentzkow, Paul Milgrom, Abhishek Nagaraj, Matt Notowidigdo, Lisa Larrimore Ouellette, Al Roth, Chad Syverson, and seminar participants at MIT Sloan, NBER Productivity lunch, the Radcliffe Institute, Stanford, UC-Berkeley Haas, and TNIT for comments, to Yali Friedman, Ben Berger, Amitabh Chandra, and Craig Garthwaite for data, and to Joey Anderson, Ryan Broll, Jeremy Brown, AnneMarie Bryson, Henry Manley, Tamri Matiashvili, Gideon Moore, Lia Petrose, Maya Roy, Mahnum Shahzad, Ralph Skinner, Liyang Sun, and Zahra Thabet for excellent research assistance. Research reported in this publication was supported by the National Institute on Aging (NIA) and the NIH Common Fund, Office of the NIH Director, through Grant U01-AG046708 to the National Bureau of Economic Research (NBER); the content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or NBER. This research was also funded in part by NIA grant P01AG005842, the Alfred P. Sloan Foundation, NSF Grant Number 1151497, the Polsky Center for Entrepreneurship and Innovation at the University of Chicago Booth School of Business, the Hultquist Faculty Research Endowment, the Knight Hennessy Scholars Program at Stanford University, the John M. Olin Program in Law and Economics at Stanford Law School, and the National Science Foundation through grant DGE-1656518 (Durvasula) to Stanford University. While writing this paper, Williams was a visiting scholar and (was subsequently and is currently) a part-time consultant at the Congressional Budget Office (CBO); the views expressed in this paper should not be attributed to CBO.

1 Introduction

Most inventions are far more costly to develop than they are to imitate and reproduce. Economists have long recognized that, absent some mechanism that allows inventors to recoup their investments in the often long, costly processes of research and development, competitive markets will offer insufficient incentives for innovation (Nelson, 1959; Arrow, 1962; Nordhaus, 1969). This intuition is, of course, much older: "*To promote the Progress of Science and useful Arts*," Article I Section 8 of the United States Constitution gave Congress the ability to grant intellectual property rights—legal protections that provide inventors with the time-limited right to exclude their competitors from the market. In this paper, we investigate the idea that, for large classes of socially valuable inventions, it is either not possible or not profitable for firms to enforce intellectual property rights. Put differently, the intellectual property rights that exist "on paper" to induce investment in research and development provide, in many settings, no meaningful incentive for innovation.

To understand the challenges of enforceability, consider three potential inventions: a protocol of diet and exercise that, if properly calibrated and carefully implemented, would substantially increase longevity; a process that would increase the precision of pharmaceutical manufacturing and reduce the risk of large-scale recalls of medicines; and a car seat for young children available for sale on an online marketplace (e.g., Amazon) that would improve over existing alternatives on metrics of safety and weight.[1] In each case, intellectual property rights are available: inventors could likely receive a patent grant from an entity like the U.S. Patent and Trademark Office. Importantly, however, these patent grants are not self-enforcing. To police the boundaries of these rights, an inventor is required to identify each instance of infringement and file suit against every infringer. When it is difficult to identify, say, that someone is combining food and physical activity in a way that infringes on a patent or that a particular pill was produced with a patent-protected method, patents are unenforceable because inventors cannot observe infringement. Even when an inventor can observe, for example, dozens of counterfeit car seats for sale by small and largely anonymous competitors, patents are unenforceable because inventors cannot identify a party to sue.

We develop a simple theoretical framework that uses the characteristics of inventions to identify settings in which these types of legal and practical gaps in intellectual property protection translate into missing private incentives for investment. We identify one such setting—research into new therapeutic uses for existing drugs—where the enforceability of intellectual property rights on otherwise comparable inventions changes sharply over time and hence allows us to test the link between intellectual property rights and private incentives central to this paper. When intellectual property rights become unenforceable, we show that research and development essentially cease.

We begin by formalizing the heterogeneity that generates these differences in enforceability across inventions. We introduce a model in the style of Nordhaus (1969), in which intellectual property rights confer some period of time under monopoly. To the standard framework, we add three complications. First, some inventions can be profitably commercialized while remaining secret. In these cases, firms can recoup their investments in research and development without formal grants of intellectual property—so long as they can

[1] Importantly, none of these inventions are amenable to protection with trade secrecy as they must be publicly disclosed to end users and regulators as a condition of sale. In Section 2, we consider the set of inventions for which secrecy *does* provide an effective incentive for innovation (e.g., Mansfield, 1986; Moser, 2005).

maintain secrecy. Second, only some inventions are eligible for formal intellectual property protection. By law, others are not. Third, of those inventions that are eligible for intellectual property rights, only some have rights that are enforceable in practice. Enforcement requires a firm to identify each instance of imitation and successfully bring suit against every infringer. When imitation is challenging or impossible to observe, or when the parties on whom liability falls are not attractive defendants, intellectual property rights that exist "on paper" offer no meaningful protection.

We say that a *missing market* arises when formal intellectual property rights are necessary to incentivize research and development, but such rights are either unavailable or unenforceable. Note that this characterization rules out a standard policy solution to the problem of inadequate incentives for innovation: canonical models linking intellectual property rights to incentives embed the idea that sufficiently strong property rights—that is, longer or broader periods of market exclusivity—can make any invention profitable to develop (e.g., Nordhaus, 1969; Gilbert and Shapiro, 1990; Klemperer, 1990). Here, when gaps in incentives arise because intellectual property rights are unenforceable, there are no "Nordhaus parameters" that can induce private investment.

This model allows us to identify large classes of (potential) inventions, across sectors of the economy, where missing markets are likely to arise. Our empirical analysis focuses, however, on a case study—investments into new uses for existing drugs—where sharp variation in the enforceability of intellectual property rights over time allows us to test for evidence of a missing market.

To fix ideas about the institutional features that enable this test, an example is helpful. In 1995, the U.S. Food and Drug Administration (FDA) approved Glucophage (metformin hydrochloride) as a treatment for diabetes.[2] Generic versions of the drug entered the market in 2002. Around this time, oncologists began to document tentative evidence that metformin may also be effective at treating or preventing cancer. Though these researchers proceeded with various "pre-clinical" studies, commercial interest in funding the clinical trials necessary to validate metformin as a treatment for human cancer was nonexistent (Gale and Gerlin, 2012). The problem? There is no mechanism that would allow a private firm to *sell* the knowledge that an existing drug can be used in a new way.[3] To be clear, the USPTO would, likely, have granted patents on methods of using metformin to treat cancer, and the FDA would have barred other firms from marketing generics for these uses.[4] But once the information about metformin's value as a treatment for cancer was known, any physician could use the information freely, without compensating the innovator. Even if the innovating firm could detect unauthorized use, enforcement would be practically impossible: the only parties on whom liability would definitively fall are the patients who would use the drug to treat their own cancer.[5] As of 2023, decades after preliminary evidence first emerged, whether metformin has potential as a treatment or even potentially as a preventative for cancer is an open question that "still warrant[s] well-

[2] NDA #020357, approved on 03 March 1995.

[3] Gale and Gerlin (2012) includes portions of an interview with one oncologist, who indicated that she was ready to begin work on this lead around 2002, but was unable to garner support from any private firm, noting that "*When they realized the results wouldn't be available until they lost their patent, they pulled out*."

[4] Section 3.2 provides details on the availability of, both, patents on methods of using existing drugs for new therapeutic indications and FDA-administered regulatory exclusivities that serve the same purpose.

[5] In a small number of cases, hospitals, physicians, insurers, and pharmacists may share in the liability—though suits against them for patent infringement are rare. Section 3 introduces the relevant institutional details.

designed clinical investigation" (Lord and Harris, 2023).

In most missing markets identified by our model, intellectual property rights would be unenforceable from the moment that they were granted. Observe, however, that the unenforceability of patents on new uses for metformin arises many years after commercialization, only when the original firm's period of market exclusivity expires. This delay—a feature of the regulatory structure for pharmaceuticals in the United States—provides our research design. For a period in each new drug's life, the FDA will bar the entry of all generic competitors. During this time, a single firm controls the market and can set a price for its drug that reflects, also, any uses that it has developed. As long as the firm retains its market exclusivity, there is no option to use the invention without compensating the innovator. Patents on any new uses are, thus, perfectly enforceable. After generic entry, as the metformin case illustrates, the likelihood that the firm can enforce such a patent drops essentially to zero.

Mapping this variation to our framework yields three predictions. First, firms will have strong incentives to invest in new uses for existing drugs soon after initial approval. Second, as market exclusivity expiration approaches, the number of years in which investments in new uses will yield profits declines—and thus, incentives should fall. Third, exclusivity expiration creates a missing market for new uses, and private research and development should cease.

Testing these predictions is the focus of our empirical work. To do so, we construct new data tracing out research and development investments associated with all new drugs approved by the FDA between 1985 and 2014. In particular, we collect records of scientific publications, clinical trials, and re-approvals for new uses. Characterizing trends in investment around market exclusivity expiration requires, first, defining some measure that captures the point in time when the firm expects its intellectual property rights to lapse and, hence, its drug to be vulnerable to generic competition. We draw on legal and regulatory analyses, as well as newly-digitized records of the intellectual property rights associated with each drug in our data, to propose and validate such a measure of expected exclusivity expiration.[6]

Using these data, we show that investments in new uses for existing drugs closely track our predictions. Ten years prior to market exclusivity expiration, roughly ten percent of drugs in our sample are re-approved for at least one new use. The likelihood of re-approval declines monotonically in each subsequent year and falls to zero immediately following market exclusivity expiration. We document similar trends for clinical trials, which capture efforts to validate links between drugs and new diseases, as well as for scientific publications, which capture "upstream" basic scientific research.

Together, these facts provide evidence consistent with—though not dispositive of—the existence of a missing market for new uses following generic entry. There remain, however, several alternative explanations for these patterns. If the set of "scientific opportunities" for new uses is gradually exhausted, research investments may naturally decline over a drug's lifecycle. Alternatively, firms may recognize that generic entry is imminent and strategically sequence research and development to bring all viable new uses to market during this initial profitable period. On the basis of several additional empirical tests, we argue that both explanations are unlikely.

First, we observe that the scientific publications linked to drugs in our sample report their sources of

[6]Many of the details associated with this process are reported in a companion paper, Durvasula et al. (2023).

funding. If the declines in research investment that we document signal the exhaustion of scientific opportunities, then we would expect to find symmetric trends in publicly and privately funded research. Instead, we document that the decline in the number of scientific publications studying drugs in our sample around market exclusivity expiration is driven entirely by a drop off in publications with private funding. Trends in publicly-funded publications are stable. This fact also provides evidence against the second concern: if scientific opportunities continue to arise over time—before and after generic entry—that commercialization efforts cease at the time of exclusivity expiration is *prima facie* evidence of missing innovation.[7]

As a second test, we make use of the fact that firms have a small number of opportunities to "preserve" the enforceability of intellectual property rights after generic entry, including by directing investments toward technologically similar drugs for which there is not yet a generic competitor. Upon market exclusivity expiration, we document that although the likelihood that a drug in our sample is approved for a new use drops to zero, the likelihood that it is re-approved as part of a "fixed dose combination" actually *increases*. Fixed dose combinations bundle multiple drugs into a single "dosage form"—metformin and the drug glyburide are combined in a single tablet under the trade name Glucovance—which is regulated as a distinct new drug and thus subject to the same restrictions on generic entry. That the number of investments in related products on which patents remain enforceable increases at the time of market exclusivity expiration provides support not only for the argument that scientific opportunities do not coincidentally drop off at this time, but also that our measure of market exclusivity is accurately capturing firm expectations.[8] Taken together, this body of evidence provides support for the idea that there are scientifically feasible new uses for existing drugs that are not profitable to develop given the structure of existing incentives.

Our empirical setting allows us not only to establish the existence of this missing market, but also to quantify its social costs. To do so, we begin by documenting causal evidence that increasing the duration of market exclusivity increases the number of new uses that are brought to market.[9] This exercise relies on the idea that firms in the pharmaceutical sector have strong incentives to file key patents on new drugs at the time of invention, often many years before the drugs are approved for sale. Sizable delays between invention and approval—due to required clinical trials and regulatory delays—mean that certain drugs have many more years of effective market exclusivity than do others, for reasons arguably unrelated to their potential for new uses (Roin, 2013; Budish et al., 2015; Gilchrist, 2016). We estimate that counterfactual periods of market exclusivity—selected to mirror policies that would provide fully enforceable intellectual property rights to new uses—would yield between 0.1 and 0.4 additional new uses per drug. As roughly 2,000 drugs that satisfy our sample criteria have been approved since the modern FDA was created in 1962, this implies

[7] Gelijns et al. (1998) observe that "it took half a century for the cardiovascular benefits of aspirin, the most widely used drug in the world, to be recognized, and nearly 40 more years before it was widely used for cardiovascular indications."

[8] Our framework and this empirical test hint at one perverse consequence of gaps in the enforceability of certain intellectual property rights. When patents are not enforceable, firms have strong incentives to seek out alternative mechanisms that allow them to exclude their competitors from the market. The example of fixed-dose combinations highlights one such option: firms might respond to the effective expiration of intellectual property rights on one drug by developing related products on which intellectual property rights remain enforceable—a practice pejoratively referred to as product hopping (Carrier and Shadowen, 2016). We do not undertake a complete welfare analysis and thus do not weigh in on the social costs of these practices, but emphasize that one cost of incomplete or unenforceable patent rights not captured by our analysis is any deadweight loss associated with solutions adopted to make certain investments profitable that produce comparatively little social value.

[9] Sections 6 and 7 clarify that while this exercise is useful to estimate the volume of missing innovation in this setting, this style of blunt patent term extension is unattractive as a policy solution to the missing markets problem.

between 280 and 800 missing new uses. Valuing each missing new use at $1 billion per year—a rough estimate of social value drawn from existing economic analyses of the social value of new drugs—indicates that the net present value of missing research and development in this market is on the order of $5 to $20 trillion.[10]

Although our back-of-the-envelope estimates of the social cost of missing new uses are rough, they are consistent with evidence offered by the scientific literature. Scientists characterize the relatively small number of chemicals that are ever approved as drugs by the FDA as "promiscuous," by which they mean that a drug that is sufficiently effective at treating *some* human disease to clear the threshold for FDA approval is very likely to be effective in the treatment of *many* diseases (Wermuth, 2006). Dozens of studies have validated this prediction. Gelijns et al. (1998), for example, document that within a sample of "blockbuster" drugs sold in 1993, nearly 90 percent had important uses beyond those for which they were originally approved. Against these estimates, our estimated range of 0.1 to 0.4 new uses per drug appears, if anything, conservative.

The idea that insufficient private incentives exist to develop new uses for existing drugs has been a long-standing concern for legal scholars, scientists, and policymakers (Gelijns et al., 1998; Mossinghoff, 1999; Eisenberg, 2005; US Institute of Medicine, 2008; Rai, 2012; Roin, 2014). This paper is, to the best of our knowledge, the first to formalize the source of missing incentives in this setting theoretically and to document underinvestment empirically. Interpreting our results against this policy-oriented literature not only confirms that the scale of underinvestment in this setting is large, but suggests that the problem is growing as advances in health data and screening technology reduce the cost of discovering potential new uses (Collins, 2011b,a, 2012; Collins and Varmus, 2015).

Evidence of a quantitatively significant missing market for new uses provides, as well, clear empirical support for the model of intellectual property and innovation incentives that we introduce. Our framework embeds and formalizes two ideas that have appeared in various forms and under many names across much of the legal and economic scholarship on incentives for innovation—that formal intellectual property rights are not necessary to incentivize the development of certain inventions (e.g., Mansfield et al., 1981; Teece, 1986; Mansfield, 1986; Levin et al., 1987; Cohen et al., 2000; Moser, 2005), and that formal intellectual property rights will not incentivize the development of others (e.g., Nelson, 1959; Arrow, 1962; Teece, 1986; Lemley and Shapiro, 2005; Eisenberg, 2005; Abramowicz, 2007; Kapczynski and Syed, 2012; Rai, 2012; Budish et al., 2015). In theoretical and empirical studies that aim to inform the design of optimal patent policy, however, every invention is assumed patentable (and patent-protected), and every patent perfectly enforceable (e.g., Machlup, 1958; Nordhaus, 1969; Scherer, 1972; Nordhaus, 1972; Klemperer, 1990; Gilbert and Shapiro, 1990; Scotchmer, 1991; Budish et al., 2015). Our modifications to the standard Nordhaus (1969)-style framework, though simple, capture the importance of legally-protected secrecy as a complement to patent protection. In particular, we formalize and test an idea central to the legal analysis in Kapczynski and Syed (2012)—that there are "domain[s] of innovation, that patents, whatever their scope, cannot adequately address."

[10] In Section 6, we collect various pieces of evidence on the social value of new uses relative to the initial approvals used to form this estimate and construct a set of scaling factors that might be applied to this estimate. Even if new uses are worth a fraction of initial approvals, our estimates imply that the social cost of this particular missing market is large.

The theoretical predictions generated by this model hinge on a causal link between intellectual property protection and incentives for innovation. Although decades of theory and centuries of policymaking have assumed such a relationship—that longer and broader intellectual property rights induce investment—there is remarkably little direct empirical support, owing to the difficulty of identifying meaningful variation in the protection provided to otherwise comparable inventions. A small number of papers—notably, Lerner (2002) and Sakakibara and Branstetter (2001)—have leveraged changes in national patent laws to test for such a relationship, but have found no effect—likely because country-level changes have relatively small impacts on global markets for innovation. Budish et al. (2015) document evidence consistent with the idea that longer patent terms induce additional research investments, but are unable to rule out alternative explanations. The model we introduce in this paper implies an alternative research design, which allows us to test for direct evidence that intellectual property rights affect the level of research and development by leveraging variation in the *enforceability* of intellectual property rights across inventions. The missing markets problem, here, creates variation in the effective patent terms (years before generic entry) provided to otherwise comparable investments (new uses). We find that increases in patent term cause increases in the number of new uses brought to market and—with the caveat that this estimate is specific to our empirical context—estimate the elasticity of research and development with respect to patent term.

We, thus, contribute more broadly to closely related literatures that study how property rights affect incentives for investment (e.g., Moser, 2005; Budish et al., 2015; Hodgson, 2024; Dix and Lensman, 2024) and how underprovision of incentives yields missing research and development (Budish et al., 2015; Krieger et al., 2022; Michelman and Msall, 2024; Dix and Lensman, 2024). Our model includes, as a special case, the problem of interest in Budish et al. (2015), who study incentives for the development of cancer treatments. Our model and empirical analyses are complementary, in certain ways, to Dix and Lensman (2024) who investigate incentives for the repurposing of existing cancer drugs, an important instance of the new uses problem. Our reduced form evidence—including evidence of a causal link between intellectual property rights and innovation, and a quantification of missing innovation that makes use of this new elasticity—complements the quantification exercise that their dynamic structural model of innovation enables. Taken together, the set of papers in both of these literatures provides support for a key prediction of our framework—that the scale of missing markets for innovation may be extraordinarily large.

This paper proceeds as follows. Section 2 introduces our conceptual framework. Section 3 provides context on the problem of new uses. Section 4 describes our data and measurement. Section 5 presents two tests that, together, establish the existence of a missing market for new uses for existing drugs. In Section 6, we present evidence on the magnitude of missing investment—in terms of missing "uses" and dollars of missing social value. In Section 7, we discuss the open question of how missing markets ought to be "fixed" if standard levers of intellectual property policy are unavailable before concluding.

2 Characterizing Missing Markets for Innovation

Not all inventions can be protected from imitation with grants of intellectual property rights—either because these rights are not available by law or because available rights are not enforceable in practice.[11] For certain inventions, these gaps in protection have no impact on incentives for research and development. For others, incomplete intellectual property rights yield *missing markets* for innovation.

This Section develops, in two parts, a simple framework that formalizes this heterogeneity. The first part introduces a set of complications to a standard Nordhaus (1969)–style model and, in doing so, allows us to define the conditions that give rise to a missing market. The second part transforms this model into a classification exercise, which uses characteristics of inventions to identify contexts where missing markets are likely to arise.

2.1 Defining Missing Markets

2.1.1 Preliminaries

A representative firm must decide whether to commercialize a potential invention, the characteristics of which it regards as exogenous.[12] Commercialization refers to the (costly) process of bringing a product or idea to market—running clinical trials to satisfy regulatory requirements, expanding manufacturing capacity to allow for production at scale, etc.

The starting point for this model is a Nordhaus (1969)–style framework, as adapted by Budish et al. (2015). A potential invention is characterized by sets of parameters, the first six of which are common to prior work.

- **Timing parameters**: The firm must decide whether to commercialize the potential invention in year t_{invent}, which we normalize to zero. Commercialization involves a deterministic delay t_{comm}.
- **Cost of commercialization**: To commercialize the potential invention, the firm incurs—in net present value terms at t_{invent}—a cost c.
- **Likelihood of successful commercialization**: Commercialization may not be successful.[13] We denote the probability of success by p_{comm}. We restrict consideration to potential inventions for which p_{comm} is greater than zero.

[11] As the introduction suggests, there are two categories of intellectual property rights of interest in this paper: grants that confer monopoly or monopoly-like rights—patents, copyrights, contract-law forms of intellectual property—which must be actively enforced; and trade secrets, which provide a default protection to inventions if the inventor took active steps to avoid disclosure. When we refer to formal grants of intellectual property rights that must be enforced, we are referring to this first category. Technically, there are other forms of intellectual property (e.g., trademarks) that neither provide any type of monopoly right nor have as their goal the provision of incentives for innovation.

[12] We use the term "invention" to refer to any instance of knowledge production—including in the form of physical products, sets of instructions, and pieces of information (Arrow, 1962; Romer, 1994; Jones, 2005).

[13] In our empirical context, for example, clinical trials may fail to enroll enough patients or may indicate that a drug is ineffective as a treatment for a particular disease.

- **Obsolescence risk**: If an invention is successfully commercialized, it may lose usefulness over time as new, substitutable alternatives are brought to market. This is captured with an exogenous risk of obsolescence $1-\gamma$ in each year following t_{comm}.
- **Discount factor**: The firm discounts future profits by a factor δ.
- **Monopoly profits and social value**: A commercialized invention that is not obsolete and produced by the firm as a monopolist yields profits π per year. The invention also yields social value v^{monop} when priced by the monopolist and v when priced by the social planner, where $v > v^{\mathsf{monop}}$.

To this standard framework, we add three additional sets of parameters.

- **Secrecy**: Some inventions can be profitably commercialized while remaining secret. That is, even without a formal grant of intellectual property, the risk of imitation is low. The parameter $p_{\mathsf{secret}} \in [0,1]$ captures the likelihood that the invention remains secret—and, thus, profitable—upon commercialization.[14] After commercialization, the firm faces a risk of losing secrecy. We capture this by assuming the firm faces an exogenous risk $1-\eta$ of losing its secrecy each year following commercialization.
- **Eligibility**: Not all inventions are eligible for protection with grants of intellectual property rights. The probability that a commercialized invention satisfies these eligibility requirements is given by $p_{\mathsf{eligible}} \in [0,1]$. The associated protection lasts for t_{patent} years.
- **Enforceability**: Grants of intellectual property rights are not self-enforcing. To enforce these rights, the firm must seek out instances of imitation and successfully bring suit against each infringer. The probability that the firm can successfully enforce its intellectual property rights is $p_{\mathsf{enforce}} \in [0,1]$.

In Section 2.2, we discuss factors that affect the value of each parameter.

2.1.2 Monopoly Duration

For each potential invention, there is some period during which, in expectation, the firm will earn monopoly profits. This *expected time under monopoly* T depends on the mechanism used to deter imitation: secrecy or formal intellectual property rights.

If the invention is protected by secrecy, the expected time under monopoly is given by

$$T = p_{\mathsf{comm}} \cdot p_{\mathsf{secret}} \cdot \sum_{t_{\mathsf{comm}}}^{t_{\mathsf{secret}}} (\delta\gamma\eta)^t. \tag{1}$$

In words, under secrecy T is determined by (i) the likelihood of successful commercialization p_{comm}, (ii) the likelihood that secrecy effectively deters imitation p_{secret}, and (iii) the total number of years over which secrecy is maintained, adjusted for discounting (by δ), the risk of obsolescence (by γ), and the risk of losing secrecy (by η).

[14] One could, instead, interpret $(1-p_{\mathsf{secret}})$ as the fraction of monopoly profits lost to imitation in the absence of a formal intellectual property grant.

If, instead, the invention is protected by a formal grant of intellectual property (e.g., a patent), the expected time under monopoly is given by

$$T = p_{\text{comm}} \cdot p_{\text{eligible}} \cdot p_{\text{enforce}} \cdot \sum_{t_{\text{comm}}}^{t_{\text{patent}}} (\delta\gamma\eta)^t. \tag{2}$$

Here, the factors p_{eligible} and p_{enforce} capture the likelihood that the invention is effectively protected by a patent, and the term t_{patent} captures the duration of protection.

2.1.3 Incentives to Invest

A profit-maximizing firm will commercialize a potential invention if and only if the expected profits exceed the costs of commercialization. That is, a firm will proceed if and only if

$$T \cdot \pi - c \geq 0. \tag{3}$$

If the invention can be more profitably commercialized under trade secrecy than under with an intellectual property grant —that is, if

$$p_{\text{comm}} \cdot p_{\text{secret}} \cdot \sum_{t_{\text{comm}}}^{t_{\text{secret}}} (\delta\gamma)^t \geq p_{\text{comm}} \cdot p_{\text{eligible}} \cdot p_{\text{enforce}} \cdot \sum_{t_{\text{comm}}}^{t_{\text{patent}}} (\delta\gamma)^t, \tag{4}$$

then the firm chooses secrecy. Otherwise, the firm chooses the intellectual property grant, and T is determined by the availability and enforceability of intellectual property rights, as in (2).

2.1.4 Missing Markets

Definition 1 (Missing Market)**.** A missing market arises when an invention's expected time under monopoly T is zero.

With (1)–(4), observe that we can write the expected time under monopoly T for all potential inventions as

$$T = \max\left(p_{\text{comm}} \cdot p_{\text{secret}} \cdot \sum_{t_{\text{comm}}}^{t_{\text{secret}}} (\delta\gamma\eta)^t, p_{\text{comm}} \cdot p_{\text{eligible}} \cdot p_{\text{enforce}} \cdot \sum_{t_{\text{comm}}}^{t_{\text{patent}}} (\delta\gamma\eta)^t \right).$$

Under what conditions is $T = 0$? First, if the invention's term of secrecy or patent protection is shorter than any delays associated with commercialization—that is, if $t_{\text{secret}} < t_{\text{comm}}$ or $t_{\text{patent}} < t_{\text{comm}}$—then there is no period in which the firm will receive monopoly profits. This case is the focus of Budish et al. (2015), who show that the missing incentives that arise under these circumstances generate a quantitatively important distortion in incentives for research and development. In particular, they document a missing market for certain types of cancer treatments and preventives.

In this paper, our focus is on a second case, which arises when $p_{\text{secret}} = 0$ and *either* $p_{\text{eligible}} = 0$ or $p_{\text{enforce}} = 0$. In words, if an invention cannot be protected via secrecy ($p_{\text{secret}} = 0$) and is either not eligible

for intellectual property protection ($p_{\text{eligible}} = 0$) or available intellectual property rights are unenforceable ($p_{\text{enforce}} = 0$), then the firm's expected time under monopoly is zero.

Observe that, in the first case, the gap in incentives that generates a missing market can be corrected with policy changes that affect the structure of intellectual property rights. Policies that affect the time required for commercialization t_{comm} (e.g., by offering accelerated approval paths), the time provided by a patent t_{patent} (e.g., by extending patent terms), or the relationship between the invention's timing parameters ($t_{\text{invent}}, t_{\text{comm}}, t_{\text{patent}}$) (e.g., by starting patent terms at commercialization instead of invention) could yield a non-zero T and thus restore incentives for innovation.[15] In the second case, however, these solutions that redesign the structures of intellectual property grants are not available—an idea conjected informally in Kapczynski and Syed (2012).

Proposition 2. *If $p_{\text{secret}} = 0$ and either $p_{\text{eligible}} = 0$ or $p_{\text{enforce}} = 0$, then neither longer ($t'_{\text{patent}} > t_{\text{patent}}$) nor broader ($\pi' > \pi$) patent terms would make commercialization profitable.*

Theoretical studies of innovation and intellectual property often characterize optimal policy in terms of two parameters—t_{patent} (capturing patent length) and π (capturing patent breadth).[16] Implicit in these analyses is the idea that an optimal balance between incentives for innovation and deadweight loss can be achieved by carefully calibrating the expansiveness of intellectual property rights. When intellectual property rights are unavailable or unenforceable, however, changes to these "Nordhaus parameters"—t_{patent} and π—have no impact on the firm's investment decision in (3). Similarly, when an invention can be profitably commercialized under secrecy, as in (4), neither of these parameters enters the firm's decision problem.

2.2 Identifying Missing Markets

In Section 2.1, we introduce three parameters—$p_{\text{secret}}, p_{\text{eligible}}, p_{\text{enforce}}$—that affect both whether an invention is commercially viable and whether standard levers of innovation policy can be used to calibrate incentives for innovation. This section provides context on each parameter.

2.2.1 p_{secret} : Can the invention be profitably commercialized while remaining secret?

For many inventions, both private and social value come entirely from public disclosure. Consider inventions that are, in effect, "recipes" (Jones, 2023) or sets of directions—such as procedures for sterilizing food products (Section 1), instructions for the use of an existing drug in the treatment of a new disease (Section 3), or protocols for the use of checklists to reduce the risk of medical error (Gawande, 2009; Kapczynski and Syed, 2012). Each of these inventions consists entirely of the knowledge that some series of steps will yield a particular outcome. Under some circumstances, firms can implement restrictions that limit how widely this information will diffuse—for example by binding recipients contractually with non-disclosure

[15] Solutions of this kind are a focus of Budish et al. (2015).

[16] It is not obvious how patent breadth ought to be incorporated into a Nordhaus (1969)-style model. Gilbert and Shapiro (1990) elect to define the breadth of a patent as the flow rate of profit available to the firm so long as the patent is in force—that is, as the profit parameter π.

and non-compete agreements (Singh and Marx, 2011; Johnson et al., 2023; Reinmuth and Rockall, 2023). In the absence of these types of contractual restraints, however, secrecy is not viable.

There are other types of inventions for which secrecy is impractical. If an invention must be placed on display to facilitate sale, it cannot be kept secret. Even if disclosure of an invention is not immediate, it may be necessary to persuade a potential customer to make a purchase. If, say, a physician determining whether to adopt a new diagnostic test requires detailed assurances about the nature of the technology, secrecy may be destroyed in the process of sale (Arrow, 1962). When there are no circumstances under which the invention can be commercialized while remaining secret, p_{secret} takes a value of zero.

For many classes of inventions, however, existing work has documented that p_{secret} is likely non-zero (e.g., Levin et al., 1987; Cohen et al., 2000; Moser, 2005, 2007). Internal manufacturing processes—including proprietary recipes, like the formula for Coca-Cola (Carr and Choi, 2023)—can be held as secrets for as long as the firm can limit their public disclosure. Other inventions may be amenable to secrecy simply because they are complex or otherwise difficult to reverse engineer. Vaccines are a classic example. Even when the chemical makeup of a vaccine is known, the technical know-how required to produce a product that is stable and safe for use in human patients poses a substantial barrier to replication (Price et al., 2020). Outside markets for health technologies, engineered secrecy is quite common. Every aspect of the "fuzzy logic" used to modulate cooking time and temperature within the award-winning Zojirushi rice cooker has been held as a trade secret since its introduction in the 1980s: the key piece of technology is embedded within the product in a way that ensures that disassembly will destroy its key inventive element (Santo, 2023).

When secrecy is a commercially viable option, state and federal laws in the United States provide formal trade secret protection.[17] As far as legally enforceable intellectual property rights go, trade secrecy is both expansive and fragile. Protection lasts until secrecy is destroyed, which may mean that protection is indefinite. But any instance of disclosure, reverse-engineering, or independent discovery is secrecy-destroying. So long as the owner takes "reasonable efforts" to maintain secrecy, these laws provide recourse in instances of misappropriation—but cannot restore an already-disclosed secret.

2.2.2 p_{eligible} : Is the invention eligible for a legally-enforceable intellectual property grant?

In the United States, government-granted intellectual property rights take many forms—including patents (utility, design, plant), copyrights, and regulatory exclusivities. Whether any invention can be protected by intellectual property rights depends both on the subject matter of the invention and on the invention's specific characteristics. Certain inventions fall within categories of subject matter excluded from specific forms of protection (e.g., most forms of DNA are ineligible for patent protection), and some inventions may be ineligible for all forms of government-administered intellectual property rights (e.g., most databases, which cannot be protected by copyrights or patents).

Patent law, in particular, draws strict boundaries around eligible subject matter. Utility patents may not be granted on inventions that claim abstract ideas, natural laws, or physical phenomena. Judicial decisions in

[17] For example, Uniform Trade Secrets Act (with 1985 Amendments), 14 U.L.A. 437 (2005); Cal. Civ. Code §§ 3426–3426.11; Defend Trade Secrets Act of 2016, 18 U.S.C. §§ 1836–1839.

recent years—in particular, *Mayo v. Prometheus*, *Association for Molecular Pathology v. Myriad Genetics*, and *Alice Corp. v. CLS Bank*—have clarified these restrictions and, in doing so, substantially narrowed the set of patentable potential inventions.[18] At present, inventions deemed to capture abstract ideas or natural phenomena without adding an additional "inventive step"—such as sequences of isolated genomic DNA,[19] methods for processing loan information through a clearinghouse,[20] and computer programs that automatically categorize digital images[21]—may not be granted patents in the United States.[22]

In our model, p_{eligible} takes a value of zero when an invention falls squarely within a category excluded from protection by law. While there remain many categories of inventions for which patent eligibility is clear—where $p_{\text{eligible}} = 1$—recent shifts in legal standards have introduced considerable uncertainty in both the tests used to determine eligibility and in the validity of previously-issued patents (Hoyt, 2022). For many inventions, then, p_{eligible} lies between zero and one.

2.2.3 p_{enforce} : Can the firm profitably enforce any intellectual property grant?

Even when an invention is eligible for formal grants of intellectual property, not all intellectual property rights are enforceable. Though many factors determine this enforceability, we highlight three: whether the firm can observe instances in which its rights are infringed, whether enforcement against particular defendants is practical and profitable, and whether the underlying intellectual property grant is strong enough to permit litigation.

If a firm cannot observe instances in which its intellectual property rights are infringed, those rights are unenforceable, and p_{enforce} takes a value of zero. To be sure, for many inventions, unauthorized uses—like "knockoffs" of luxury handbags and counterfeit consumer electronics (Robbins, 2018)—are readily apparent. Advances in technology, including reverse-image searching, digital watermarking, and algorithmic plagiarism detection, have continued to expand the types of infringement that are easy for inventors to detect (Eckhause, 2022).

In many contexts, however, infringement is extremely difficult to observe. Manufacturing processes crucial to the success of an industry can easily be copied and used internally by competing firms, with no external indication of infringement (Price, 2014). When firms are unable to protect these processes with secrecy, they may be able to find alternative ways of creating observability. Teece (1986) highlights one strategy used by firms licensing methods of petroleum refining to other parties within the petrochemical

[18] See Mayo v. Prometheus, 566 U.S. 66 (2012) (holding that a claimed method optimizing drug dosages based on natural correlations is not patent eligible because it recites a law of nature without adding an inventive concept beyond routine practices); Association for Molecular Pathology v. Myriad Genetics, 569 U.S. 576 (2013) (holding that naturally occurring DNA sequences—even when isolated—are not patent eligible, though cDNA may be eligible because it is not naturally occurring); and Alice Corp. v. CLS Bank, 573 U.S. 208 (2014) (holding that claims directed to abstract ideas implemented on generic computer technology are not patent eligible absent an inventive concept).

[19] Association for Molecular Pathology v. Myriad Genetics, 569 U.S. 576 (2013).

[20] Buysafe, Inc. v. Google, Inc., 765 F.3d 1350 (Fed. Cir. 2014).

[21] Content Extraction and Transmission, LLC v. Wells Fargo Bank, 776 F.3d 1343 (Fed. Cir. 2014).

[22] Even if an invention has subject matter eligible for intellectual property protection, it may fail to meet other statutory requirements. Copyright protection, for example, attaches only to works that meet a minimum threshold of originality (U.S. Copyright Act, Title 17), and patents are granted only to inventions that are deemed novel, non-obvious, and useful (35 U.S.C. §§ 101, 102, 103). Roin (2016) observes that these statutory requirements have the effect of generating large classes of potentially valuable health technologies that cannot be patented.

industry: the sellers included, in their patent-protected processes, a specialized chemical catalyst produced only by the original seller. To use the method, other firms were required to purchase this input controlled by the patent-holding firm, thus deterring unauthorized imitation. Other mechanisms, including intermediaries (e.g., regulators and large institutions), can have a similar effect (Kapczynski and Syed, 2012).

Even if infringement is observable, enforcing intellectual property rights may still not be practical or profitable. One difficulty arises from legal rules that specify who, technically, infringes certain patents. In the United States, patents on methods—specific ways of using a product or carrying out a set of instructions—are directly infringed only by the individual or entity performing each step of the method. To understand what this means in practice, consider the problem at the center of *Ormco Corp. v. Align Technology*.[23] Ormco held a patent on a method for using orthodontic retainers to straighten teeth. Align sold competing retainers, to be used in the same way. Although Align was, technically, copying Ormco, its action did not directly infringe Ormco's patent. Rather, infringement occurred each time a patient used the retainer to straighten her teeth—thus *performing* the method. To enforce its patents, Ormco would have been required to file suit against each retainer-wearing defendant. In this case—unlike in our empirical context—Ormco would not have necessarily been suing its own customers. Nonetheless, individuals are rarely attractive defendants in cases like this, both because these suits are likely to engender backlash and because individuals have comparatively shallow pockets that limit monetary damages. There are many instances in which infringers are essentially "judgment proof," either because they lack financial resources or they are beyond the practical reaches of litigation.

Finally, even when infringement is observable and a suitable defendant can be identified, firms may be deterred from enforcing intellectual property rights if they are concerned about risks associated with litigation. In particular, not all grants of intellectual property are legally valid, which the scrutiny of litigation is likely to uncover. Lemley and Shapiro (2005) document that roughly half of all litigated patents are invalidated. If the firm anticipates a high probability of invalidation, it may opt not to enforce its rights at all.

2.3 Summary

Figure 1 summarizes the conditions under which gaps in the availability or enforceability of intellectual property rights give rise to a missing market, in the sense of Definition 1.

3 The New Uses Problem

3.1 Background

Effective therapies exist for only a fraction of known diseases. As of 2025, treatments have been developed for approximately 20 percent of recognized medical conditions (EveryCure, 2025). Among the subset of diseases with well-characterized molecular causes—those linked to specific genetic mutations, protein

[23] Ormco Corp. v. Align Technology, Inc., 498 F.3d 1307 (Fed. Cir. 2007).

dysfunctions, or other biochemical abnormalities—this figure is lower: effective therapies are available for roughly five percent (Collins, 2011b).

Scientists have long argued that efforts to repurpose existing drugs may be particularly effective in expanding access to high-quality therapeutic options. In particular, some have suggested that systematic efforts to develop new uses for existing drugs could "convert cancer into a treatable chronic disease" (Telleria, 2012), unlock treatments for many or even all of the 8,000 rare diseases (Muthyala, 2011), and yield breakthroughs in diseases that have long resisted therapeutic intervention, such as Alzheimer's (Corbett et al., 2012; Butcher, 2013).

Drug repurposing—the process of identifying and developing new therapeutic applications for existing compounds—has clear advantages over de novo drug discovery. Since repurposed drugs have already been tested for safety, the costs of bringing them to market are substantially lower. Estimates suggest that developing a new use for an existing drug costs $300 million, compared to $1.2 billion for a development of a truly new drug (Sahoo, 2007). Repurposed drugs also reach patients more quickly, with an average 3- to 12-year timeline to approval, versus 12- to 16- years for new drugs (Dudley et al., 2011). Success rates are also higher. The Institute of Medicine estimates that 30 percent of repurposed drug trials succeed, compared to just 10 percent for new drugs (Collins, 2011a).

Despite these advantages, investment in repurposing is quite rare (EveryCure, 2025). Part of the challenge is thought to be timing. Evidence on new uses often emerges only with substantial delay, typically long after the original drug's patent has expired. Gelijns et al. (1998) observe that "it took half a century for the cardiovascular benefits of aspirin, the most widely used drug in the world, to be recognized, and nearly 40 more years before it was widely used for cardiovascular indications."

In the absence of large-scale clinical trials that confirm a new use, physicians may prescribe drugs off-label for alternative indications. While certain off-label uses of drugs are clinically validated, many others are either ineffective or harmful (Eguale et al., 2012). Even when substantial evidence supports an off-label use, various barriers—such as insurer reluctance to cover off-label prescriptions—can limit its adoption. Berger et al. (2021) find that expansions in drug market size do not occur when evidence of a new use is initially produced by a clinical trial; rather, significant increases in utilization occur only after the use has been approved by the FDA, consistent with the idea that regulatory approval plays an important role in facilitating market adoption.

3.2 A Missing Market for New Uses

In this section, we show that the conditions that give rise to a missing market, in the sense of Definition 1, are satisfied in the case of new uses for existing drugs. To illustrate this, we walk through each step of the characterization exercise introduced in Section 2.

p_{secret} : **Can the invention be profitably commercialized while remaining secret? No.**

It is challenging to imagine how information that a drug has a new therapeutic use could be profitably commercialized while remaining secret. Under federal law in the United States, drugs must carry labels

specifying each FDA-approved therapeutic indication.[24] This legal requirement aside, the economic value of a new use arises only if it is widely disclosed: physicians must know the indication to prescribe the drug appropriately, pharmacists must be aware to dispense it correctly, patients must know how and why to take the medication, and insurers must be able to process reimbursements properly. Like other inventions that are essentially "recipes," secrecy is impractical. Thus, $p_{\mathsf{secret}} = 0$.

p_{eligible} : **Is the invention eligible for a legally-enforceable intellectual property grant? Yes.**

New uses for existing drugs are eligible for two distinct forms of intellectual property protection in the United States. First, they may be protected by method-of-use patents. Clinical trials demonstrating a drug's efficacy in treating a previously unrecognized disease or condition provide the basis for such patents, even if the drug itself is already known and commercially available.[25]

Second, new uses are eligible for regulatory exclusivities administered by the FDA. Specifically, the FDA grants a three-year period of "new clinical investigation exclusivity" (NCI) to incentivize firms to develop new indications, dosage regimens, patient populations, or formulations of previously approved drugs. During this three-year exclusivity period, the FDA is prohibited from approving generic applications (ANDAs) for the specific product formulation associated with the new use.[26]

Eligibility for both patents and regulatory exclusivities for new uses are clear under current law. Hence, $p_{\mathsf{eligible}} = 1$.

p_{enforce} : **Can the firm profitably enforce any intellectual property grant? Only for a fixed period of time.**

Patents on new therapeutic uses for existing drugs are fully enforceable so long as the innovator firm retains market exclusivity over the underlying drug product. Because no other firm can legally market the drug during this period, there is no opportunity for infringement to occur.

This enforceability arises directly from the regulatory framework established under the Hatch-Waxman Act of 1984, formally known as the Drug Price Competition and Patent Term Restoration Act. Hatch-Waxman established a streamlined pathway—an Abbreviated New Drug Application (ANDA)—for generic drug entry. Generic manufacturers seeking FDA approval through an ANDA must demonstrate that their products are equivalent, in a chemical sense, to the approved innovator drug.[27] Additionally, they must

[24] See 21 U.S.C. § 352(f); 21 C.F.R. § 201.57(c).

[25] In re Marshall, 578 F.2d 301, 304 (C.C.P.A. 1978).

Although recent judicial decisions noted in Section 2.2 have placed strict limits on patent eligibility—particularly by excluding inventions that claim natural laws or abstract ideas—method-of-treatment patents have consistently been treated as categorically patent-eligible. In Natural Alternatives International, Inc. v. Creative Compounds, LLC (Fed. Cir. 2019), the Federal Circuit emphasized this categorical eligibility, reversing a district court decision invalidating method-of-treatment claims related to dietary supplements, stating explicitly that "[t]hese are treatment claims and as such they are patent eligible."

[26] To qualify for new clinical investigation exclusivity, the innovator firm must perform clinical studies defined by the FDA as "an investigation in humans, the results of which (1) have not been relied upon by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety in a new patient population, and (2) do not duplicate the results of another investigation relied upon by FDA to demonstrate a previously approved drug's effectiveness or safety in a new patient population." (21 CFR §314.108)

[27] The key advantage of this process is that generic firms using the ANDA pathway are not required to provide independent evidence of the safety and effectiveness of their product. They need only demonstrate its equivalence to an innovator drug, for which this showing has already been made. As part of the "bargain" associated with this streamlined pathway, there are restrictions

certify that all relevant patents listed by the innovator in the FDA's Orange Book are either invalid, not infringed, or expired.[28] Until these conditions are satisfied, the FDA bars generic entry.[29]

Once generic entry occurs, however, enforceability collapses. Several institutional factors combine to make enforcement impractical or impossible. The firm would, ideally, like to keep its competitors from profiting from the idea of using the now-generic drug for patent- or exclusivity-protected uses. However, there is no mechanism that would allow it to verify that the brand-name version of the drug was dispensed for a patient with disease B and the generic version for disease A. A physician writing a prescription can easily choose to prescribe the generic version for both uses, regardless of whether a patent is currently in force on one. Generic substitution laws in the United States, which either require or encourage pharmacists to dispense generic forms of a drug even if a prescription lists the brand name version, offer an additional complication.

The nature of patent liability also exacerbates this problem. Courts have consistently shielded generic manufacturers from liability unless they explicitly induce infringing use. Selling a generic drug, even if widely used off-label for patented indications, does not by itself constitute inducement.[30] Although liability for method-of-use patents could theoretically attach to pharmacists, physicians, or insurers, such suits are rare and legally complex. Most often, the legal liability falls squarely on patients themselves, who directly "practice" the patented method by taking the drug to treat their medical conditions. Eisenberg (2005) emphasizes the impracticality—and social undesirability—of holding individual patients liable for patent infringement. These factors, together, mean that it is essentially impossible to enforce these grants of intellectual property after generic entry.

Thus, p_{eligible} shifts abruptly from one to zero at the point of generic entry, creating precisely the missing market characterized in Definition 1.

3.3 Empirical Signatures

The conditions described in Section 3.2 generate testable empirical predictions. Consider an innovator drug that receives FDA approval at time $t = 0$. For some fixed period, the innovator enjoys market exclusivity guaranteed by FDA regulation. Patents on any newly discovered indications are, during this time, fully enforceable. Since each new use can be commercialized without risk of imitation until exclusivity expires, incentives for investing in new uses are strongest at $t = 0$. As the date of exclusivity expiration approaches, the length of time during which any newly-identified use can be protected from competition decreases—that is, a new use identified at year $t + 1$ has one fewer year of enforceability than a use identified at year t.

This framework, thus, suggests three empirical signatures of a missing market for new uses:

on the timing and procedure for generic entry.

[28] Specifically, the generic firm must address each patent listed in a regulatory document maintained by the FDA, called the Orange Book. We introduce these records in Section 4.4 as a source of data used in our empirical analysis.

[29] If a generic company markets its product without FDA approval, it violates: 21 U.S.C. § 355(a), prohibiting introduction into commerce of a "new drug" without approval; 21 U.S.C. § 331(d), which specifically prohibits introducing or delivering for introduction into interstate commerce any unapproved new drug; and 21 U.S.C. § 352 (misbranding provisions), since an unapproved drug by definition lacks required labeling and approval information. The FDA can immediately seek injunctions to halt sales, issue warning letters, seize the offending products, or recommend criminal prosecution. Violating these statutory provisions also exposes the generic manufacturer to civil liability, regulatory penalties, and criminal charges.

[30] Warner-Lambert v. Apotex Corp., 316 F.3d 1348 (Fed. Cir. 2003)

1. Firms will have strong incentives to invest in discovering and commercializing new uses soon after initial approval, when the potential duration of enforceable monopoly rights is longest.

2. As the date of market exclusivity expiration approaches, incentives to invest in new uses decline monotonically, as the expected time under monopoly for a new use decreases with each year.

3. Upon market exclusivity expiration and subsequent generic entry, p_{enforce} drops to zero and creates a missing market. Investment in new uses should, thus, fall to zero.

Section 4 introduces data that allow us to test these predictions empirically. These tests are introduced in Section 5.

4 Data and Measurement

4.1 Example: Lilly's Gemzar

The data we construct are best introduced with an example. In 1996, the FDA approved Lilly's Gemzar for the treatment of pancreatic cancer.[31] The molecule in Gemzar responsible for its pharmacological action—its *active moiety*—is called gemcitabine.[32]

Early efforts to develop gemcitabine focused on its potential as an antiviral. When preclinical studies in the early 1990s documented that it was effective at killing leukemia cells *in vitro*, research effort shifted toward the treatment of cancer (Hertel et al., 1990). At the time of Gemzar's initial approval, Lilly was also investigating other potential uses, including gemcitabine as a treatment for smallpox.[33] Gemzar was re-approved by the FDA in 1998 for the treatment of non-small cell lung cancer,[34] in 2004 for the treatment of breast cancer,[35] and in 2006 for the treatment of ovarian cancer.[36] By 2010, across all indications, sales of Gemzar generated approximately $800 million per year.[37]

Our interest is primarily in the timing of these research investments into new uses, relative to the end of Gemzar's period of market exclusivity. In light of the discussion in Section 3, patent expiration itself may be an imperfect proxy for this exclusivity period, as certain portions of a patent's term may be unenforceable

[31] NDA #020509. See https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020509Orig1s000rev.pdf.

[32] The distinction between a drug's "active moiety" (the key pharmacological agent) and its "active ingredient" (the pharmacological agent, plus any stabilizing chemicals) is technical but significant for regulatory determinations that hinge on a drug's novelty. For our purposes, use of active moieties instead of active ingredients simplifies a series of medication name matching procedures. Concretely, Gemzar's "generic name" or "active ingredient" is often listed across databases as *gemcitabine*, *gemcitabine hydrochloride*, or *gemcitabine hci*. Each is chemically and therapeutically equivalent, but this type of variability makes the string matching central to our empirical work extremely challenging. For each, the active moiety is *gemcitabine*. A.1.3 provides more details on the distinction between these objects, on the value of using active moieties to implement a series of string matches across datasets, and on our crosswalk from various forms of drug names (as are listed in nearly all input datasets) to active moieties.

[33] For example, in one of our datasets (NDA Pipeline, introduced in Section A.3), we observe clinical trials in the years after Gemzar's initial approval for treatment of various types of cancer and also as a treatment for hepatitis and smallpox.

[34] NDA #020509, supplement #005.

[35] NDA #020509, supplement #029.

[36] NDA #020509, supplement #039.

[37] See https://www.sec.gov/Archives/edgar/data/818686/000081868611000014/gemzar260111.htm ("Annual sales of Eli Lilly and Company's Gemzar® were approximately $814 million in the United States in 2010, based on IMS sales data").

in practice. The timing of generic gemcitabine approval underscores this concern. According to the FDA's "Orange Book" database—an administrative record that collects all patents on approved drugs for which a claim of patent infringement could "reasonably be asserted"—Gemzar was protected by two patents.[38] The first-filed (and first-expiring) patent covered gemcitabine's chemical structure, while the second covered a method of using chemicals like gemcitabine to treat tumors in mammals.[39] The first generic version of Gemzar was approved on November 15, 2010, the day the chemical patent expired. The method-of-use patent, which remained in force until May 7, 2013, did not prevent generic entry.[40]

Section 4.2 details our approach to identifying drugs, like Gemzar, for which we track research investments into new uses. Section 4.3 introduces our measures of research investment—scientific publications, clinical trials, and re-approvals for new uses. In Section 4.4, we return to the challenge of determining a drug's period of market exclusivity using data on generic entry and patent expiration. Section 4.5 summarizes our data construction and presents basic summary statistics. Appendix A provides additional details.

4.2 Measuring Drug Approvals

We construct a census of new drugs approved by the FDA between 1985 and 2014 using the FDA's administrative database, drugs@FDA.[41] We classify a drug an **innovator** and include it in our primary sample if it satisfies two criteria:

1. It was approved under a New Drug Application (NDA).

2. It represents the first approval of a unique combination of chemical components.

Context on each of these criteria is helpful to understand the scope of our data. The first restriction limits our analysis to small-molecule drugs, which are relatively simple, stable chemical compounds synthesized through chemical processes. It excludes biologics—large, complex molecules derived from living

[38] The formal name of the "Orange Book" administrative record is *Approved Drug Products with Therapeutic Equivalence Evaluations*. Details on its history and contents are available in Durvasula et al. (2023). The main text of the Orange Book collects records of "therapeutic equivalence evaluations" for approved drugs—determinations of the equivalence of generic products to approved brand-name drugs.

When we refer to the Orange Book, we are referring to its appendices, which collect records of all patents and "regulatory exclusivities" associated with each brand-name drug. These records were made available as part of the 1984 Hatch Waxman Act, and coverage extends only to small molecule (i.e., non-biologic) drugs. The Hatch Waxman Act is formally called the Drug Price Competition and Patent Term Restoration Act, and is codified at 21 U.S.C. ch. 9 § 301. 21 CFR 314.54 lays out the listing requirements for patents and regulatory exclusivities.

[39] The first patent is U.S. Patent No. 4,808,614, and the second patent is U.S. Patent No. 5,464,826.

[40] This simplified description of patent protection, litigation, and generic approval for Gemzar captures the details that are central to our empirical analysis. In Durvasula et al. (2023), we offer a much more extensive case study of Gemzar.

[41] Our sample begins in 1985, one year after the 1984 Hatch Waxman Act introduced the modern system of pharmaceutical patent protection and generic drug regulation. The Hatch Waxman Act increased terms of patent protection for certain new drugs and develop a pathway for generic entry. From a practical perspective, it led to the creation of the Orange Book database that is central to our measurement of market exclusivity, introduced in Section 4.4. We select 2014 as an end point for two reasons. First, a key table in the drugs@FDA database that we use to identify re-approvals of drugs for new indications is unavailable in later years, and we have been unable to obtain analogous records via Freedom of Information Act requests. Second, for drugs approved in later cohorts, measures of market exclusivity may be censored (e.g., if a firm is still applying for new patents or regulatory exclusivities).

organisms—which are subject to an entirely distinct legal and regulatory framework in the United States.[42]

The second restriction ensures that we focus on research incentives in the period following a drug's first approval.[43] Many drugs are approved under multiple brand names. Acetaminophen, for example, is available both as a generic and under the brand names "Tylenol" and "Panadol." Ibuprofen, too, is available both as "Advil" and "Motrin." This restriction keeps only the first of these brand-name approvals.

For each approval and re-approval event in our sample, we construct data on the drug's uses—the specific conditions for which it is approved.[44] We collect text descriptions of these uses from multiple sources, including FDA approval packets, company press releases, scientific articles, and other publicly available records. Whenever possible, we use the FDA's full-text drug labeling service (FDALabel) to retrieve official drug labels. We supplement data on labels—which are primarily available from 2005 forward—with data from drug approval packets, dated company press releases, scientific articles, and other internet searches.

To standardize uses across drugs, we assign each approval or re-approval one or more International Classification of Diseases codes, based on its Tenth Revision (ICD-10). These alphanumeric codes systematically classify diseases, symptoms, and related health conditions. Our final dataset records the most granular ICD-10 code available for each approval, though our empirical analyses often aggregate these codes. For example, while a drug may be assigned G43.1 (Migraine with Aura), we aggregate our data to a higher level, such as G43 (Migraine) or G (Diseases of the Nervous System).

4.3 Measuring Research Investments

For each drug in our sample, we construct three measures of research and development into new uses: scientific publications, clinical trials, and FDA re-approvals for new uses.

Scientific Publications We collect records of scientific publications from the National Library of Medicine's PubMed database. PubMed indexes nearly every biomedical publication and, importantly for this analysis, curates links to chemicals mentioned in the text of each paper. For each innovator drug, we identify all publications indexed with its chemical components. We track, also, whether each scientific publication received any funding from a public agency.

To match drug names in FDA records to standardized PubMed terms, we develop a crosswalk procedure, detailed in Appendix A.2. In short, we clean and standardize drug names from FDA administrative records, then iteratively link them to standardized forms of chemical names in PubMed. This process successfully maps approximately 75 percent of drugs in our final sample to a PubMed term.

[42] Biologic drugs include gene therapies, monoclonal antibodies, and vaccines. A different set of statutes govern federal research incentives for biologics, and the FDA applies a different set of standards for generic ("biosimilar") approval. One important distinction, from the perspective of our empirical analysis, is that our data construction relies on the existence of a mapping between small-molecule drug patents and approved drug products, the FDA Orange Book. No similarly complete document exists for biologic drugs.

[43] This restriction is similar to, but not the same as, the FDA designation of "new molecular entity." NMEs are a strict subset of our sample. See Appendix A.1.2 for details.

[44] We are grateful to Ben Berger, Amitabh Chandra, and Craig Garthwaite for sharing a crosswalk between drugs and indications, which covers a subset of our period of interest. We build on Berger et al. (2021) to produce a crosswalk that covers our full sample period.

Clinical Trials We use clinical trial activity as a proxy for drug commercialization. To maximize coverage over our sample period, we compile trial records from four sources: NDA Pipeline (1982-2001), Pharmaprojects (1995-2010), Cortellis (1995-2016), and ClinicalTrials.gov (2010-2016). As with scientific publication records, the challenge in using these data is that drug names in FDA administrative records often do not match those in these external databases. Unlike PubMed, where drug names are indexed with standardized terms, clinical trial databases often contain inconsistent formatting and typographical errors. To address this, we develop a distinct linkage procedure for each database, detailed in Appendix A.3. Using this approach, we successfully match nearly 70 percent of drugs in our final sample to at least one clinical trial record.

Our final dataset includes trial records for all four sources. To avoid concerns about inconsistencies in coverage, double-counting, and other errors in measurement across datasets, our primary measure of trial activity is a binary indicator that takes a value of one if an innovator drug has any active clinical trial in a given year and zero otherwise.

New Use Re-Approvals FDA administrative records classify applications into three types: new applications, supplemental applications, and generic drug applications. We collect records of all approvals within the supplemental applications category that were tagged as "new and modified indications." As a point of comparison, we also collect records of all other re-approvals associated with supplemental applications.

4.4 Measuring Market Exclusivity

The framework introduced in Section 2 offers a simple prediction: when intellectual property rights on new uses become unenforceable, private firms will lose any incentive to pursue further research and development. Empirically, then, we are interested in measuring trends in investment and commercialization in the periods around expected market exclusivity expiration. There are two natural proxies for a firm's expectations regarding timing: the date on which generic approval actually occurs, and the date on which all patents on an innovator drug are slated to expire. The first captures market participants' rational expectations, and the second reflects the role of legal barriers to competition. Although it is straightforward for us to measure both dates—using, respectively, data from drugs@FDA and the FDA Orange Book—there are several practical challenges with both measures.

The difficulty in using date of generic approval as a proxy for expected market exclusivity expiration is that more than half of innovator drugs in our sample (548 / 990, 55%) never experience generic entry. This is not a peculiar feature of our data. Although a series of legal reforms in the 1980s—including the 1984 Hatch Waxman Act—are credited with increasing generic entry for small-molecule drugs, FDA (2025) lists more than 350 ever-approved small-molecule drugs with no active patents or forms of market exclusivity for which there is no approved generic. [45]

While we observe at least one form of intellectual property for every drug in our sample, by construction, using the date of patent expiration as a proxy is challenging for three reasons. First, new drugs approved

[45] Scott Morton (1999) documents evidence of limited generic availability and analyzes the determinants of these entry decisions. For a recent analysis of challenges that limit generic entry in the "patent afterlife," see Hemel and Ouellette (2023a).

for sale in the United States are, often, protected both by patents and by non-patent "regulatory exclusivities." The FDA will deny approval to a competing generic product so long as certain exclusivities are in force, and these exclusivities may run sequentially or concurrently with patents.[46] Second, new drugs are, increasingly, protected by many patents.[47] The median innovator drug approved in 1990 was protected by a single patent grant. In 2014, the median drug had 5 associated patents. These patent portfolios can confer periods of *nominal* market exclusivity that far exceed that provided by a single patent—though as the Gemzar case highlighted, not all of these patents will limit generic entry. Third, and relatedly, would-be generic competitors are incentivized—as part of the regulatory design of the 1984 Hatch Waxman Act—to "challenge" patents on brand name drugs by asserting that any patents in force are invalid, unenforceable, or not infringed by the generic.[48] Successful challenges allow generic entry before the expiration of all patents. There are, thus, many potential measures that might be based on the expiration of various patents and regulatory exclusivities.

Our primary measure of market exclusivity is constructed as follows. For all drugs, we begin by assuming that firms expect all patents and regulatory exclusivities to bind.[49] If a generic competitor is approved prior to this date, however, we revise our measure. That is,

$$\text{market exclusivity} = \min\{\text{generic approval}, \text{expiration of all patents/exclusivities}\}.$$

This approach leverages the strengths of both proxies—capturing both the market's rational expectations and the legally defined barriers to competition—while correcting for the limitations of each. In effect, we are selecting an upper bound on the firm's expected period of market exclusivity.[50]

To construct this market exclusivity measure for each innovator drug in our sample, we collect records of generic competitor approval and records of all patents and exclusivities. Specifically, we identify the first approval of a generic competitor for each drug in our sample in Drugs@FDA, as the first approval of the same combination of active moieties via the FDA's generic approval pathway.[51] We also collect records

[46] Regulatory exclusivities are often called quasi-patents, in recognition of the fact that they also allow a firm to exclude its competitors from the market for some fixed period of time. They differ from patents, however, in two key regards. First, regulatory exclusivities in the pharmaceutical sector are awarded by the FDA on the basis of its own assessments of a product. Second, exclusivities are—in contrast to the forms of intellectual property considered in Section 2—self-enforcing.

[47] For more details on "patent portfolios" in pharmaceutical markets, see Hemphill and Sampat (2012); Durvasula and Ouellette (2025).

[48] 21 U.S.C. § 355(j)(5)(B)(iv). Under the Hatch Waxman Act, the first (successful) generic challenger receives a bounty in the form of exclusive rights to the generic market for a 180-day period. See Hemphill (2006) for an analysis of the incentives that this system creates for agreements between generic and brand-name firms.

[49] We restrict consideration to four regulatory exclusivities that we determined, in Durvasula et al. (2023), are "generic blocking" in the sense that the FDA will not approve a generic form of the active moiety while these exclusivities are in place: new chemical entity exclusivity, orphan drug exclusivity, pediatric exclusivity, and generic antibiotic incentives now exclusivity. Technically, there are sixteen types of FDA-granted regulatory exclusivities. Table 5 in Durvasula et al. (2023) provides a list.

[50] In Appendix A.5 and Durvasula et al. (2023), we consider alternative measures in detail.

[51] This definition of generic approval introduces an important simplification. Generics are typically approved at the level of a particular product (e.g., atorvastatin in a 10mg tablet) and may not be approved for every dosage or form that is available for the brand-name product. In some cases, these limited approvals reflect the existence of patents and exclusivities that protect some forms of a drug but not others. The full details of the Gemzar case study are reported in Durvasula et al. (2023) and provide context on this type of product-by-product entry. In other cases, limited entry is part of a negotiated settlement. A second feature of this definition is not an assumption or simplification, but is worth flagging: we focus on the timing of generic approval, rather than generic entry. Hemphill and Sampat (2011) establish that these two dates are typically close in time. In a small number of cases,

of patents and regulatory exclusivities in the FDA Orange Book, as digitized in the NBER Orange Book Dataset, for each of our sample years. Appendix Figure A1 plots the distribution of this market exclusivity measure for our sample of innovator drugs.

4.5 Sample Construction & Summary Statistics

There are 1,102 drugs that meet our criteria for innovator drugs. In most analyses, we restrict consideration to drugs with at least one patent or regulatory exclusivity. We also exclude a small number of observations for which our measure of market exclusivity takes a negative value. [52] This yields a final sample of 990 drugs. Table 1 presents summary statistics.

5 Empirical Tests

This Section introduces a set of empirical tests for the predictions introduced in Section 3.3—that firms will have strong incentives to invest in new uses for drugs soon after initial approval; that as market exclusivity expiration approaches, the number of years in which investments in new uses will yield profits declines; and that private research and development should cease upon exclusivity expiration.

5.1 Timing of Research and Development

Figure 2 presents the simplest test of these predictions by comparing our two variables of interest: the probability that a drug is re-approved for any new use (y-axis) in each year relative to market exclusivity expiration (x-axis). Innovator drugs in our sample receive, on average, approximately 13 years of market exclusivity.[53] Consistent with our theoretical framework, the probability of new use approval is highest shortly after initial drug approval, peaking approximately ten years prior to exclusivity expiration. At this time, approximately seven percent of drugs are re-approved for a new use, and this likelihood declines monotonically over time. Within three years of market exclusivity expiration, the likelihood of re-approval for a new use is nearly zero.[54]

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however, there may be lengthy delays between generic approval and entry—if, for example, there is some agreement between the parties to delay generic entry. For an example of this type of delay, see FTC v. Actavis, Inc., 570 U.S. 136 (2013).

[52] There are nine drugs that are excluded because time under market exclusivity is negative: NDA #19008 (bretylium); NDA #19931 (sulfacetamide); NDA #21794 (dapsone); NDA #22041 (hydroxocobalamin); NDA #22556 (carbinoxamine); NDA #50606 (vancomycin); NDA #50640 (oxacillin); NDA #50763 (mitomycin); NDA #204031 (acetaminophen; oxycodone). We reviewed FDA records and drug approval histories. In each case, although our data construction method properly captures the first NDA approved by the modern FDA—that is, since the 1962 passage of the Kefauver–Harris Amendment to the Federal Food, Drug, and Cosmetic Act created the modern regulatory system—we did not identify an earlier NDA approved by the pre-1962 FDA. Generic versions of these much older drugs were approved before the drugs we flagged as innovators. There are a small number of other difficulties that arise when drugs in our sample were grandfathered in when regulatory schemes were re-designed in the 1960s and 1980s. We offer details in Durvasula et al. (2023).

[53] Average and median measures of market exclusivity have, perhaps surprisingly, remained essentially constant across our period of interest, despite large increases in the total number of patents protecting each innovator drug. See Hemphill and Sampat (2012) and Durvasula and Ouellette (2025) for extended discussions of these trends.

[54] As Section 4.4 notes, our market exclusivity measure abstracts from some complications in pharmaceutical markets. Recall that we define market exclusivity as the earlier of: generic approval and the expiration of all patents and regulatory exclusivities. Although the timing of generic approval is tightly linked to the timing of generic entry, these two dates need not coincide. In complex cases, the timing of generic entry following regulator approval may be negotiated to include some period of delay (Hemphill,

In Appendix B, we demonstrate robustness of this trend to several alternative specifications. Appendix Figure A4 replicates this trend in a balanced panel. Appendix Figure A3 examines re-approvals for all types of supplemental new drug applications—including new strengths, dosages, and patient populations. Although incentives to invest in these alternative formulations may also decline as market exclusivity expiration approaches, many such re-approvals are not immediately exposed to generic competition. For instance, generic approval of a 10 milligram tablet formulation of atorvastatin does not create direct competition for alternative formulations, such as a 40 milligram liquid suspension. Generic competitors must individually challenge patents and demonstrate bioequivalence for each distinct formulation, making immediate generic entry more difficult and thereby reducing—but not entirely eliminating—incentives to invest in these types of reformulations as market exclusivity expiration approaches. Consistent with this prediction, we observe a much more gradual decline in this measure of re-approvals following market exclusivity expiration.

In Figures 3, 4, and 5, we consider two additional measures of research effort: clinical trials and scientific publications. Figure 3 plots the probability that any clinical trial studying an innovator drug is active in each year relative to exclusivity expiration. The likelihood of trial activity peaks roughly 18 years before expiration, declining monotonically thereafter. Though the likelihood of any active trial never drops to zero, this is not surprising given the contents of our clinical trial data. As we include any clinical trial, of any phase and with any sponsor, this figure captures Phase 4 "post-marketing surveillance" trials, academic studies that aim to refine the use of the drug in clinical practice, and foreign studies intended to satisfy the requirements of other regulatory agencies.[55] Appendix Figure A5 indicates that this trend is robust to use of a balanced panel.

Figure 4 presents trends in scientific publications. Although the total number of scientific publications linked to innovator drugs declines gradually over the exclusivity period, the average annual number of publications per drug remains roughly stable, around 40, in the ten years before and after exclusivity expiration. That the production of scientific publications exhibits little response to changes in market incentives is, perhaps, unsurprising. While clinical trials and FDA approvals capture commercial effort, scientific publications are more closely linked to "basic" research. One interpretation of the trend in Figure 4, in light of Figures 2 and 3, is thus that there may be some leads on new uses for existing drugs that are reported in scientific publications, but never studied in a clinical trial or commercialized. Examples of these types of discoveries by scientists are central to arguments—including those in the introduction of this paper—that there may be underinvestment in new uses.[56]

Scientific publications allow us to test, more directly, the prediction in our model that gaps in the enforceability of intellectual property will affect *private* investment incentives. Our data record, for each publication, whether its authors disclosed a source of public funding. Figure 5 reproduces Figure 4, with

2006) or a restriction on sales volume and pricing.

[55] As Section 4 noted, constructing clinical trial data that covers our time period of interest requires drawing on four distinct sources of data, with different amounts of detail for each study. Gaps in trial sponsor and phase information limit our ability to refine this sample to include a narrower set of trials. Even if we had sponsor information, the fact that trials may be run by entities other than the firm that eventually markets a drug make this type of restriction conceptually challenging to implement.

[56] For example, the following publications formed the basic of claims about a link between each existing drug and a new indication: Alzheimer's Disease (bexarotene): Naik (2012); LaFerla (2012); cancer (glucophage): Gonzalez-Angulo and Meric-Bernstam (2010); Bodmer et al. (2010); infant heart defects (acetaminophen): Hammerman et al. (2011).

these publicly-funded publications plotted separately. The total number of publicly-funded publications (red) is essentially stable, around ten, year-on-year across our full period of interest. Consistent with our model, the decline in scientific publications over time in Figure 4 appears to be driven entirely by a decline in publications with exclusively private funding (blue).

Together, these trends in research investments over time provide evidence consistent with, though not dispositive of, a missing market for new uses after market exclusivity expiration. However, two alternative explanations are plausible. First, the set of scientifically viable opportunities for new uses might be naturally exhausted over a drug's lifecycle, such that the drop off in research investment reflects around exclusivity expiration captures only that there are no potential new uses left to develop. Second, and relatedly, firms may be sequencing their investments strategically. The timing of market exclusivity expiration is not a discontinuity and is known to all market participants in advance. It may be that firms thus choose to commercialize all potential new uses before this date.

On the basis of the evidence presented thus far, we view both explanations as unlikely. The stability of publicly-funded scientific publications suggests that research opportunities continue to emerge over time, even as private incentives fall. That scientific opportunities for new uses continue to arise across a drug's useful life, potentially decades after market exclusivity expiration as in the case of aspirin highlighted in Gelijns et al. (1998), firms cannot commercialize all uses in the period immediately following initial approval. In what follows, we construct a set of additional empirical tests consistent with our interpretation.

5.2 Alternative Mechanisms to Preserve Enforceability

Our second empirical test leverages the fact that firms can, in some cases, maintain the enforceability of intellectual property rights by investing in closely related products not yet subject to generic competition. Fixed-dose combinations—drugs dispensed as single "dosage forms" (e.g., a single tablet) that contain two or more distinct drugs—provide one such opportunity.[57] Fixed-dose combinations often represent substantial improvements in the quality of care. For example, the widely-used HIV treatment and preventive Truvada is a single tablet that contains two distinct drugs, emtriciabine and tenofovir disoproxil fumarate, neither of which on its own offers the same therapeutic beenfits.[58] Fixed-dose combinations are also often preferred by patients and providers as they simplify complex treatment regimens and increase prescription adherence.[59] For our purposes, however, the relevant feature of a fixed-dose combination is that even if its components have generic competitors, these components are not perfect substitutes for the fixed-dose combination. That is, even when our framework predicts that firms will have no incentive to continue developing components after generic entry, they may retain incentives to develop and improve on combinations.

[57] Dix and Lensman (2024) study incentives for the development of combination therapies for which the individual components are dispensed separately.

[58] Truvada (emtriciabine; tenofovir disoproxil fumarate), NDA#021752, was approved by the FDA on August 2, 2004. A generic version, manufactured by Teva Pharmaceuticals, was approved on June 8, 2017. Emtriciabine was approved on July 2, 2003, and a generic approved on April 17, 2017. Tenofovir disoproxil fumarate was first approved on October 26, 2001, and a generic was approved on January 17, 2012.

[59] Combination drugs have many advantages for patients, chief among which is simplicity. The development of the first single-tablet regimen for HIV, Atripla (Efavirenz/emtricitabine/tenofovir), was lauded as a significant improvement for patients, many of whom had previously been taking up to 36 distinct pills per day. See Pollack (2006). Analyses of claims data suggest that treatment adherence is higher in single-tablet regimens than in multi-tablet regimens. See Silverman (2018).

Evidence of this type of redirection of effort cuts against the concern that scientific opportunities associated with component drugs are exhausted coincidentally around the time of generic entry.

Thus, we examine whether firms shift investments toward fixed-dose combinations as exclusivity expiration approaches. Specifically, we restrict attention to innovator drugs composed of a single active moiety and track combination products containing the same moiety. Figure 6 documents that, in the year of exclusivity expiration, the likelihood that a new indication for a combination drug is approved more than doubles. The likelihood of a combination approval remains at this elevated level in the following years, as the likelihood of new use re-approvals on the innovator drug itself falls to zero.

This fact has two implications worth emphasizing. First, that the number of investments in related products on which patents remain enforceable *increases* at the time of market exclusivity expiration counsels against the idea that scientific opportunities coincidentally drop off at this point in time. Second, that the change in approval patterns arises in the year that our measure assigns as the expected point of market exclusivity expiration suggests that we are accurately capturing firm expectations.[60]

6 Quantification

Section 5 provides evidence consistent with the existence of a missing market for new uses: when intellectual property rights become unenforceable, research and development sharply decline. This section introduces an additional empirical exercise, which provides more direct evidence of two claims central to the framework in Section 2—that longer intellectual property rights induce additional investments in research and development, and that intellectual property enforceability is a key determinant of these incentives.

We leverage variation in the periods of market exclusivity provided to drugs in our sample, introduced by various plausibly exogenous delays in the drug development process. If gaps in private incentives—rather than scientific opportunities—explain the trends in Figures 2 through 5, then drugs with longer periods of market exclusivity should have a larger number of realized new uses. The intuition for this relationship is similar to that underlying the gradual declines in measures of investment documented in the previous section: increases in our measure of market exclusivity affect the number of new uses that are profitable to commercialize on the margin.

In addition to providing a test for the existence of a missing market, this variation allows us to develop a (rough) quantification of its magnitude. To determine how many new uses are "missing," we consider how many new uses would have been realized under counterfactual market exclusivity durations—and scale each missing use by a measure of its social value drawn from existing literature.

As a preliminary matter, it is worth emphasizing that this procedure for determining the quantity of missing new uses is not intended to illustrate an attractive counterfactual policy lever. In what follows, we consider how many additional new uses would have been developed had the innovator drug received

[60] It is worthwhile to note that the pattern we are documenting is consistent with practices that are often labeled as "product hopping" (Carrier and Shadowen, 2016), wherein firms respond to the loss of market exclusivity on one product by directing innovation toward products that are still protected by enforceable patents.This practice can impose real social costs. We do not undertake a complete welfare analysis of innovation decisions around exclusivity expiration, but note that any such analysis must take care to account for both incentives for innovation and the deadweight loss associated with delayed generic entry.

many additional years of market exclusivity. In effect, we are imposing counterfactual blunt patent term extensions, which would have the effect of delaying generic entry for all uses of a drug. Whether this type of policy is welfare improving is, of course, an empirical question and is one that is beyond the scope of this paper. It seems reasonable to speculate, however, that the social costs of large-scale delays in generic entry on the scale of our counterfactuals (7 to 20 years) are likely large. In the final section of the paper, we return to the question of how this problem of missing markets might be solved—in our empirical context and more generally.

6.1 How Many New Uses are Missing?

6.1.1 Do drugs with longer market exclusivity periods have more realized new uses?

To estimate the quantity of missing new uses, we begin by documenting causal evidence that longer periods of market exclusivity increase the number of commercialized new uses.

In Section 4.4, we define a measure of market exclusivity for which there is substantial variation across drugs in our sample: the average innovator drug receives 12.9 years of exclusivity, but drugs at the 10th and 90th percentiles of this measure receive, respectively, 5.5 and 42.5 years.[61] These differences arise in two ways. First, recall that our primary measure of market exclusivity is intended to account for various complicating aspects of patents on pharmaceuticals—in particular, that most innovator drugs in our sample are protected by multiple overlapping patents and regulatory exclusivities, only some of which are likely to bind. These secondary patents and regulatory exclusivities can, in some cases, push a drug's market exclusivity period beyond the statutory twenty-year patent term. Second, various delays in the drug development process can erode a drug's effective patent life. Firms in the pharmaceutical sector have strong incentives to file the primary patents on an innovator drug as soon as possible—both to protect their investments from competitors and to avoid creating "prior art" that would make the drug unpatentable for lack of novelty. At least three types of delays between patent filing and initial drug approval can decrease effective patent terms: commercialization lags due to differences in clinical trial lengths (Budish et al., 2015), delays in clinical trial initiation (Gilchrist, 2016), and delays in patent prosecution (USPTO, 2025).

Figure 7 Panel A plots the relationship for drugs in our sample between this measure of market exclusivity and the number of realized new uses, as a binned scatterplot with an overlaid line of best fit. Table 2 Panel A formalizes this relationship in a regression framework. In particular, for innovator drug i, we estimate the regression

$$y_i = \alpha + \beta \cdot \text{exclusivity}_i + \mu_i + \varepsilon_i \tag{5}$$

where the dependent variable y_i captures the number of re-approvals of innovator drug i for a new or modified indication and μ_i is an approval year fixed effect. The estimate of interest is β, the coefficient on our measure of each drug's market exclusivity exclusivity_i. Columns (1) and (2) report results using the measure of market exclusivity introduced in Section 4.4—the earlier of generic approval and the expiration of all patents and exclusivities. The relationship between this measure of exclusivity and the quantity of realized new uses is

[61] Appendix Figure A1 plots the distribution of this measure.

positive and significant in all specifications. with and without the approval year fixed effect μ_i. We return to the interpretation of these estimates in Section 6.1.2.

As a preliminary matter, however, a natural concern with the interpretation of this relationship is that market exclusivity terms are not randomly assigned across drugs. In fact, to the extent that firms apply for secondary patents with the goal of delaying generic entry, one may be concerned that firms can, in effect, endogenously determine some aspect of this duration. Figure 7 Panel A and Table 2 Panel A, then, may capture several related effects, including the causal effect of longer market exclusivity on innovation, as well as the strategic behavior of firms that are choosing to extend periods of exclusivity on certain drugs.

To address this concern, we construct an alternative measure of market exclusivity that captures sources of variation that decrease effective patent term—clinical trial durations, clinical trial delays, and patent prosecution delays—but excludes all secondary patents. For each drug, we define its *minimum patent exclusivity* as the time between its initial approval and the expiration of its earliest patent and all FDA-administered regulatory exclusivities. By focusing on the minimum period of exclusivity—rather than the maximum period that firms can secure by accumulating secondary patents—we retain variation across drugs that is plausibly exogenous. On this measure, the average drug in our sample has 9.4 years of (minimum patent) exclusivity, and the 10th and 90th percentiles are 5 and 35 years.[62]

Figure 7 Panel B plots the relationship between this minimum patent measure of exclusivity and the number of realized new uses. In Table 2 Panel A, Columns (3) and (4) reproduce the regression specifications introduced above. Again, the relationship between these measures is positive and significant.

Our preferred estimates are reported in Columns (2) and (4) of Table 2 Panel A and include year of approval fixed effects, which account for the concern that earlier-approved drugs have had more years in which to realize additional new uses. In both specifications, the estimated coefficient is roughly 0.02. That these estimates coincide is reassuring given our concerns about the endogeneity of our primary measure of market exclusivity (Column (2)).

There is one additional econometric challenge for this exercise, which arises because nearly three quarters of innovator drugs in our sample ($N = 725, 73\%$) have zero re-approvals for new uses. This mass point at zero has the potential to bias the estimates in Table 2 Panel A (e.g., Mullahy, 1998). To address this concern, in Table 2 Panel B, we report estimates from a two-part model that considers the extensive and intensive margins separately. On the extensive margin, we recode the outcome variable y_i to take a value of one if there are any re-approvals of innovator drug i and zero otherwise. We report estimates from a logit model. On the intensive margin, we restrict consideration to those drugs with at least one re-approval and estimate, via ordinary least squares, the effect of market exclusivity on the number of re-approvals.

On the extensive margin, we find a significant, positive relationship across specifications between the duration of market exclusivity and the approval of any new indication. Estimated coefficients—0.26 in Column (1) and 0.42 in Column (2)—suggest that an additional year of market exclusivity increases the

[62] Appendix Figure A2 plots the distribution of this measure. In 52 cases (5%), this minimum patent measure of exclusivity is longer than a statutory twenty-year patent term. This arises, in nearly all cases, because the earliest-expiring patent was filed after the drug's initial approval. While it is generally true, as we note above, that firms have strong incentives to file key patents before approval, this is not always the case. On inspection, many of these later-filed patents appear to be method-of-use patents on drugs for which there is no Orange Book patent protecting the active ingredient. Durvasula et al. (2023) provide additional details on the difficulty of identifying whether a patent protects a drug's active ingredient at scale.

odds of observing any re-approval for a new uses by a factor on the order of 2 to 8 percent.[63] The intensive margin restriction, however, leaves us underpowered to estimate an effect. Estimated coefficients from each specification are positive and comparable in magnitude to those reported in Panel (A), but none are significantly different from zero.

6.1.2 Calculating the elasticity of research and development with respect to exclusivity duration

This exercise allows us to estimate, directly, the elasticity of research investments with respect to market exclusivity, a key parameter for the design of optimal patent policy that has been, to date, difficult to estimate (Nordhaus, 1969; Budish et al., 2016).[64] We emphasize that this estimate is specific to our empirical context, which is peculiar in a variety of ways—including that market exclusivity is set by the structure of a complex regulatory system and that the investments of interest are improvements to existing technologies.

The estimates reported in Table 2 Panel A lend themselves to a straightforward interpretation: an additional year of market exclusivity would yield, on average, 0.2 new uses. To realize one additional use per drug would thus require providing an additional 50 years of exclusivity to the average innovator drug. This provides a starting point from which we can quantify the social costs of missing incentives for new uses. In Section 6.1.3, we use this elasticity to estimate the number of uses that would have been developed had intellectual property rights on new uses been enforceable for a longer period of time.

To contextualize this estimate relative to prior work, we calculate the implied elasticity in percentage terms. We benchmark both the dependent variable (the number of new use approvals) and our measures of exclusivity at their sample means. Let $\bar{y} = 0.437$ be the average number of new use approvals per innovator drug and $\bar{x}$ be the average years of exclusivity (13.35 for our primary measure and 10.24 for the "minimum patent" measure). Given our coefficient estimate of 0.02, the point elasticity at the mean is $\beta \cdot \frac{\bar{x}}{\bar{y}}$. For our primary exclusivity measure and the minimum patent exclusivity measure, respectively, this implies an elasticities of approximately 0.61 and 0.47.[65] Interpreted directly, these estimates imply that doubling the average market exclusivity would increase the expected number of re-approvals by approximately 47 to 61%.

Two points of comparison for our estimate appear in Budish et al. (2015) and Abrams (2009). Budish et al. (2015) estimate the semi-elasticity of research investment with respect to a one-year change in the commercialization lag—t_{comm} in Section 2—for new cancer therapies as 7-23%. Abrams (2009) uses changes in the duration of patent term introduced by the adoption of the 1995 Agreement on Trade-Related Aspects of Intellectual Property Rights to estimate the responsiveness of patent filings to changes in patent

[63] We obtain these estimates by exponentiating the logit coefficients to obtain the corresponding odds ratios: $e^{\beta} - 1$. The coefficient of interest β in Column (1) is 0.026, which corresponds to an odds ratio of $e^{0.026} - 1 \approx 0.026$, or a 2.6% increase in odds per year.

[64] In particular, Budish et al. (2016) write: "A key parameter needed to inform optimal patent policy design is the elasticity of research investments with respect to the patent term. Estimating this elasticity is conceptually difficult because it requires constructing a counterfactual in which we can infer that some scientifically feasible inventions would have been brought to market under an alternative patent policy design. Despite a near half-century of research effort, we have essentially no credible empirical evidence on this elasticity."

[65] Primary exclusivity measure: $= 0.02 \times \frac{13.35}{0.437} \approx 0.61$.
Minimum patent measure: $= 0.02 \times \frac{10.24}{0.437} \approx 0.47$.

term length—t_{patent} in Section 2. In that context, a one year increase in patent term is estimated to generate a 66% increase in patent filings.

Our estimates imply that adding one year of market exclusivity increases the average number of approvals for new uses by 0.02—roughly a 4.6% increase relative to the average of 0.437. That our estimate is smaller than that in either Budish et al. (2015) or Abrams (2009) is, in several ways, unsurprising. First, note that our context may provide the cleanest setting in which to isolate the effect of intellectual property duration on research investments. Budish et al. (2015) capture an effect that reflects both patent duration and corporate short-termism and, thus, may be an over-estimate. We may also expect Abrams (2009) to offer an over-estimate of the object of interest because increases in patent duration may affect firms' propensity to file patents on existing inventions; patent filings may increase even if there is no actual increase in research investment. Second, our context is somewhat narrow. Inventions in our setting are clinically validated links between drugs and new diseases, which in effect function as improvements to existing products. Eisenberg (2005) provides an additional, context-specific explanation: qualitative evidence suggests that firms may be hesitant to invest in new uses for commercially successful drugs if there is some risk that additional clinical trials will yield "bad news," such as large numbers of adverse events in a particular patient population, that would threaten the profitability of the entire market.

6.1.3 How many new uses are missing?

Figure 7 and Table 2 indicate that more new uses are commercialized when innovator drugs have longer periods of market exclusivity. While this establishes a causal relationship between exclusivity and investments in research and development, it leaves open a question of magnitude: how many new uses would have been developed had patents on these inventions been fully enforceable? As discussed in Section 3, the existing scientific literature provides little guidance on the absolute number of potential new uses for each drug—other than suggesting that most existing drugs likely have many therapeutic targets.

To estimate the number of missing new uses, we will consider how many new uses would have been developed under counterfactual periods of market exclusivity.[66] As a lower bound, suppose that the average innovator drug received market exclusivity equivalent to the full statutory patent term of twenty years. Given that average market exclusivity in our data is approximately thirteen years, this counterfactual adds seven years of exclusivity. As an upper bound, suppose that a new use identified at the end of the innovator drug's period of exclusivity received its own fully enforceable patent term of twenty years. This counterfactual, which adds twenty years of exclusivity for the average innovator, approximates a scenario in which patents on later-discovered new uses are fully enforceable.

Estimates from Columns (2) and (4) of Table 2 Panel A, imply that, counterfactually, 0.14 new indications would have been developed in the lower bound case and 0.4 in the upper bound case. Since 1962, when the modern FDA was established, the agency has approved roughly 2,000 drugs that satisfy our criteria for an innovator drug. Thus, our estimates indicate that between 280 and 800 new uses would have been

[66] By limiting ourselves to fixed market exclusivity extensions, we also need not make the assumption that innovator firms in our data could—with indefinite periods of exclusivity—ever identify every new indication for a drug. If ideas for new uses are "scarce" in the sense of Scotchmer (2004), then it is unlikely that the original firm would identify every possible lead.

developed under these counterfactual periods of market exclusivity.

6.2 How Valuable are New Uses?

The welfare implications of missing new uses depend on whether these re-approvals would have translated into real improvements in patient health. Though previous studies have concluded that, in general, new drugs significantly increase life expectancy, there is enormous heterogeneity in estimates of social value. Philipson and Jena (2006) estimate, for example, that the social value of survival gains from breakthrough HIV/AIDS therapies in the late 1980s was $1.4 trillion over a twenty-year period in the United States alone, while other studies suggest that many "me-too" drugs—drugs that provide little clinical differentiation from existing therapies—contribute relatively little to social welfare (Dranove et al., 2014). There is, to our knowledge, no previous work that aims to classify individual products, systematically, by a comprehensive measure of social value.[67]

We determine, first, a reasonable estimate for the average social value of a new drug's initial approval. We then return to the question of whether, and how, this estimate ought to be scaled to apply to the case of new uses for existing drugs. To establish a benchmark for initial approvals, we draw on two complementary approaches, which capture both the therapeutic and scientific value of drug approvals.

Our first approach makes use of drug quality ratings that value the health benefits of new therapeutics in terms of "quality adjusted life years" (QALYs). There are a variety of frameworks that are used to calculate QALYs but, in short, these measures aim to capture the value of both wellbeing improvements and increases in life expectancy in standard units. We use estimates from Shafrin et al. (2023) who consider all drugs approved by the FDA between 2011 and 2021 for which a published cost-effectiveness analysis was available—approximately 50% of approvals. Shafrin et al. (2023) estimate that the average drug added 1.04 QALYs per patient relative to the standard of care, though many drugs provided less than 0.5 QALYs per patient and a small number provided multiple QALYs.

We assume, on the basis of the Shafrin et al. (2023) analysis, that the average new drug adds one QALY relative to the standard of care. In the United States, cost-effectiveness analyses typically value each QALY at $100,000.[68] To generate an estimate of the average social value of a new drug, then, we need only scale this average QALY estimate, valued at $100,000, by a measure of average market size. For this, we select a value from industry reports: (IQVIA Institute for Human Data Science, 2021) indicates that a typical specialty drug is used to treat roughly 10,000 to 50,000 patients per year, with an average market size of 40,000. If we assume an incremental benefit of 0.5 to 1 QALY per patient per year, on average, the annual social value of an initial approval is between $2 billion (0.5 QALY $\times$ 40,000 $\times$ $100,000) and $4 billion (1.0 QALY $\times$ 40,000 $\times$ $100,000).

[67] To be clear, this reflects the inherent difficulty of this exercise. Trusheim et al. (2010) write, "[i]t is difficult if not impossible to quantify reliably, objectively and unambiguously the extent to which new biopharmaceuticals embody significant innovation and address unmet medical needs." This difficulty arises, in part, because drugs may be both scientific advancements—which offer little therapeutic impact for current cohorts of patients but enable follow-on innovation—and therapeutic advancements—which immediately improve patient health.

[68] Cutler (2004) also values life-years at $100,000, though Hemel and Ouellette (2023b) note that this estimate is "extraordinarily low relative to the values that federal agencies use in other contexts."

Our second approach draws, instead, on dollar-denominated estimates of the social value of new drugs, as reported in existing economic analyses. As with estimates of QALYs, there is enormous heterogeneity in these estimates. For example, Philipson and Jena (2006) estimate that the initial antiretroviral drugs generated annual social value on the order of tens of billions of dollars, while Yin et al. (2012) estimate that a class of drugs for leukemia—tyrosine kinase inhibitors—produced roughly $6 billion per year in the years following initial approval. Sertkaya et al. (2014) report that new antibiotics yield annual social value between $24 million and $600 million. Although these figures vary considerably by therapeutic area, they consistently suggest that innovative drugs generate annual social benefits in the range of hundreds of millions to several billion dollars.

The final question we must address is whether new uses of existing drugs are, on average, more or less valuable than initial approvals. Estimates from health services research typically find that new uses tend to offer lower incremental therapeutic benefits than the use associated with an initial approval. A recent analysis of drug approvals in the United States and European Union from 2011 to 2020 found that roughly one-third of new uses had high therapeutic value, compared to nearly half of first indications (Vokinger et al., 2023). In oncology, first indications typically deliver nearly double the QALY gain per patient—around 0.99 QALYs—relative to second or third indications, which average approximately 0.5–0.6 QALYs. Nonetheless, new uses can still generate substantial social value. Berger et al. (2021) show that approval of a new use increases, on average, the share of patients taking a drug by approximately 4.1 percentage points—a nearly 40% increase relative to baseline. Even if the incremental per-patient benefit of new uses may be lower, the expansion in patient access may generate considerable social value.[69]

Given these measures, we conclude that the average annual social value of an initial approval ranges between $500 million and $4 billion. To reflect the fact that new uses offer, on average, less therapeutic benefit than initial approvals, a scaling factor between one-third and one-half might be appropriate—implying a final range of approximately $250 million to $2 billion annually per new use.

6.3 The Social Cost of a Missing Market for New Uses

To quantify the social cost of a missing market for new uses, we calculate the present value of a single missing new use, as

$$PV = \frac{\text{annual social value}}{r - g}$$

where r and g are the social discount rate and long-run population growth rate, respectively. We choose standard, if somewhat conservative, values for each and let $r = 0.05$ and $g = 0.01$. Using the estimate that an initial approval generates $1 billion in social value per year, on average, the present value of one missing approval is thus $25 billion.

Scaling this by our estimate of the number of missing new uses (280 to 800) implies that the social

[69] As complementary evidence, we assess one measure of value—market size—in our own data, using data drawn from the Medical Expenditure Panel Survey on prescriptions written for diseases associated with initial approvals and new uses. n roughly one quarter (26%) of cases, new uses are approved for indications in different disease areas than the initial approval (where disease areas are defined broadly, e.g., ICD-10 Category G: Diseases of the Nervous System, Category J: Diseases of the Respiratory System). Although the exercise is necessarily rough, we find that, on average, the market size for a new use is roughly 70% that of each drug's initial indication.

cost of a missing market for new uses is on the order of $7 to $20 trillion from 1962 to 2014. If new uses have roughly one-third to one-half the value of initial drug approvals, this range shifts accordingly, suggesting social costs instead on the order of approximately $2 to $10 trillion. Although these estimates are necessarily imprecise, the qualitative conclusion is clear: in just one market, the social costs of the missing markets problem appear to be extraordinarily large.

7 Discussion

In this paper, we investigate the idea that there are large classes of potential inventions for which private incentives to invest in research and development are missing. We develop a theoretical model that clarifies conditions under which these incentive gaps arise—when inventions are at risk of immediate imitation in the absence of intellectual property protection, but intellectual property rights are either unavailable or unenforceable—and predicts that *missing markets* will arise across sectors of the economy. In doing so, we formalize a set of ideas that have long been central to theoretical studies of innovation and intellectual property—that stronger and broader intellectual property rights induce additional investment in research and development, and that not all inventions are amenable to protection with any existing form of intellectual property. Our empirical work offers, to our knowledge, the first direct tests of both. We identify a setting, investments into new uses for existing drugs, in which there is sharp variation in the enforceability of intellectual property rights on otherwise comparable inventions over time. In particular, institutional features of this setting are such that intellectual property rights shift from perfectly enforceable to entirely unenforceable at a specific point in time. We show that when enforceability drops to zero, so too does private investment. Plausibly exogenous variation in these periods of enforceability allows us to provide causal evidence that longer periods of (enforceable) intellectual property protection yield higher levels of research and development.

We use this elasticity of research and development with respect to intellectual property duration to estimate counterfactual changes in the commercialization of new uses that would have occurred had intellectual property rights been fully enforceable. That is, we quantify the size and value of a missing market for new uses. We estimate that, since 1962, between 280 and 800 new uses could have been commercialized but were not. Estimates from the scientific literature on the therapeutic potential of existing drugs suggest that this range may be conservative (Gelijns et al., 1998; Wermuth, 2006). Using measures of the value of a new use drawn from the literature, we estimate that the social cost of this *particular* missing market is on the order of $5 to $20 trillion in present value terms. Although these estimates are necessarily rough, they suggest that the social costs of the missing market problem, in general, may be extraordinarily large.

The potential scale of this problem makes more salient the question of solutions. Is it possible to "fix" a missing market? Our theoretical model rules out one standard tool deployed by policymakers to correct inadequate incentives for innovation. Necessarily, neither longer nor broader periods of formal intellectual property protection—what we term "Nordhaus parameters"—affect incentives to develop potential inventions in missing markets. The model does, however, highlight two alternatives. First, a policymaker could attempt to change the parameters—p_{eligible} and p_{enforce}—that give rise to a missing market. Second, missing

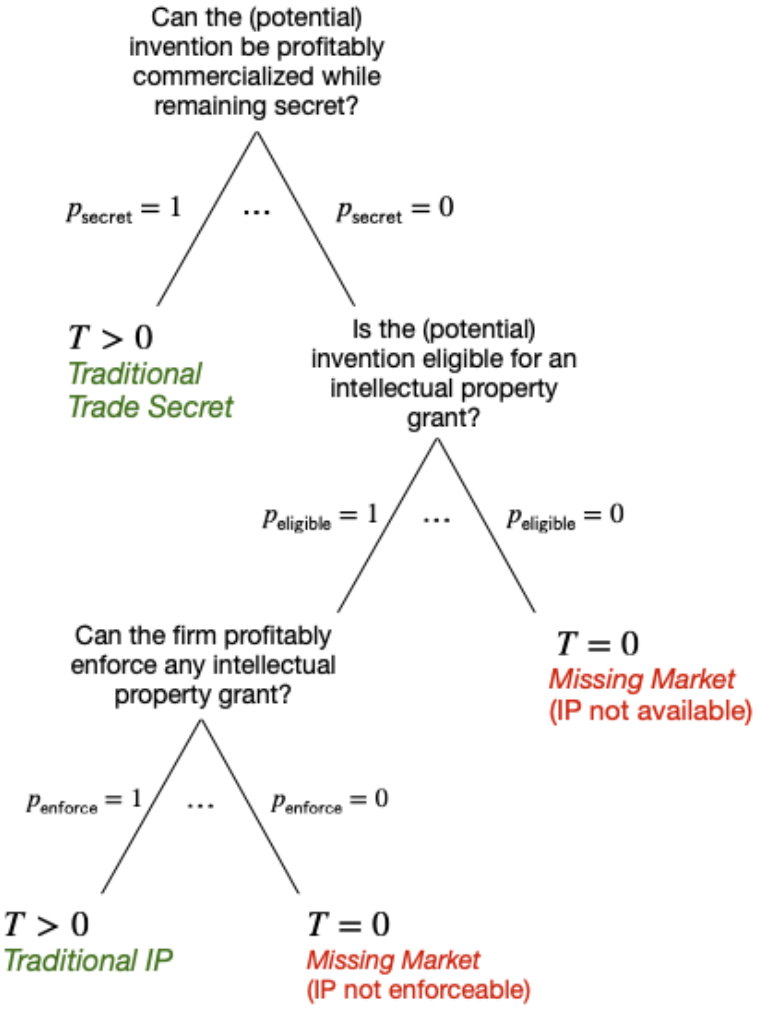
markets might be natural targets for funding mechanisms that detach innovation incentives from private-sector profitability, such as traditional forms of public subsidies and more innovative mechanisms like prizes and advanced market commitments.

Whether the categories of potential inventions that are currently excluded from intellectual property protection by law—for which $p_{\text{eligible}} = 0$—were appropriately chosen is an ongoing topic of debate (Critharis, 2022). In the absence of additional empirical evidence on the welfare consequences of more expansive eligibility rules, it is challenging to justify large-scale policy change on this dimension. One can imagine, however, a variety of context-specific solutions to the problem of enforceability ($p_{\text{enforce}} = 0$). Roin (2014), for example, proposes a solution in the specific context of new uses, which would use electronic health records to enable use-specific pricing. In other settings, digitization and the expansion of data collection efforts may allow for similarly bespoke remedies.

More generally, though, our conclusions provide empirical support for the importance of efforts to design innovation policy levers beyond intellectual property. In the new uses case, where potential new uses are "technologically close" in the sense of Barder et al. (2005) and Kremer et al. (2020), grants, prizes, and advanced market commitments may all be successful in eliciting specific missing research investments—say, a large-scale clinical trial that, at last, investigates metformin as a cancer treatment.

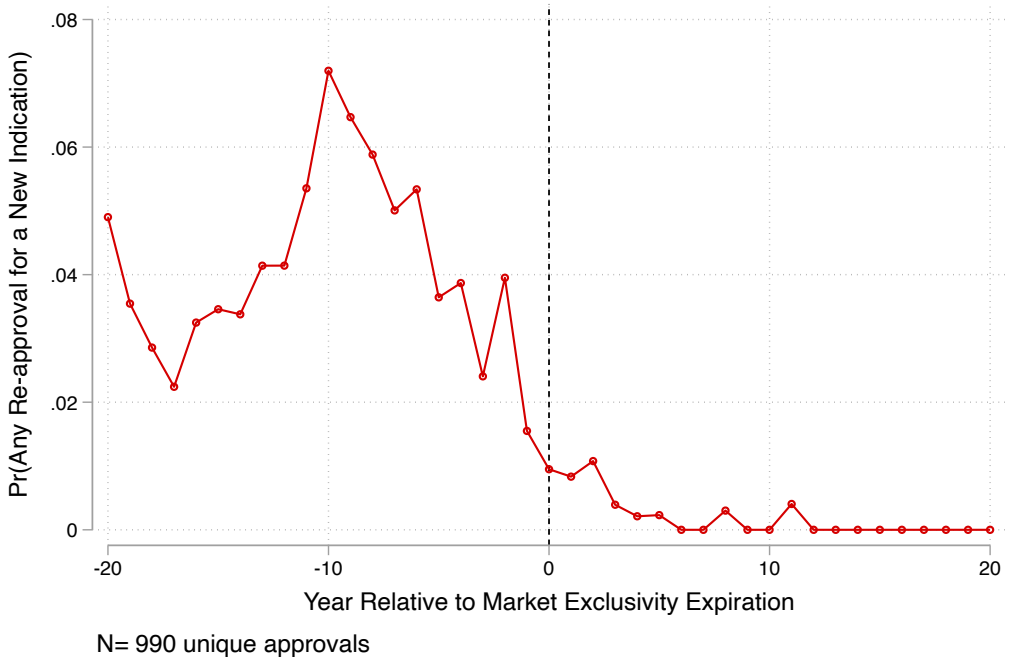
Figures and Tables

Figure 1: Missing Markets for Innovation



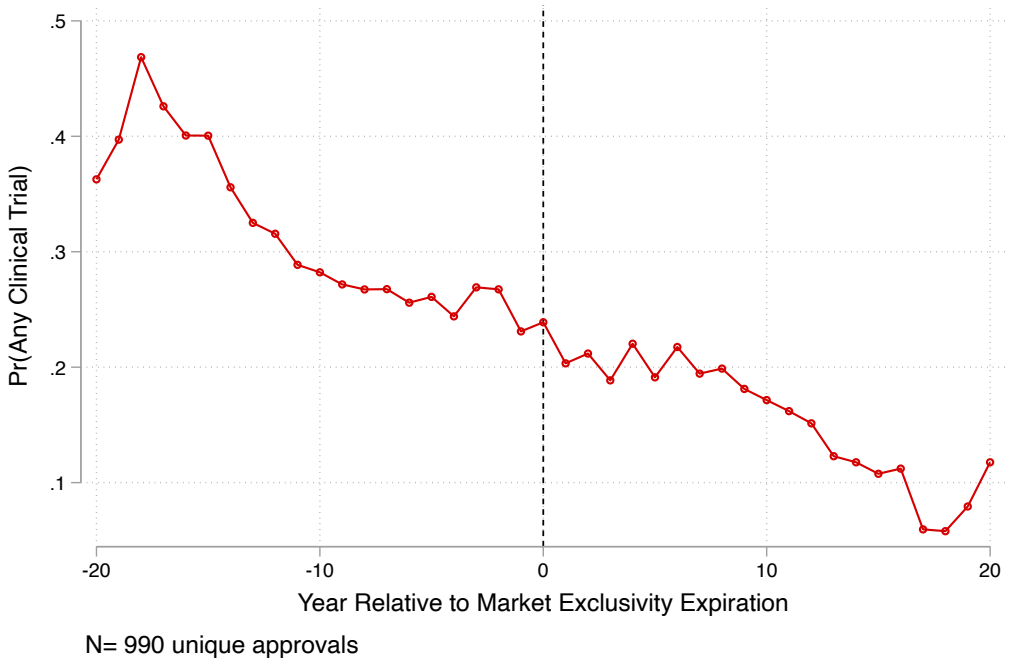
Notes: Figure summarizes the framework introduced in Section 2.1.

Figure 2: New Use Approvals Relative to Exclusivity Expiration



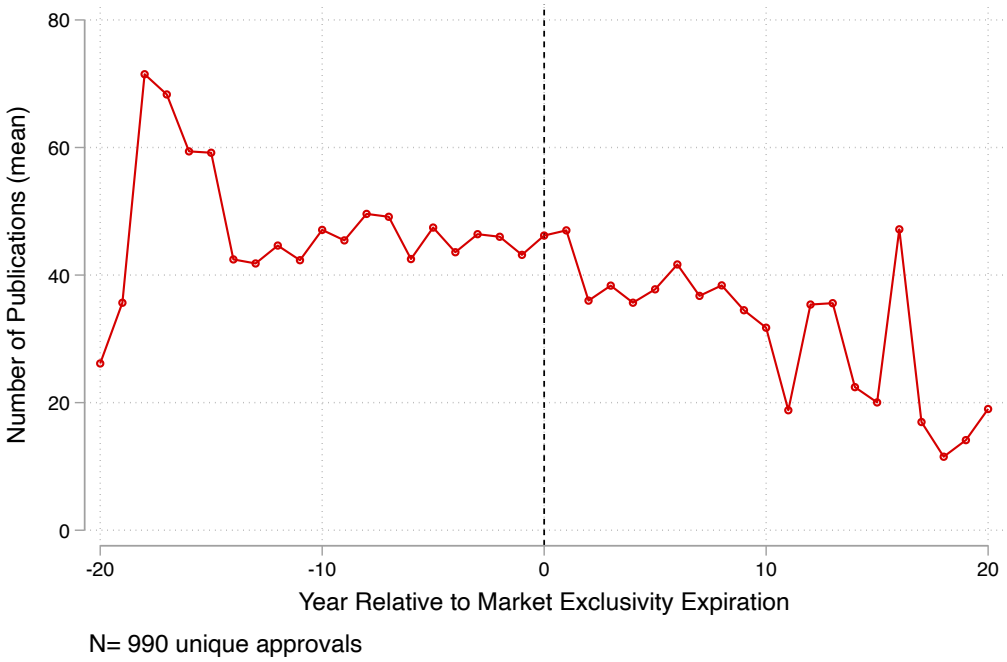
Notes: Figure plots the probability of re-approval for a new use for the sample of innovator drugs defined in Section 4.5 ($N = 990$). Market exclusivity expiration is defined as the earlier of two events: expiration of all patents and regulatory exclusivities linked to the innovator drug in the FDA's Orange Book, or FDA approval of a generic drug with an identical set of active moieties. We plot the probability of re-approval for a new indication for the twenty years preceding and following exclusivity expiration for all drugs in our sample. Appendix Figure A4 reproduces this analysis using two balanced panels (ten-year and five-year). Appendix Figure A8 plots trends in re-approvals of new uses in calendar time (year relative to initial approval).

Figure 3: Clinical Trials Relative to Exclusivity Expiration



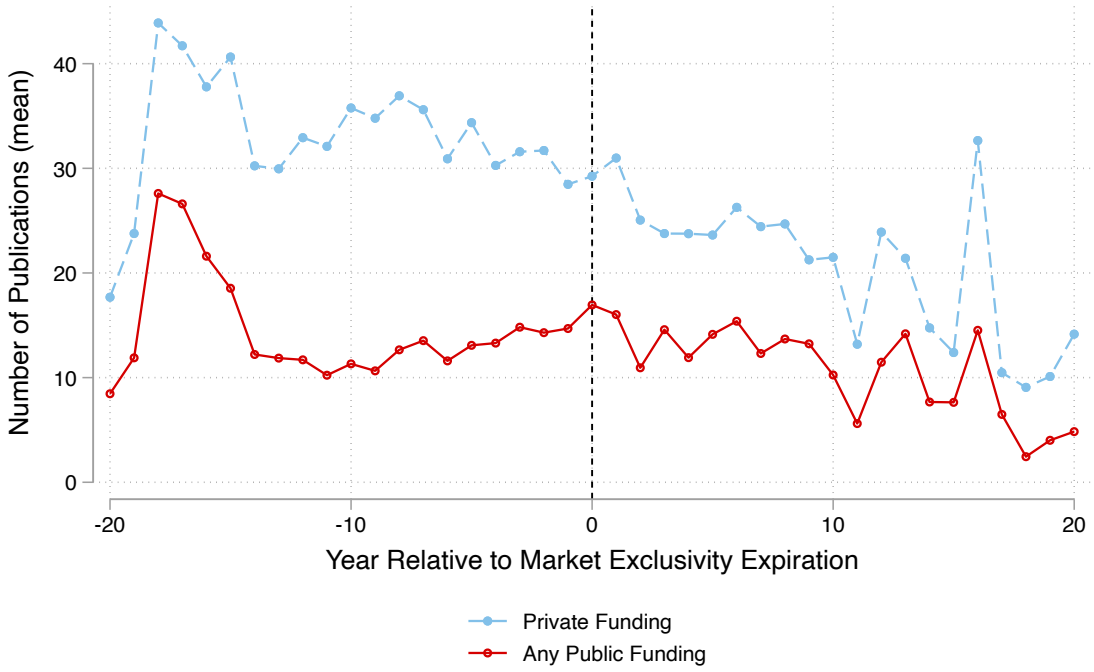
Notes: Figure plots the probability of any active clinical trial in each relative year for the sample of innovator drugs defined in Section 4.5 ($N = 990$). Market exclusivity expiration is defined as the earlier of two events: expiration of all patents and regulatory exclusivities linked to the innovator drug in the FDA's Orange Book, or FDA approval of a generic drug with an identical set of active moieties. We plot the probability of any active clinical trial in each of the twenty years preceding and following exclusivity expiration for all drugs in our sample. Appendix Figure A5 reproduces this analysis using two balanced panels (ten-year and five-year). Appendix Figure A9 plots trends in clinical trials in calendar time (year relative to initial approval).

Figure 4: Scientific Publications Relative to Exclusivity Expiration



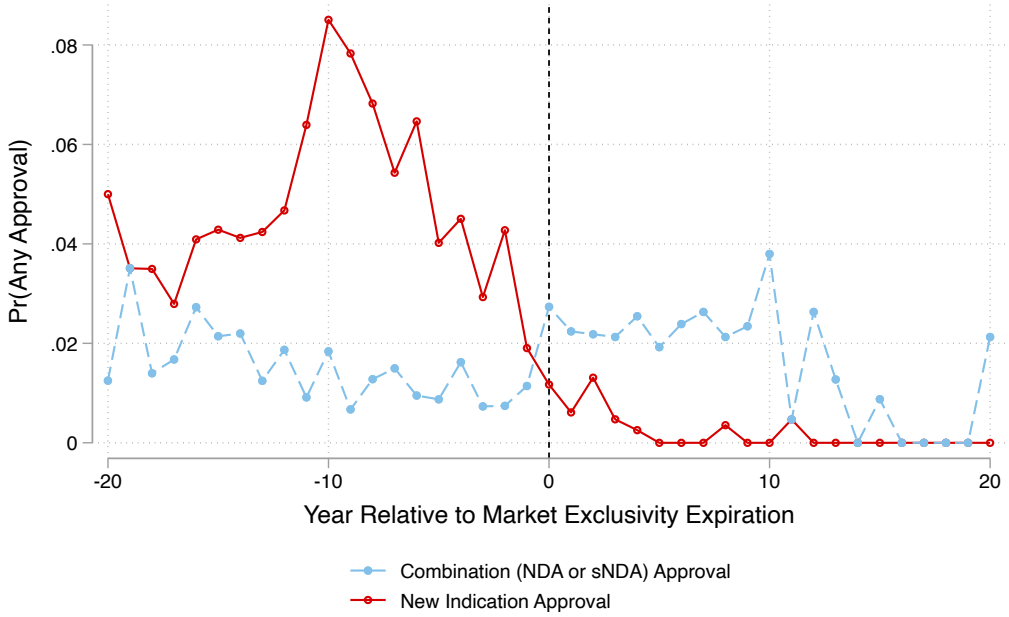
Notes: Figure plots the average number of scientific publications published in each relative year for the sample of innovator drugs defined in Section 4.5 ($N = 990$). Market exclusivity expiration is defined as the earlier of two events: expiration of all patents and regulatory exclusivities linked to the innovator drug in the FDA's Orange Book, or FDA approval of a generic drug with an identical set of active moieties. We plot the average number of scientific publications indexed in PubMed associated with the innovator drug in the twenty years preceding and following exclusivity expiration for all drugs in our sample. Appendix Figure A6 reproduces this analysis using two balanced panels (ten-year and five-year). Appendix Figure A9 plots trends in publications in calendar time (year relative to initial approval).

Figure 5: Scientific Publications Relative to Exclusivity Expiration



Notes: Figure plots the average number of scientific publications published in each relative year for the sample of innovator drugs defined in Section 4.5 ($N = 990$). Publication counts are plotted separately for publications that acknowledge receiving any public research support (red solid line) and publications that do not (blue dashed line). Market exclusivity expiration dates are defined as the earlier of two events: expiration of all patents and regulatory exclusivities linked to the innovator drug in the FDA's Orange Book, or FDA approval of a generic drug with an identical set of active moieties. Appendix Figure A7 reproduces this analysis using two balanced samples (ten-year and five-year).

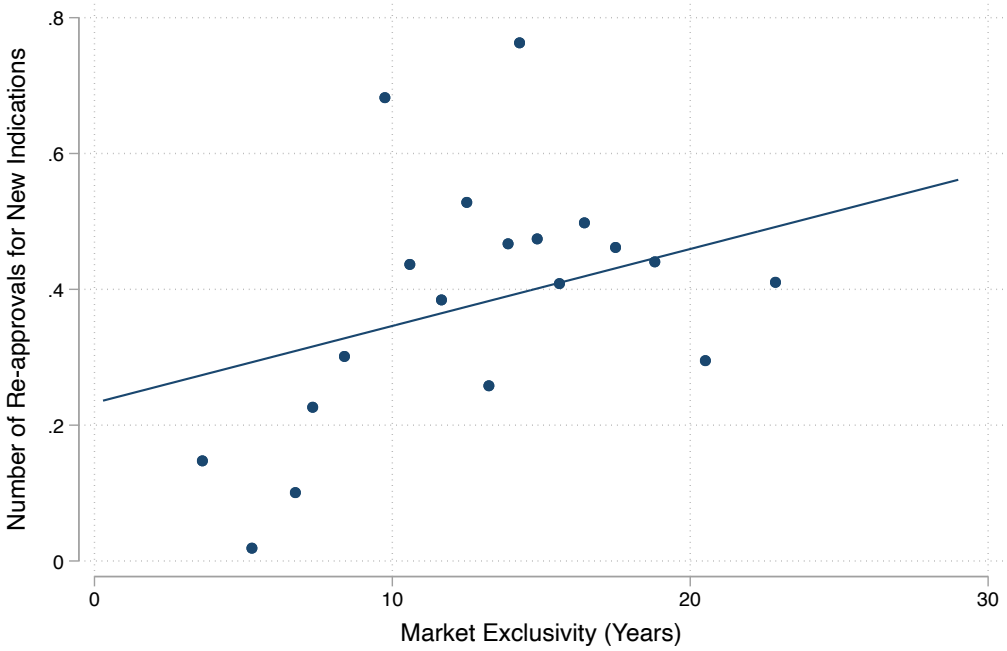
Figure 6: Combination Approvals



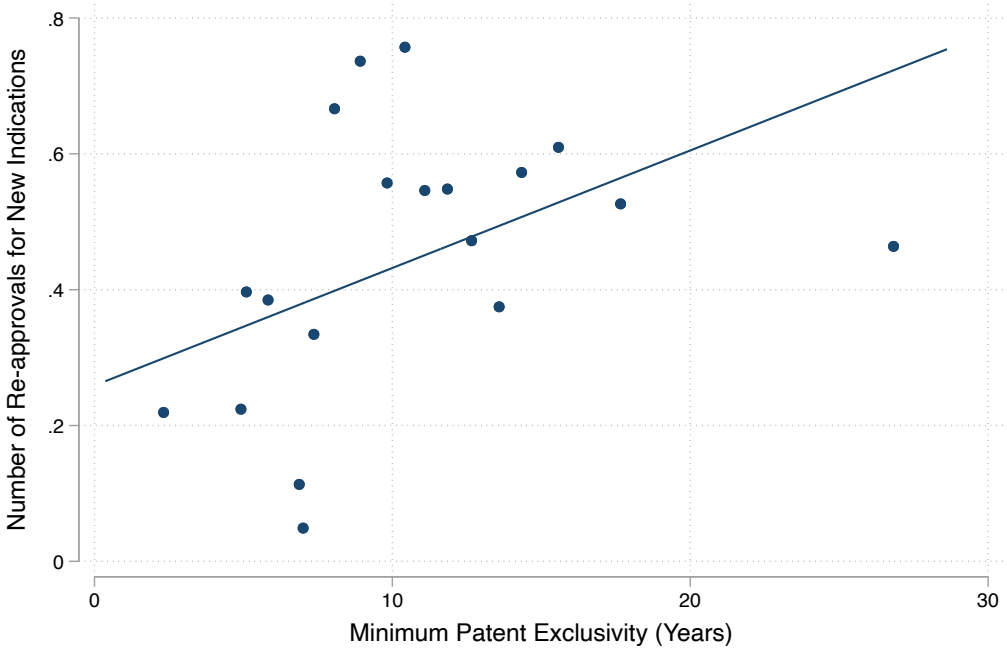
Notes: Figure plots two measures of FDA approvals for a subset of innovator drugs with a single active moiety ($N = 792$). We impute zeroes in each relative year if a single-moiety innovator drug never appears in a combination drug. Market exclusivity expiration is defined as the earlier of two events: expiration of all patents and regulatory exclusivities linked to the innovator drug in the FDA's Orange Book, or FDA approval of a generic drug with an identical set of active moieties. We plot the probability of re-approval for a new indication and as a combination for the twenty years preceding and following exclusivity expiration for all drugs in our sample.

Figure 7: Volume of New Uses Relative to Exclusivity

Panel A: Market Exclusivity



Panel B: Minimum Patent Exclusivity



Notes: Figure plots the relatonship between a measure of market exclusivity (x-axis) and the number of re-approvals for new uses (y-axis) for the sample of innovator drugs defined in Section 4.5 ($N = 990$). Both the x- and y-axes are residualized by the year of innovator drug approval, as year of approval is mechanically related to the total number of realized new uses. The scatterplot is binned into ventiles of market exclusivity (20 bins), with the mean value of the exclusivity measure added back to ease interpretation. A line of best fit is included. Panel A uses a measure of market exclusivity that captures the number of years between the drug's initial approval and the earlier of the expiration of all patents and regulatory exclusivities or generic approval. Panel B uses a measure of market exclusivity that captures the number of years between the drug's initial approval and expiration of the earliest expiring patent and all regulatory exclusivities.

Table 1: Summary Statistics

	Mean	Median	SD	Min.	Max.	# obs.
Years to Generic Entry	11.27	11.47	4.52	0.21	28.19	442
Market Exclusivity (years)	12.90	13.37	5.48	0.18	42.46	990
Minimum Patent Exclusivity (years)	9.35	8.37	4.55	0.18	35.32	956
Number of Re-Approvals	14.87	11	13.43	0	87	990
Number of Re-Approvals (new/modified indication)	0.52	0	1.18	0	10	990

Notes: Table shows summary statistics for the sample of innovator drugs defined in Section 4.5 ($N = 990$). Innovator drugs are defined as the first FDA approvals of unique combinations of active moieties.

Table 2: Market Exclusivity and New Indication Approvals

Panel A: *re-approvals for new/modified indication*

	(1)	(2)	(3)	(4)
Market Exclusivity Exclusivity	0.013	0.020	—	—
(years)	(0.006)	(0.006)		
Minimum Patent Exclusivity	—	—	0.037	0.023
(years)			(0.008)	(0.008)
Approval Year FEs	no	yes	no	yes
Observations	990	990	990	990
Panel B: Two-part model				
Extensive Margin	*any re-approvals for new/modified indication*			
Market Exclusivity Exclusivity	0.026	0.042	—	—
(years)	(0.012)	(0.014)		
Minimum Patent Exclusivity	—	—	0.083	0.059
(years)			(0.015)	(0.018)
Approval Year FEs	no	yes	no	yes
Observations	990	990	990	990
Intensive Margin	*# re-approvals for new/modified indication*			
Market Exclusivity Exclusivity	0.015	0.020	—	—
(years)	(0.017)	(0.018)		
Minimum Patent Exclusivity	—	—	0.017	0.011
(years)			(0.021)	(0.022)
Approval Year FEs	no	yes	no	yes
Observations	256	256	256	256

Notes: Table shows the relationship between measures of market exclusivity and the number of realized new uses, estimating 5 in the text. Observations are the sample of innovator drugs defined in Section 4.5. We report estimates using two measures of market exclusivity: "market exclusivity" captures the number of years between the drug's initial approval and the earlier of the expiration of all patents and regulatory exclusivities or generic approval, and "minimum patent exclusivity" captures the number of years between the drug's initial approval and expiration of the earliest expiring patent and all regulatory exclusivities. Panel A reports estimates for a pooled sample, estimated via ordinary least squares. Panel B reports estimates from a two-part model, as described in Section 6.1.1. All specifications include approval year fixed effects.

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A Data Construction

A.1 Drug Approvals

Our primary source of data on drug approval and generic entry is the **Drugs@FDA** database, which is provided online and regularly updated by the U.S. Food and Drug Administration (FDA). With the exception of the following categories, this database contains most novel drug products:

- drugs not approved by the FDA
- drugs under review by the FDA for which action has not yet been taken
- over-the-counter (OTC) products approved for marketing through any process other than the submission of a New Drug Application (NDA) or a Biologic License Application (BLA)
- drugs sold outside of the U.S. that are not approved for marketing within the U.S.
- dietary supplements, which do not require FDA approval for domestic sale
- biological products (regulated by the Center for Biologics Evaluation and Research)
- animal drugs (regulated by the Center for Veterinary Medicine)

We use data from three Drugs@FDA files:

1. Application-level data: *application.txt*
2. Product-level data: *Product.txt*
3. Supplemental approval data: *RegActionDate.txt*

The Drugs@FDA data structure changed on 06 November 2016. After this date, many details in the Supplemental Approval data file were no longer available, and the file *RegActionDate.txt* was no longer published.[70] We use the latest available version of the database referred to as "Drugs@FDA 1.0," dated 25 October 2016, obtained via the Internet Archive's Wayback Machine.

A.1.1 Background on the FDA approval process and data files

With few exceptions, drugs that are prescribed in the United States must first be approved by the FDA. FDA approval indicates that, for its intended population, a drug's benefits outweigh both known and potential risks.[71] A brief primer on the vocabulary of drug applications and key features of the approval process provides helpful context for the data in this paper.

Application numbers: The FDA assigns six-digit application numbers to three key types of applications: new drug applications (NDAs); abbreviated new drug applications (ANDAs), and biologic license applications (BLAs). Each application may be differentiated by its: (i) unique active ingredients; (ii) dosage form; and (iii) strength.

[70] We have been unable to obtain analogous records from the FDA covering more recent years.
[71] See https://www.fda.gov/drugs/development-approval-process-drugs for details.

New drug applications (NDAs): An NDA is submitted when there exists sufficient evidence on the safety and effectiveness of a drug to meet the FDA's requirements for new drug marketing. NDAs are typically submitted for all novel, brand-name drugs.

Abbreviated new drug applications (ANDAs): An ANDA is submitted for the approval of a generic drug that is the "therapeutic equivalent" of any previously approved drug. Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

Biologic license applications (BLAs): A BLA is an application submitted for the approval of a biological product.

Application-level data The Application data file contains information on 20,560 drug approvals; 15,341 are NDAs, 5,082 are ANDAs, and 137 are BLAs.

Product-level data The Product data file contains information for each application that includes—among other variables—a record of drug ingredients that are associated with each application. Specifically, the file includes the following variables:

Active ingredients: An active ingredient in a drug is defined by the FDA as any component that provides pharmacological activity or another direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. Several NDAs and ANDAs may have the same active ingredients.

Dosage form: A dosage form is the physical form in which a drug is both produced and dispensed. These include tables, capsules, and injectable forms.

Strength: The strength of a particular drug product captures how much of the active ingredient is present in each dosage form.

Supplemental approval data The RegActionDate data file contains records of all approvals associated with each NDA and ANDA. This file contains 128,906 approvals, which correspond to 17,299 unique application numbers. In addition to initial marketing approvals, this file contains records of "supplementary new drug applications" (sNDAs).

An sNDA is an application to the FDA requesting some change to the agency's approval for the drug. Changes may include new or modified indications, modifications to the labeling (i.e., the packaging affixed to a dispensed prescription), a new route of administration, or a new patient population for the drug. All changes of this kind must be approved by the FDA to ensure that the conditions that supported initial approval are still satisfied.

There are more than 50 categories of approval actions that can be granted using an sNDA. These approval types include standard approvals (which appear in our data as "N" type approvals), presubmissions ("M"), and manufacturing changes ("SCM"). For each approval, the FDA includes its action date which is the date at which the application was approved.

A.1.2 Identifying "innovator" drugs

We use data from drugs@FDA to define our base sample of new medicines. We call a drug an **innovator** if it meets the following criteria:[72]

1. It was approved under a New Drug Application (NDA) to the FDA.
2. It is the first approval of a unique combination of components

Determining whether a drug meets the first criterion is straightforward. Records in the Drugs@FDA database (applications file) are assigned one of three application types: "A" (abbreviated new drug application), "B" (biologics license application), or "N" (new drug application). We restrict consideration to applications of type "N."

Determining whether a drug meets the second criterion is more challenging—and foreshadows the medication name matching procedures discussed throughout this appendix. The core challenge is determining what constitutes a *unique component* in a drug. Many drugs are part of "substance sets" that include closely related products, which are pharmacologically and physiologically equivalent. Consider a drug molecule that contains a hydrogen atom. Replacing this hydrogen with "a metal or its equivalent" will form a salt, while replacing it with "an organic radical" will form an ester (Ward (2019), citing Amarin Pharm. Ireland Ltd. v. FDA, 106 F. Supp. 3d 196, 199 n.1 (D.D.C. 2015)). In many cases, these slight modifications have no clinically significant effects. However, these modified forms often appear as distinct active ingredients in the Drugs@FDA database. For example, *acetazolamide* and its salt form *acetazolamide sodium* both appear as active ingredients in our data. If we treated unique active ingredient strings as unique drug components for the purpose of constructing this sample, we would overcount the number of innovator products by incorrectly categorizing salts, esters, and other small chemical modifications to drugs as entirely new inventions.

Instead, we follow the FDA's own practice when evaluating the novelty of products and define innovator drugs in terms of unique *active moieties*: the part of the larger molecule that is responsible for the physiological or pharmacological action of the drug substance.[73] For the example above, *acetazolamide* is the active moiety in both *acetazolamide* and *acetazolamide sodium.* Thus, we construct our sample of innovator drugs by identifying the initial approvals of unique combinations of *active moieties* by the FDA.

Active moiety crosswalk To the best of our knowledge, there is no standard crosswalk from active ingredient strings, as appear in Drugs@FDA, to active moieties.[74] We construct such a crosswalk, using the

[72] This is conceptually similar to, but not the same as, the FDA classification "new molecular entity" (NME). NMEs are defined as new drugs whose active ingredients are chemical substances that are marketed for the first time in the United States. Put differently, NMEs are drugs for which the FDA has not previously approved some component. NMEs are a strict subset of our sample definition. Our modification is to include first approvals of unique combinations of ingredients, even if every component has been previously approved by the FDA.

[73] Debates about whether the FDA should refer to "active ingredients" or "active moieties" when, for example, making determinations about various types of market exclusivity have been ongoing since the 1980s. See Ward (2019) for a more detailed discussion.

[74] The International Nonproprietary Names (INN) initiative maintained by the World Health Organization attempts to deal with exactly this problem. The description of the INN program reads: "When the INN Programme was initiated, it was decided that in

Drugs@FDA Product file as our input data.[75]

We begin by standardizing strings of active ingredients recorded in the database. We ensure text is lower case, components (for drugs that are combinations of multiple ingredients) are alphabetized and separated by semicolons, and extraneous punctuation is removed. Next, we separate each active ingredient string into its component parts. For example, *abacavir; lamivudine; zidovudine* is split into its three pieces. For each component in a drug, we manually review PubChem, chemistry textbooks, and online resources to identify the active moiety in the drug. We reconstruct strings for combination drugs, again ensuring that the component active moieties are alphabetized and formatted consistently.

Of the 25,976 unique active ingredient strings in our data, we determine that the active moiety and active ingredient are identical in 12,510 cases.

Defining our sample We drop 6 application numbers that are present in the Application file but do not have corresponding data in the Product file. All application numbers in the Product file have matching data in the Application file.

We begin by constructing a sample of initial drug approvals. We focus on records with an "N" (standard approval) doctype designation in the Supplement data file. There are 140 unique applications with multiple associated "N" approvals. For these 140 cases, we select the earliest approval recorded as the initial approval date for that application. We also drop 1,126 applications for which we never observe an "N" approval in our data. Thus, we construct a preliminary dataset that includes 16,171 initial approvals.

We merge these records onto the Application and Product files to yield a dataset with information on initial drug approval and product characteristics for 15,361 applications. Excluded from this sample are 836 applications without records in the Product and Application files, and 4,895 applications that have records in the Product and Application files but no corresponding approval histories in the Supplement file.

Finally, we impose the two restrictions described above to construct a sample of innovator drugs, which are unique at the active moiety level. We begin by dropping 122 drugs approved under BLAs.[76] We drop 77 instances in which active moiety groups have no products that were approved under NDAs.[77] We drop 737 drugs based on their dates of approval: 250 instances in which drugs were initially approved before 1962, when the Kefauver-Harris Drug Amendment was signed into law; and 487 drugs approved between 1962 and 1985, when the regulatory structure introduced by the 1984 Hatch Waxman Act was implemented.[78]

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such situations, in order to limit the number of published INNs, an INN should be selected for one member of such a group only. This approach, which concerns especially substance sets formed by salts or esters of the same active moiety was validated in the 20th report of the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances (Technical Report Series No. 581)." See https://www.who.int/publications/i/item/inn-05-167-3 for details. Note that INNs may not always map onto drugs names as used in the United States. For example, "paracetamol" is the INN for "acetaminophen."

[75] In the interest of developing resources that can be re-used in research, we use the most current version of the Drugs@FDA database at the time this work was completed, dated 05 January 2023. Recall that this version of the Drugs@FDA database lacks information on product re-approvals central to our analysis. All other fields remain complete, however.

[76] Most BLAs are approved through the FDA's Center for Biologics Evaluation and Research (CBER). The sample of BLAs approved through CDER and indexed in Drugs@FDA is not representative of biologic drugs as a class.

[77] Examination of these cases indicates that these are instances where products were either (i) never approved as FDA brand-name drugs (e.g., application number 077394 was processed as an abbreviated new drug application in 2005, corresponding to "sodium bicarbonate" - baking soda); or (ii) correspond to innovator drugs that were approved before our dataset begins in 1962 (e.g. various applications related to penicillin, which was widely used beginning in the 1940s).

[78] The Kefauver-Harris Drug Amendment, often referred to as the "Drug Efficacy Amendment," introduced the requirement that

We identify **1,102** unique combinations of active moieties that meet our criteria for "innovator" drugs. These drugs are our primary sample.

A.1.3 Linking "innovator" drugs to generic competitors

We designate any drug that is approved under an ANDA a "generic."[79] There are 8,322 application numbers in our dataset approved under ANDAs. To determine the first generic entrant for an innovator drug, we consider the set of all ANDAs with identical sets of active moieties and select the drug product with the earliest approval date. If there are multiple generic drugs within an active ingredient group being approved on the earliest date—which we observe for 186 unique products—we pick the drug with the lowest application number as our earliest generic entrant. We observe at least one generic entrant for 451 drugs in our sample—41%.

A.1.4 Counting approvals and re-approvals

We construct two measures of drug approvals and reapprovals. As noted above, a drug's initial approval is identified by searching for records with an "N" (standard approval) doctype, and we ensure that there is only one initial approval per drug. We construct a measure of "all approvals" associated with a drug, by identifying all approvals without an "N" doctype. Supplementary approvals associated with doctype "SE1" are approvals for new indications. We count SE1 approvals to generate a measure of approvals for new uses.

A.2 Scientific publications

We collect a measure of research investments from the National Library of Medicine's PubMed database. PubMed collects information on biomedical scientific publications, with curated links to chemicals mentioned in the text of each paper. Chemical names are standardized to match terms in the "Medical Subject Headings" (MeSH) vocabulary, a controlled thesaurus maintained by the NLM. As of 2022, there were more than 30,000 entries in MeSH. Each MeSH term has an associated unique ID (UI). It is important to note that although each term corresponds to at most one UI, one UI can be associated with multiple synonymous terms. If chemical names are tagged with UIs, then, the numerical identifiers can allow us to identify and properly group synonyms.

For each active moiety in our innovator drug sample, we identified the corresponding MeSH term and UI. We used a crosswalk between MeSH terms and UIs drawn from the PubMed database.[80] When active

drug manufacturers demonstrate the effectiveness and safety of drugs before approval. Manufacturers were also required, after this point, to disclose accurate information about side effects. Cheap generic drugs could no longer be re-branded as brand name (expensive) drugs and re-marketed as "breakthroughs."

[79] This designation is standard and consistent with FDA language. In FDA documents, ANDA and 'generic' are often used interchangeably. See https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm for drugs@FDA descriptions of ANDAs for generic products

[80] Specifically, we used the "chemicals" table from the bulk version of PubMed. We constructed a list of all unique MeSH terms reported in the "substname" field and their associated UIs reported in the "substUI" field. As these fields are added by indexers at the National Library of Medicine (and not constructed by authors themselves), we did not verify the accuracy of these substname-substUI links. However, we did note that, as expected, each substname is associated with one substUI, as expected, and that the same substUI is associated with multiple substnames.

Table A1: Clinical Trials Datasets

dataset	version	file names	years of coverage	proprietary
NDA Pipeline	received in April 2007	nda_trials.dta	1982–2001	no
Pharmaprojects	current through May 2011	trend_accnum_year.dta	1995–2010	yes
Cortellis	current through 2016	trialid_singledata.dta trialid_drug_primary_intervention.dta	1995–2016	yes
ClinicalTrials.gov	downloaded from AACT; version dated 20220728	studies.txt; browse_interventions.txt; interventions.txt; interventions_other_names.txt	2010–2016	no

Notes:

moiety strings matched the text description of MeSH terms precisely, we assigned both the MeSH term and UI to the active moiety. When there was no precise match, we searched the web-based MeSH browser, to determine if there may be an alternative formatting, spelling, etc. that resulted in a match. In our sample of 1,102 innovator products, we successfully identified a MeSH UI for 810 (74%).

Comparatively few combination drugs have associated MeSH UIs. When MeSH terms exist for combination drugs, formatting is standardized (e.g. "hydrocortisone, urea drug combination" (MeSH UI: C010017)). However, of the 351 combination drugs in our sample of innovator products, only 78 have a MeSH UI.

For the set of non-combination drugs, we impute zero publications if there is no associated MeSH UI. For the sample of combination drugs, we proceed differently. We collect counts of all publications that reference every component of the combination drug (e.g., for "hydrocortisone, urea drug combination," we collect all publications that reference both “hydrocortisone” and “urea”). In our primary analyses, we use these counts as our measures of scientific publications.

We also collect flags from PubMed that indicate whether a publication received any funding from a public agency. We draw on information from the “grants” table of PubMed and designate a publication as have any public funding if there is any entry associated with one of three variables in PubMed: Grant ID, Acronym (Grant Agency), Grant Agency.

A.3 Clinical trials

A.3.1 Datasets

We collect information on clinical trials as one measure of drug development. To maximize coverage over our sample period, we draw records from four datasets. Table A1 summarizes the coverage of each dataset.

NDA Pipeline

We collect records from the NDA Pipeline dataset, maintained by F-D-C Reports. The NDA Pipeline is a reference document covering drug developments during the previous calendar year. Each observation

includes a text description of the stage of development for a given drug compound. We use data from 1982 to 2001.

Pharmaprojects

We collect additional information on drug development between 1995 and 2010 from Pharmaprojects, a proprietary dataset that records events associated with drugs at various stages of the development pipeline.[81] Pharmaprojects is compiled and sold by Citeline. Employees gather information from company websites, reports, and press releases. Every company in the database verifies information related to their listed drugs. Pharmaprojects reports trials that are newly initiated and ongoing in each annual report.

Citeline's documentation associated with the dataset notes: "There is continual two-way communication between Pharmaprojects staff and their contacts in the pharmaceutical and biotechnology industries; both to gather new data and importantly, to verify information obtained from other sources."

Cortellis

We also collect records on drug development between 1995 and 2015 from Cortellis, a proprietary dataset that, like Pharmaprojects, records details on drug development activity.[82]

ClinicalTrials.gov

We supplement these records with data drawn from ClinicalTrials.gov, the largest repository of clinical trial records in the world, for clinical trials initiated between 2010 and 2016. Since 2007, sponsors of trials regulated by the U.S. Food and Drug Administration are required, by law, to register clinical trials with ClinicalTrials.gov. Since 2005, registration in a global registry has been required as a condition of publication in any journal associated with the International Committee of Medical Journal Editors.

A.3.2 Data construction

NDA Pipeline

NDA Pipeline records include the following information: document publication year, firm name, trade name of drug, generic name of drug, abbreviation of drug name, description of study, status, and miscellaneous notes. We identify developments about clinical trials by searching for keywords within the "status" variable. Specifically, we keep records where the status variable includes either "phase" (as in, "Phase I trial") or "clinical." We drop records where the description includes either "preclinical" or "pre-clinical."

As these records are intended to provide annual updates on drug development pipelines, clinical trial records are best interpreted as reports of trials that were active in the year prior to publication. That is, they reflect firm decisions about project *continuation*, rather than project *initiation*. Since these documents were

[81] Our version of Pharmaprojects is current through May 2011.

[82] Details on the contents of Cortellis are available here: https://cortellislabs.com/api/clinical/. There are a small number of records for trials initiated before 1995, which appear to be incomplete (e.g., there is one trial in the Cortellis data that is active in the year 1981). We do not include these records in our sample.

published one year after the relevant clinical developments, we subtract one from the year of publication to generate a variable capturing the year in which a trial was conducted.

We link records to our baseline sample of FDA-approved active moieties using the generic name of the drug. We standardize the formatting of the string (remove punctuation, alphabetize components, remove extraneous characters, etc.) and attempt two merges. First, we attempt to merge the generic name of the drug in this dataset to the active ingredients associated with our baseline sample. For observations that do not successfully merge, we next attempt to link generic names to the active moieties associated with our baseline sample. We impute annual trial counts of zero for all active moieties approved during this time period.

Our final dataset includes records associated with 543 FDA-approved active moieties (or combinations) tested between 1981 and 2000. The most studied drugs in our sample are paclitaxel and thalidomide.[83]

Pharmaprojects

We use data from Pharmaprojects on the status of drug development projects. We collect information on clinical trial developments by, similarly, searching within a variable about project status ("originator status"). As with NDA Pipeline data, we keep records where the status variable includes either "phase" (as in, "Phase I trial") or "clinical." We drop records where the description includes either "preclinical" or "pre-clinical." Pharmaprojects records provide annual updates on drug development projects and, thus, also capture project *continuation*, rather than project *initiation.*

Our linking procedure with Pharmaprojects data is identical to the linking project for NDA Pipeline. We link records to our baseline sample of FDA-approved active moieties using the generic name of the drug. We standardize the formatting of the string (remove punctuation, alphabetize components, remove extraneous characters, etc.) and attempt two merges. First, we attempt to merge the generic name of the drug in this dataset to the active ingredients associated with our baseline sample. For observations that do not successfully merge, we next attempt to link generic names to the active moieties associated with our baseline sample. We impute annual trial counts of zero for all active moieties approved during this time period.

Our final dataset includes records associated with 613 FDA-approved active moieties (or combinations) tested between 1995 and 2011. The most studied drug in our sample is paclitaxel.

Cortellis

We also collect data from Cortellis that—like the Pharmaprojects data—collects data on drug development typically sold for the purposes of "competitive intelligence." Cortellis includes one record per clinical trial and includes variables that capture start year and end year. We transform these data into records that indicate whether a given trial on a drug was active in each year.

[83] Paclitaxel is a type of chemotherapy that can treat various forms of cancer, originally approved in 1992. See https://www.nytimes.com/2005/01/08/business/new-form-of-breast-cancer-drug-approved.html. Thalidomide was approved by the FDA in 1998 to treat leprosy and has since been reapproved to treat various forms of cancer. Given its (notorious) history of causing birth defects, its distribution is tightly controlled. See https://www.nytimes.com/1998/07/17/us/thalidomide-approved-to-treat-leprosy-with-other-uses-seen.html.

Our linking procedure with Cortellis data is identical to that used for NDA Pipeline and Pharmaprojects. We, again, impute annual trial counts of zero for all active moieties approved during this time period.

Our final dataset includes records associated with 990 FDA-approved active moieties (or combinations) tested between 1995 and 2016. The most studied drug in our sample is docetaxel.

ClinicalTrials.gov

We use data from ClinicalTrials.gov to supplement records from NDA Pipeline, Pharmaprojects, and Cortellis. Although ClinicalTrials.gov was made available to the public in 2000, we collect records beginning in 2010, by which time trial registration had become more common.[84] We collect records of all trials, regardless of trial phase, that were active between 2010 and 2016. ClinicalTrials.gov allows us to construct two measures of trial activity: trial initiation decisions (using trial start years) and trial continuation decisions (using trial active years). To facilitate integration with NDA Pipeline and Pharmaprojects data, our main analyses use trial continuation decisions measured using trial active years. There are a number of concerns about the completeness and accuracy of ClinicalTrials.gov records (see, for example, Zarin et al. (2017); Tse et al. (2018)). Given these limitations, we report analyses that consider the likelihood of any clinical trial associated with a given drug in each year, rather than considering the total number of trials.

As ClinicalTrials.gov is administered by the National Library of Medicine, we follow the same procedure to link records used for PubMed data. Trial sponsors report the interventions (therapies, behavioral treatments, drugs, etc.) associated with each study using standardized MeSH terms, in the file *browse_interventions*. We link MeSH terms associated with clinical trials to the MeSH terms associated with each drug in our baseline sample. We impute annual trial counts of zero for all active moieties approved during this time period with no matching trial records.

Our final dataset includes records associated with 1,013 FDA-approved active moieties (or combinations) tested between 2010 and 2016. The most studied drug in our sample is docetaxel.

A.3.3 Clinical trials sample

We construct a sample of clinical trials by appending records for NDA Pipeline, Pharmaprojects, and ClinicalTrials.gov. Our primary measure of trial activity is an indicator variable that takes a value of one if there was any active clinical trial associated with an innovator drug in a given year. Although our data do enable us to consider the total volume of clinical trials, we prefer to focus on a binary measure to avoid introducing concerns about differences in measurement and coverage across the four datasets.

[84] In 2005, the International Committee of Medical Journal Editors (ICMJE) began requiring trial registration as a condition of publication. In 2007 the requirements for submission to ClinicalTrials.gov were expanded after Congress passed the Food and Drug Administration Amendments Act of 2007 (FDAAA) (PDF). Section 801 of FDAAA (FDAAA 801) required more types of trials to be registered and additional trial registration information. For more details, see https://clinicaltrials.gov/ct2/about-site/history.

A.4 Drug-disease crosswalk

We construct data on the specific therapeutic uses (indications) associated with each drug approval and re-approval in our sample. For each approval/re-approval event, we collect text descriptions of the associated indications from a variety of sources. Where possible, we use FDA application number and date of (re-)approval to retrieve the relevant drug label from the FDA's full-text drug product labeling service, FDALabel.[85] We supplement data on labels—which are primarily available from 2005 forward—with data from drug approval packets[86], dated company press releases, scientific articles, and other internet searches.

For each text description, we identify a set of associated alphanumeric codes from the International Classification of Diseases, Tenth Revision (ICD-10), a classification system of diagnosis codes representing conditions and diseases, related health problems, abnormal findings, signs and symptoms, injuries, and external causes of injuries and diseases. We use online searches to identify an initial set of "likely" ICD-10 codes. We verify the accuracy of these codes using online code look-up tools, intended for hospital staff who are completing billing tasks.[87] A second researcher verified the accuracy of a random 20 percent sample of codes. We report the most granular ICD-10 code available, but use in our analyses a truncated (less specific) version. Concretely, instead of using **G43.1** (Migraine with Aura), we use **G** (Diseases of the Nervous System) and **G43** (Migraine).

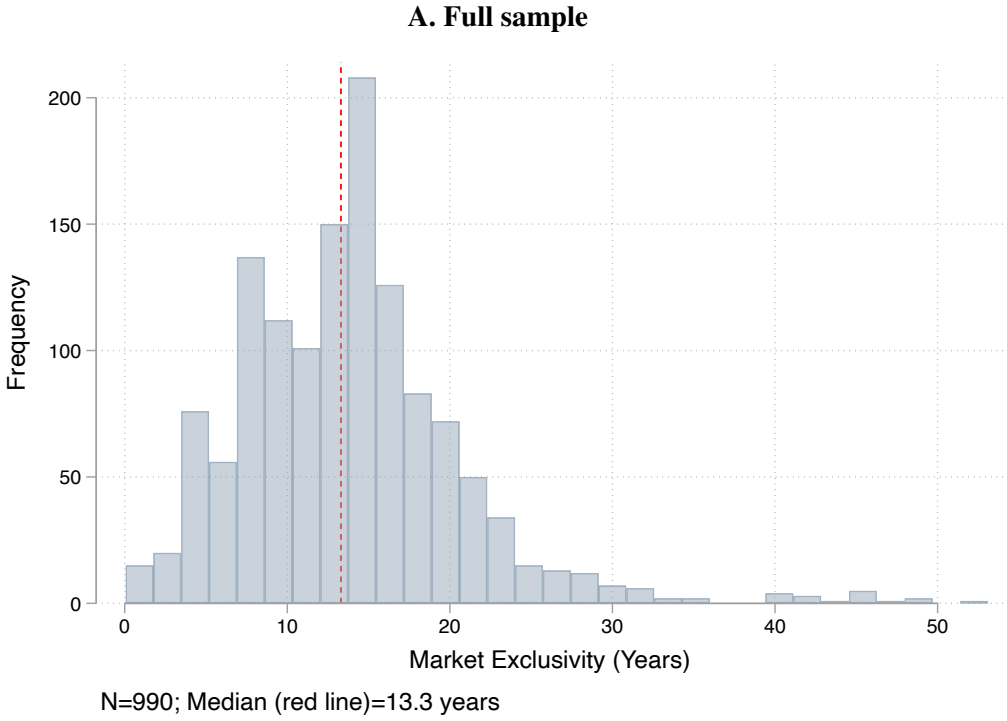
[85] https://www.fda.gov/science-research/bioinformatics-tools/fdalabel-full-text-search-drug-product-labeling

[86] Drug approval records are available for many drugs beginning in 1995 through the Drugs@FDA interactive search tool: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

[87] For example, https://icdcodelookup.com/icd-10/codes

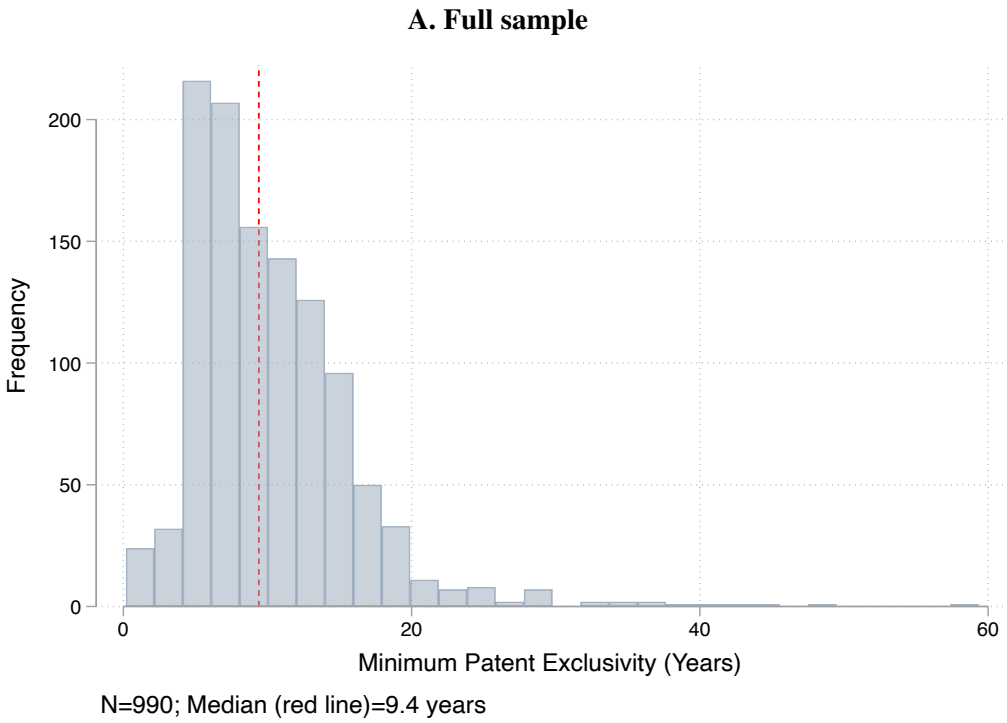
A.5 Distribution of Market Exclusivity

Figure A1: Market Exclusivity



Notes: Figure is a histogram that plots the distribution of the market exclusivity measure defined in the text as the number of years between an innovator drug's initial approval and the earlier of the expiration of all patents and regulatory exclusivities and generic entry. The distribution of this measure is plotted for the sample of innovator drugs defined in Section 4.5.

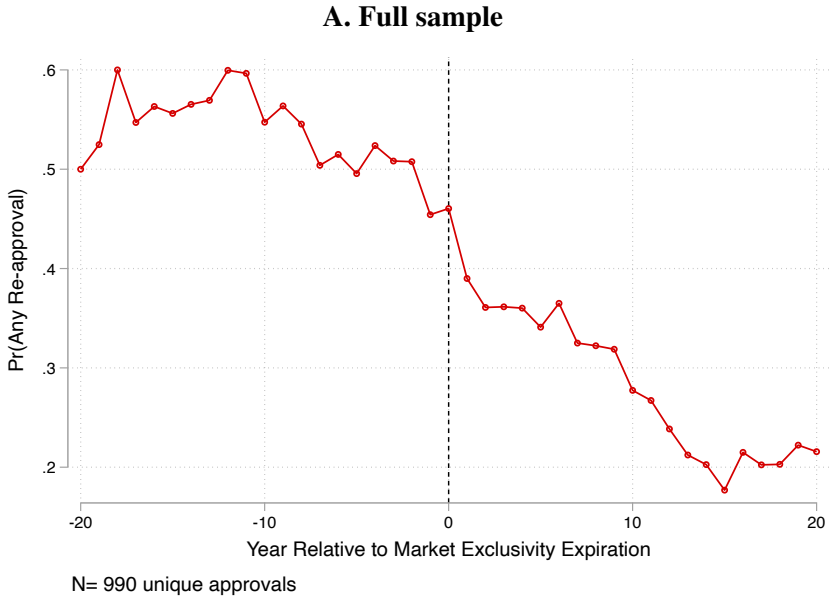
Figure A2: Minimum Patent Exclusivity

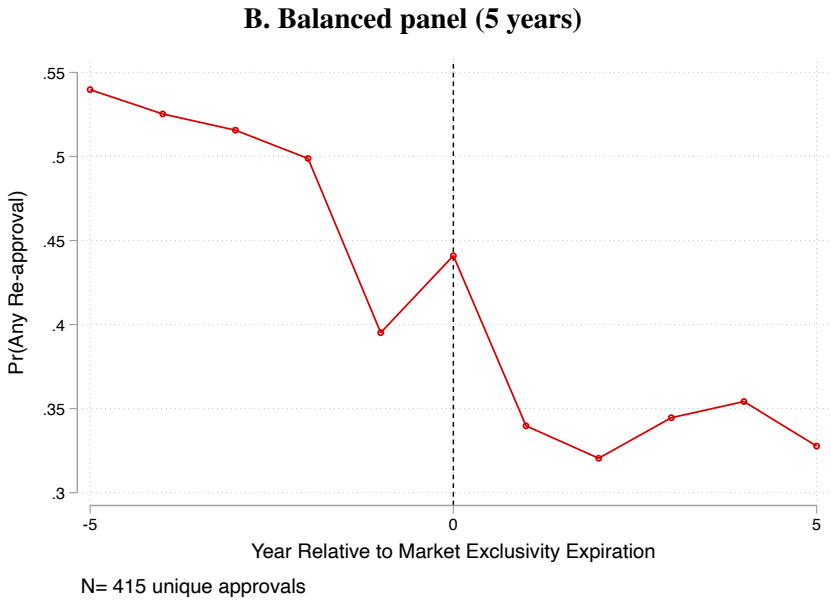


Notes: Figure is a histogram that plots the distribution of the minimum patent exclusivity measure defined in the text as the number of years between an innovator drug's initial approval and the expiration of all regulatory exclusivities and the earliest expiring patent. The distribution of this measure is plotted for the sample of innovator drugs defined in Section 4.5.

B Additional Results

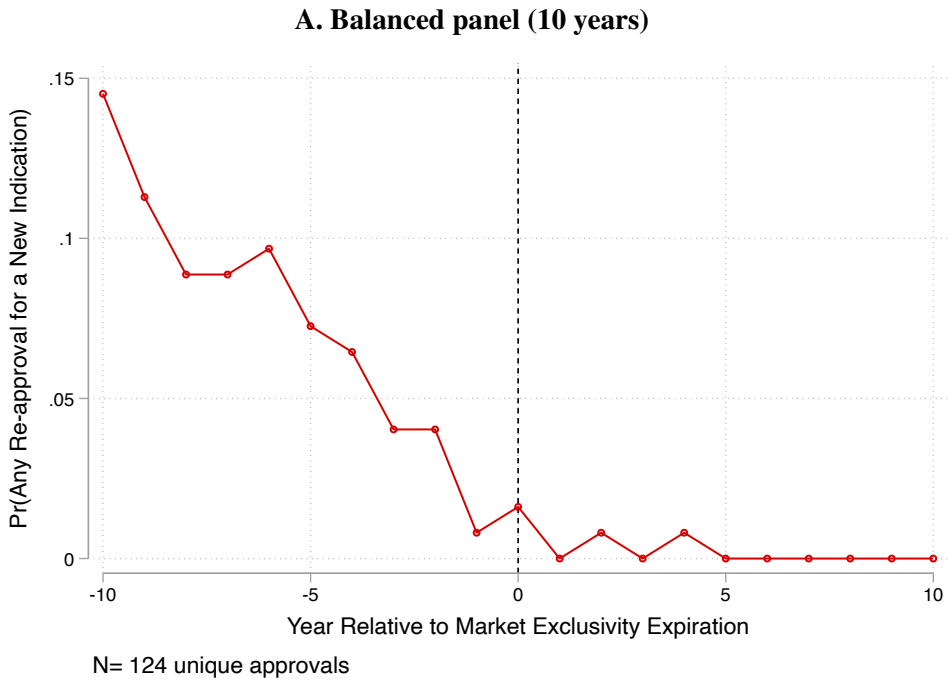
Figure A3: All Approvals

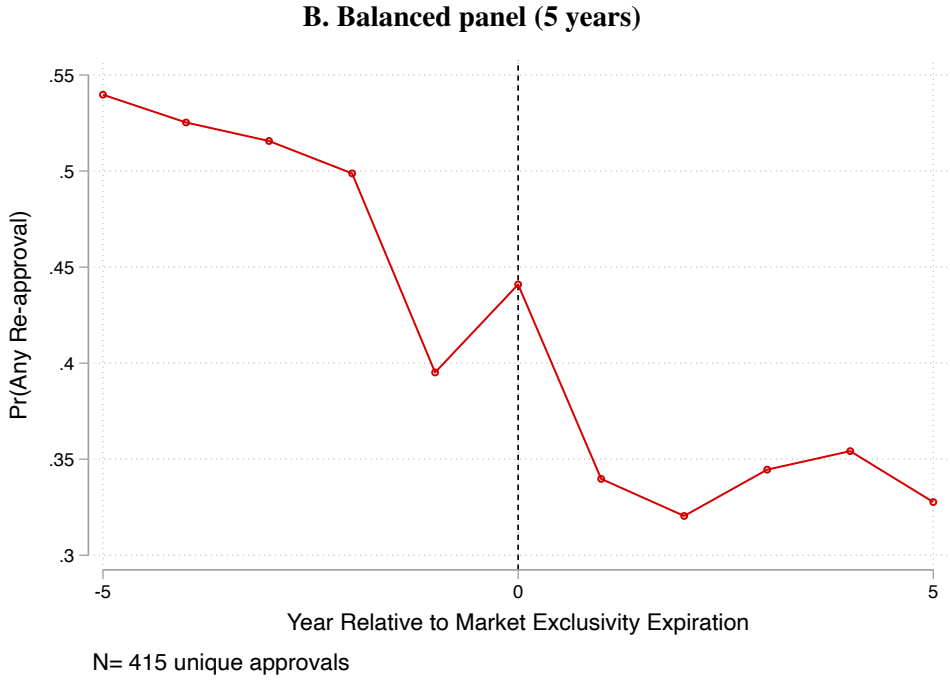




Notes: Figure plots the probability of any re-approval (e.g., new use, new dosage form, etc.) for the sample of innovator drugs defined in Section 4.5 ($N = 990$). Market exclusivity expiration is defined as the earlier of two events: expiration of all patents and regulatory exclusivities linked to the innovator drug in the FDA's Orange Book, or FDA approval of a generic drug with an identical set of active moieties. We plot the probability of re-approval for the twenty years preceding and following exclusivity expiration for all drugs in our sample. Panel A is an unbalanced panel. Panel B is a balanced panel, with five years of data before and after exclusivity expiration.

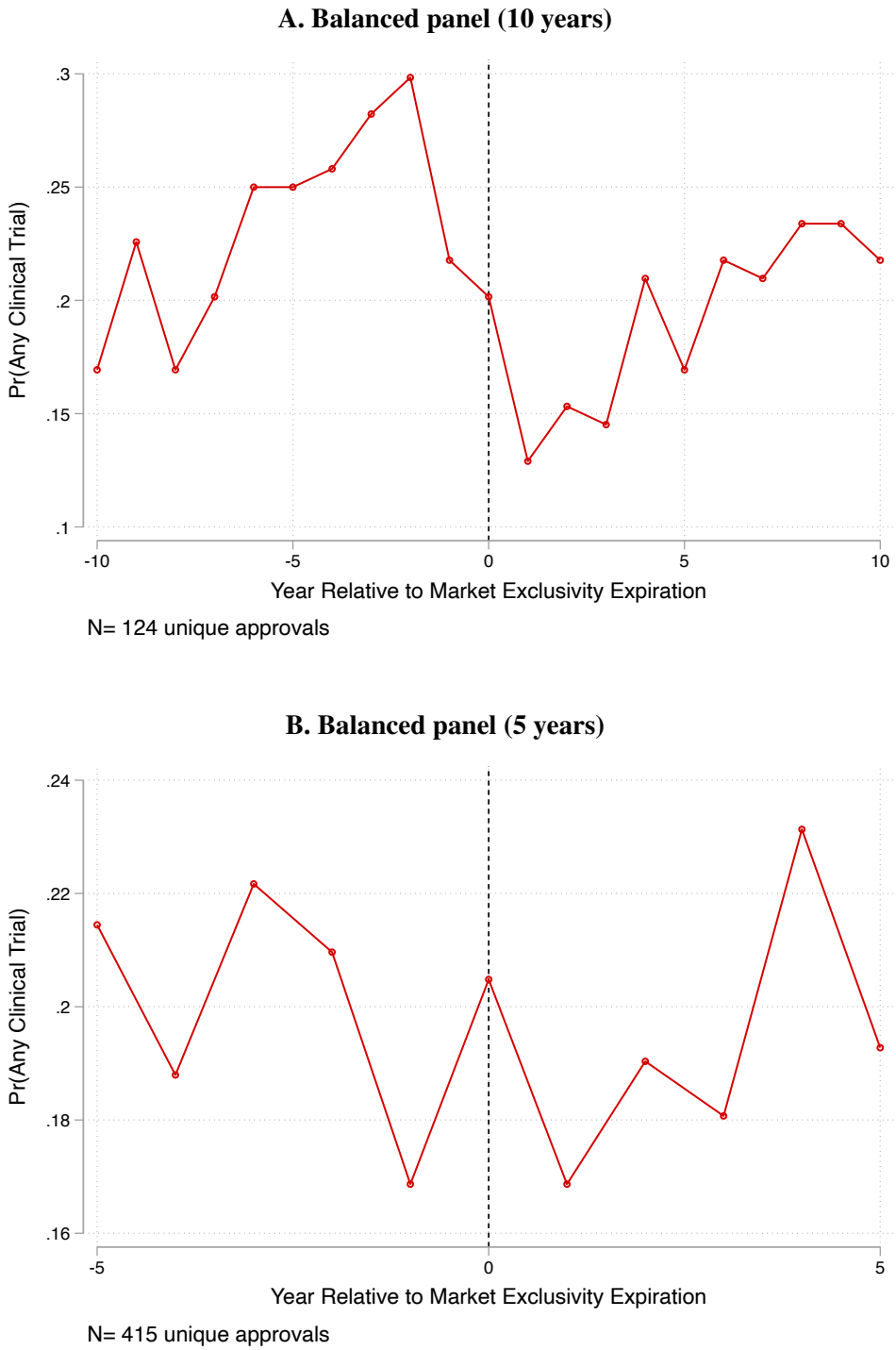
Figure A4: New Use Approvals, Balanced Panel





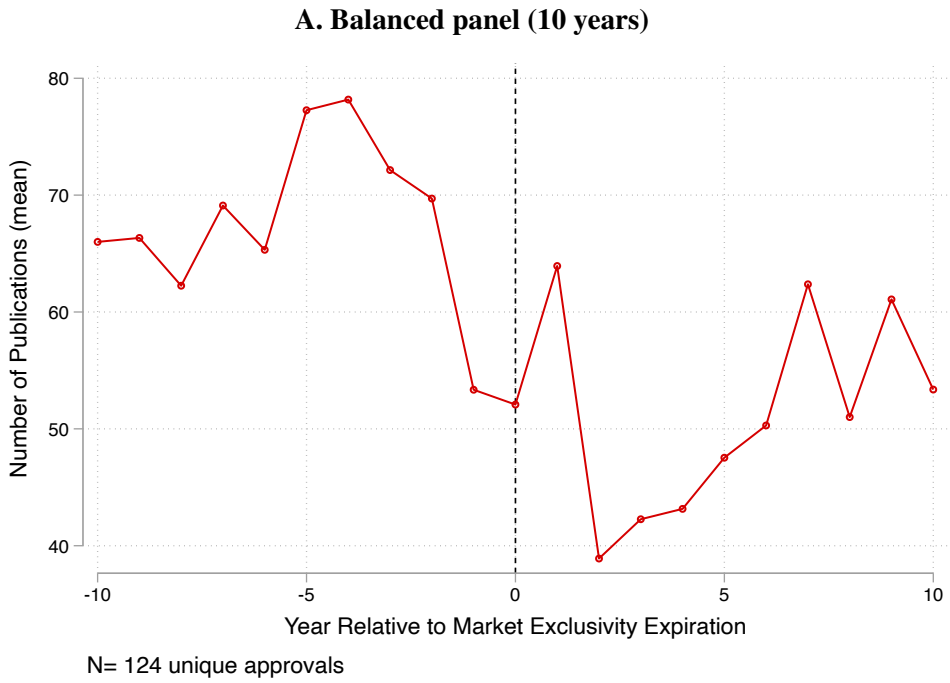
Notes: Figure plots the probability of re-approval for a new use for the sample of innovator drugs defined in Section 4.5 ($N = 990$). Market exclusivity expiration is defined as the earlier of two events: expiration of all patents and regulatory exclusivities linked to the innovator drug in the FDA's Orange Book, or FDA approval of a generic drug with an identical set of active moieties. We plot the probability of re-approval for a new use for the twenty years preceding and following exclusivity expiration for all drugs in our sample. Panel A is a ten-year balanced panel. Panel B is a five-year balanced panel.

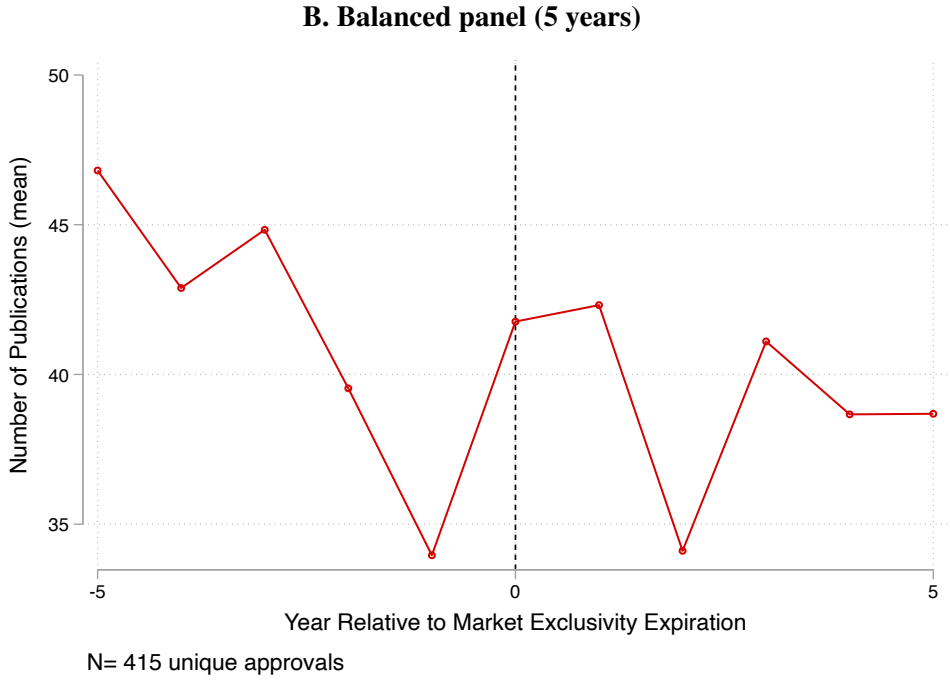
Figure A5: Clinical Trials, Balanced Panel



Notes: Figure plots the probability of any active clinical trial in each relative year for the sample of innovator drugs defined in Section 4.5 ($N = 990$). Market exclusivity expiration is defined as the earlier of two events: expiration of all patents and regulatory exclusivities linked to the innovator drug in the FDA's Orange Book, or FDA approval of a generic drug with an identical set of active moieties. We plot the probability of any active clinical trial in each of the twenty years preceding and following exclusivity expiration for all drugs in our sample. Panel A is a ten-year balanced panel. Panel B is a five-year balanced panel.

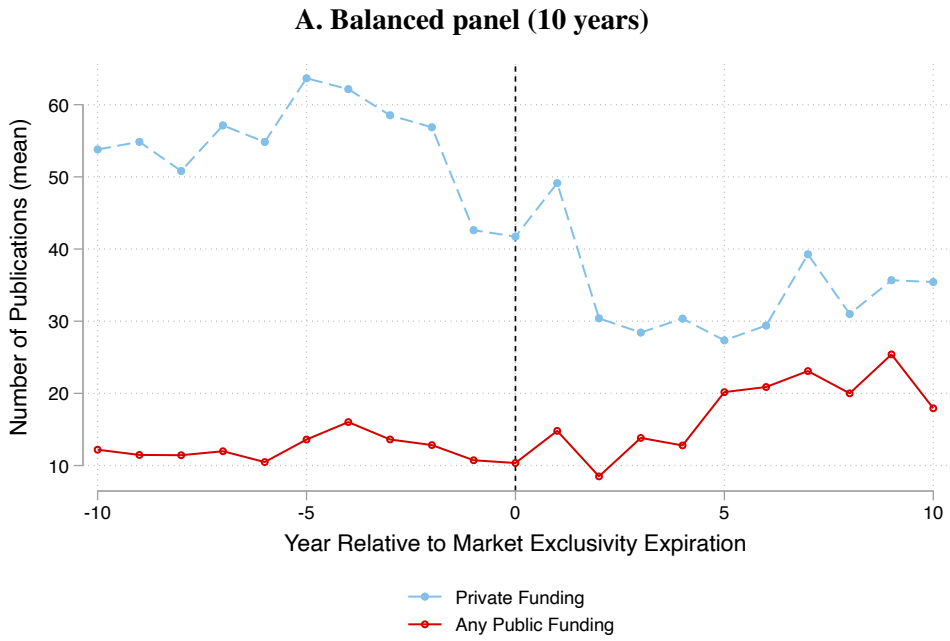
Figure A6: Publications, Balanced Panel



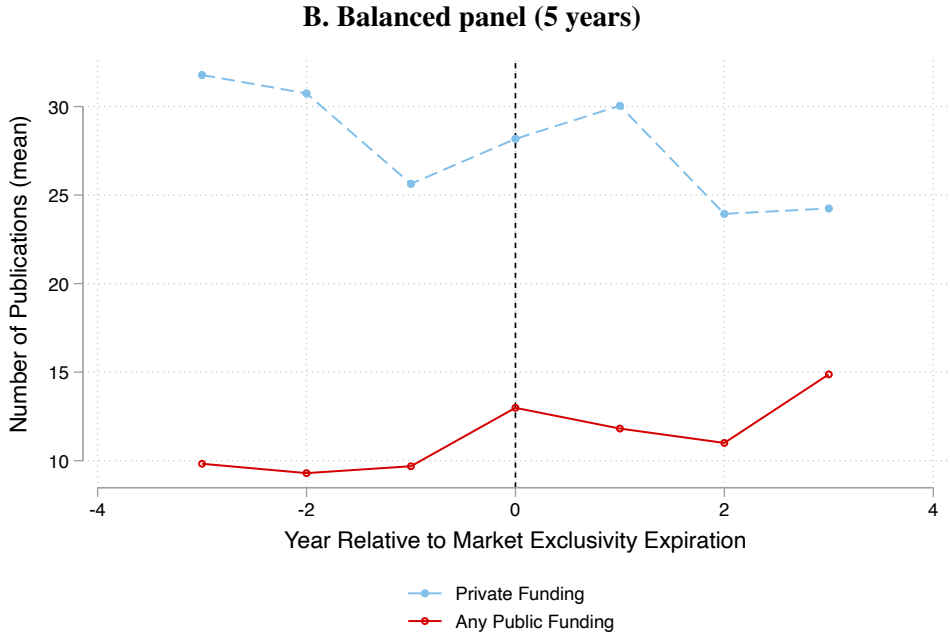


Notes: Figure plots the average number of scientific publications published in each relative year for the sample of innovator drugs defined in Section 4.5 ($N = 990$). Market exclusivity expiration is defined as the earlier of two events: expiration of all patents and regulatory exclusivities linked to the innovator drug in the FDA's Orange Book, or FDA approval of a generic drug with an identical set of active moieties. We plot the average number of scientific publications indexed in PubMed associated with the innovator drug in the twenty years preceding and following exclusivity expiration for all drugs in our sample. Panel A is a ten-year balanced panel. Panel B is a five-year balanced panel.

Figure A7: Publications (Funding Source), Balanced Panel



N= 124 unique approvals

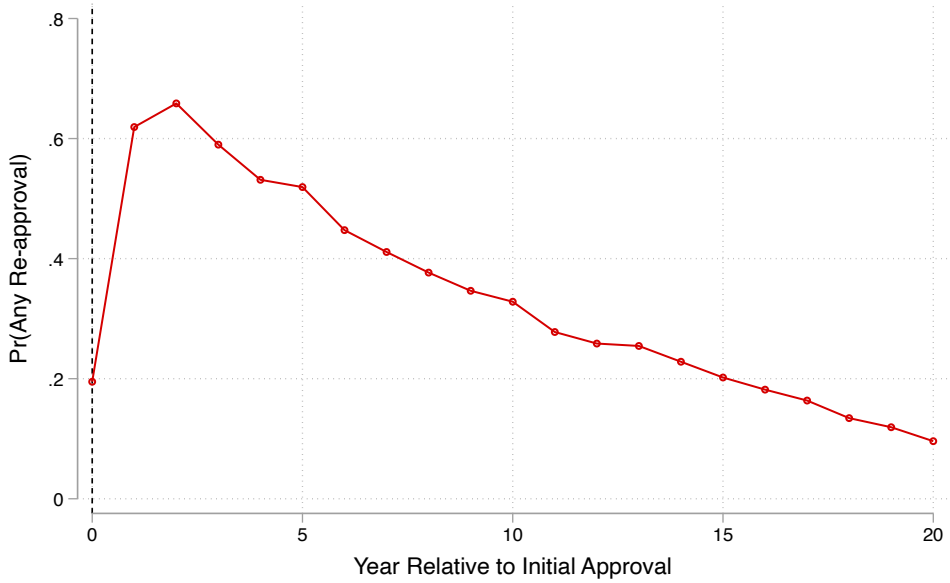


N= 499 unique approvals

Notes: Figure plots the average number of scientific publications published in each relative year for the sample of innovator drugs defined in Section 4.5 ($N = 990$). Publication counts are plotted separately for publications that acknowledge receiving any public research support (red solid line) and publications that do not (blue dashed line). Market exclusivity expiration dates are defined as the earlier of two events: expiration of all patents and regulatory exclusivities linked to the innovator drug in the FDA's Orange Book, or FDA approval of a generic drug with an identical set of active moieties. Panel A is a ten-year balanced panel. Panel B is a five-year balanced panel.

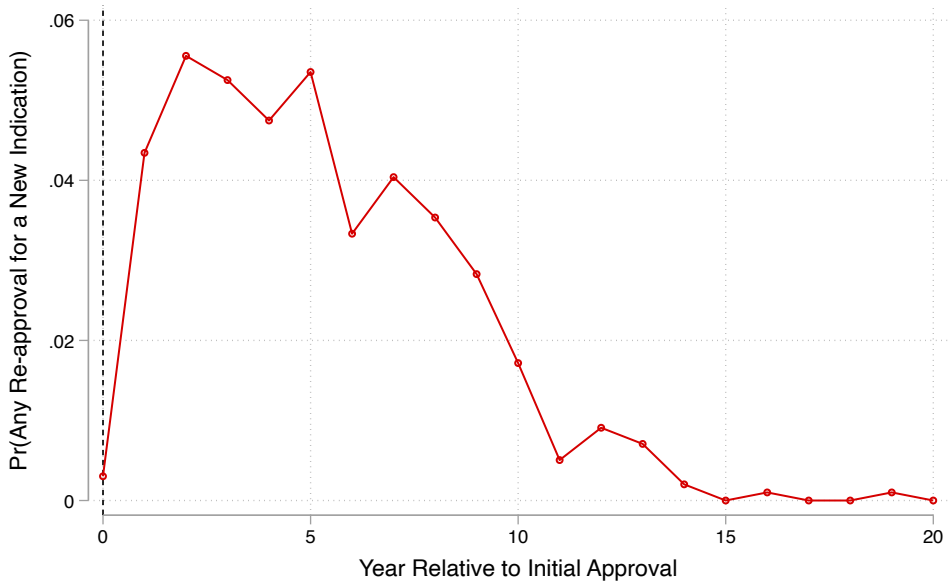
Figure A8: FDA Approvals, Calendar Time

A. All Re-approvals



N= 990 unique approvals

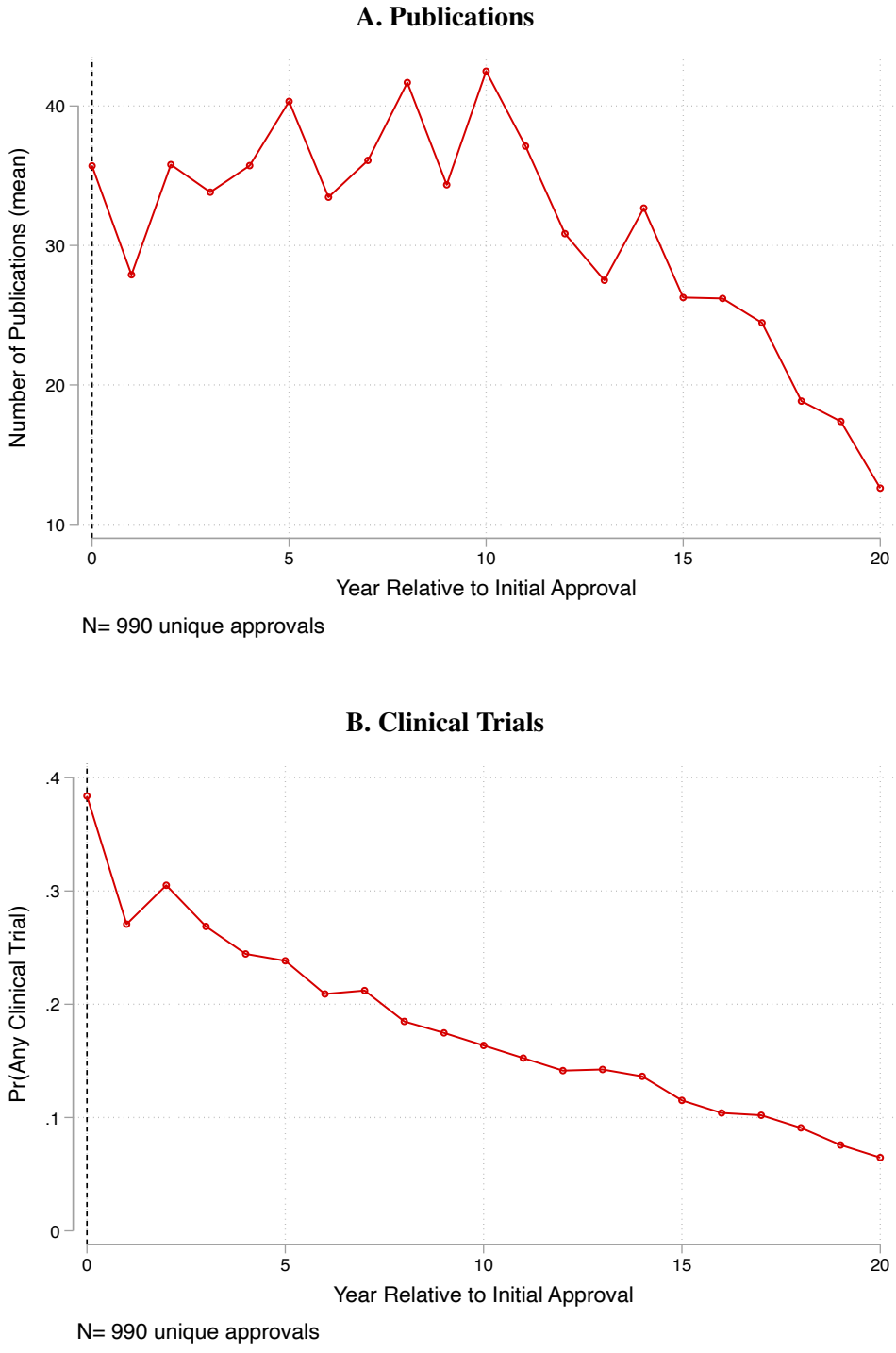
B. New Use Approvals



N= 990 unique approvals

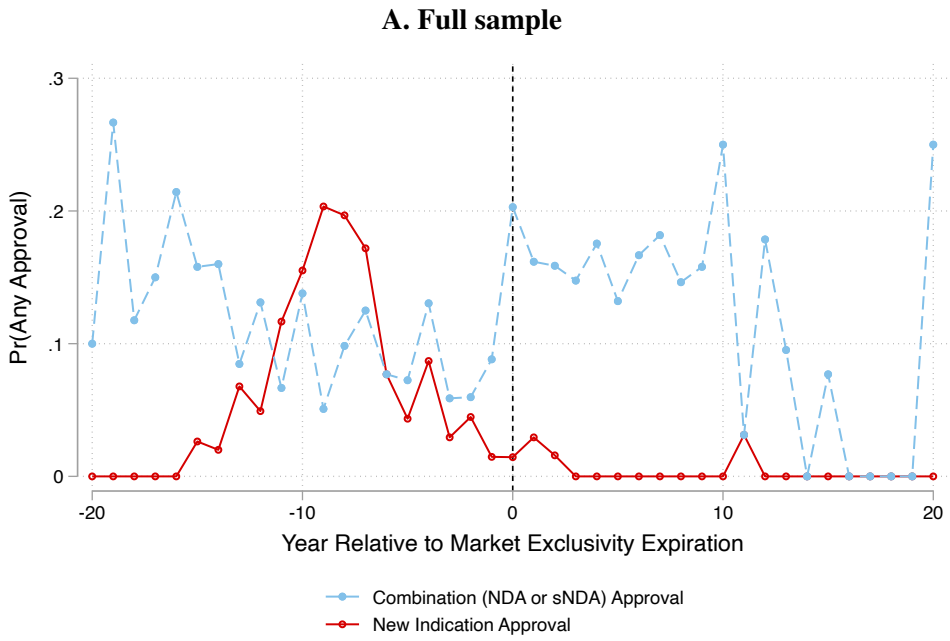
Notes: Panel A plots the probability of any re-approval (e.g., new use, new dosage form, etc.) for the sample of innovator drugs defined in Section 4.5 in calendar time. Panel B plots the probability of re-approval for a new use for the sample of innovator drugs defined in Section 4.5 ($N = 990$).

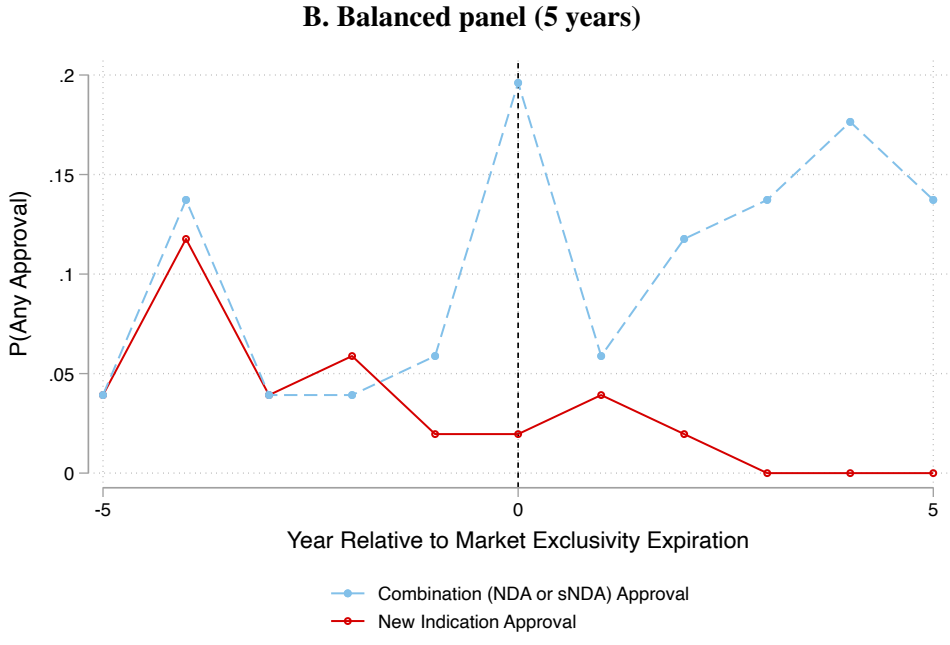
Figure A9: Research Investments, Calendar Time



Notes: Panel A plots the average number of scientific publications published in each relative year for the sample of innovator drugs defined in Section 4.5 in calendar time. Panel B plots the probability of any active clinical trial in each relative year for the sample of innovator drugs defined in Section 4.5 ($N = 990$) in calendar time.

Figure A10: Combination Approvals





Notes: Figure plots two measures of FDA approvals for a subset of innovator drugs with a single active moiety. We restrict consideration to the set of single-moiety innovator drugs that ever appear in a combination drug ($N = 140$). Market exclusivity expiration dates are defined as the earlier of two events: expiration of all patents and regulatory exclusivities linked to the innovator drug in the FDA's Orange Book, or FDA approval of a generic drug with an identical set of active moieties. Panel A shows the probability of re-approval for a new indication for the twenty years preceding and following exclusivity expiration for all drugs in our sample. Panel B takes a balanced panel approach, including only those drugs that can be observed for a full five years before and after market exclusivity expiration.