Policy Incentives for Pharmaceutical Innovation*

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Abstract

Pharmaceutical firms' incentives to develop new drugs stem from expected profitability. We explore how policies that shape these expectations influence pharmaceutical innovation. First, we estimate the effects of extending market exclusivity for antibiotics, a drug class where private returns to development historically had not internalized the high social value of new innovation. Using a difference-in-differences approach leveraging implementation of legislation that approximately doubled the market exclusivity period for certain antibiotics, we find that the policy increased innovative activity at multiple stages of drug development, from patenting to preclinical activity to phase 3 clinical trials. Building on these empirical findings, we calibrate a structural model of firms' drug development decisions to generalize our findings beyond antibiotics. We simulate counterfactual policies (exclusivity extensions and price controls), highlighting how differences in average market size and revenue timing shape policy effectiveness across therapeutic areas.

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1 Introduction

Pharmaceutical innovation has led to significant decreases in mortality and morbidity (Dunn et al., 2022), accounting for over one-third of life expectancy gains between 1990 and 2015 (Buxbaum et al., 2020). However, the development of drug candidates into marketable products requires significant investments in R&D, primarily funded by private investment within pharmaceutical companies (DiMasi et al., 2016). To encourage innovation, private investment in drug development is rewarded with statutory monopolies in the form of patents and market exclusivity periods, which trade off static inefficiencies from market power for long-term gains through innovation (Finkelstein, 2004).

In this paper, we take two approaches to study how policies that alter market size affect drug innovation. First, we evaluate the effects of extending market exclusivity on innovation for antibiotics, a drug class where private returns to development historically had not internalized the high social value of new drugs in combating antibiotic resistance (Årdal et al., 2019; Outterson et al., 2015). Second, we calibrate a structural model of firms' drug development decisions on data across a wider set of therapeutic areas to simulate how effectively different counterfactual policies can stimulate innovation for different therapeutic areas.

Our empirical analysis of antibiotics leverages the Generating Antibiotic Incentives Now (GAIN) Act, legislation addressing growing concerns over antibiotic resistance. The GAIN Act, first introduced in Congress in 2010 and enacted in 2012, extended the market exclusivity period for certain "Qualified Infectious Disease Products" (QIDPs) by an additional five years, a significant extension given the baseline exclusivity period of five years.[1] Market exclusivities granted by the U.S. Food and Drug Administration (FDA) represent an important policy lever and subject of study: while patent lengths have remained more or less constant over time, FDA exclusivities have been modified to achieve innovation objectives, such as increasing innovation in therapeutic areas with low private returns relative to social value (e.g., pediatric exclusivity and orphan drug exclusivity).

We estimate the causal effects of the GAIN Act using a difference-in-differences approach, with identification hinging on the law's specific criteria for QIDP designation. The GAIN Act only granted additional exclusivity to small-molecule antibiotic and antifungal drugs, but not other infectious disease products like antivirals and vaccines.[2] Accordingly, our

[1] This refers to the five years of exclusivity granted to New Chemical Entities (NCEs). Orphan Drugs are granted seven years, whereas drugs containing a previously approved active ingredient(s) may only obtain three years.

[2] The eligibility restriction to small-molecule products implies that even vaccines targeting prevention of bacterial or fungal illnesses do not qualify for QIDP designation.

analysis compares innovation before and after the GAIN Act for antibiotic and antifungal drug candidates (treated group) versus antivirals and vaccines (control group). We explore the effects across a variety of innovation-related outcomes. We also explore how market exclusivity interacts with patent exclusivity in affecting outcomes.

We use data from *Cortellis*, a comprehensive source for development milestones and related patenting activity for drugs in development. This allows us to estimate the GAIN Act's impact on a range of outcomes, including: patent filings, preclinical studies, phase 1 through phase 3 clinical trials, and U.S. market launch. The breadth of our outcome variables allows us to capture innovation regardless of whether the innovation has directly led to a newly approved drug by the end of our analysis window, which helps to account for the long timelines typical of drug development and reflects our belief that innovation related to eventual "failed" drugs could have positive social value in terms of knowledge spillovers or future repurposing.[3]

We find that the GAIN Act partially reversed a decades-long decline in antibiotic innovation, implying that market exclusivity policies can increase innovation, even in areas believed to have limited market potential. We find large effects at many stages, including a nearly 50 percent increase in patents and a delayed, but statistically significant, 33 percent increase in preclinical studies, suggesting an eventual increase in the number of antibiotics entering the development pipeline. We also estimate an approximately 85 percent increase in phase 3 trial initiations among drugs in clinical development, indicating drugs moving deeper through the pipeline. Consistent with our interpretation that these effects are caused by the expansion in expected market size for treated indications post-GAIN Act, we find larger effects for drugs with older, but not yet expired patents; these drugs are more dependent on market exclusivity to protect revenues and point to the important interactions between different policies that independently influence market expectations.

Building on our empirical results, we then estimate a structural model of firms' drug development decisions as a function of market size on a range of therapeutic areas. We adapt and extend a model in development at the Congressional Budget Office (CBO) that in recent years has been used to predict the effect of the 2022 Inflation Reduction Act's (IRA) drug price negotiation provisions on drug innovation (Adams, 2021, 2025). This broader framework allows us to generalize our findings beyond antibiotics and consider alternative policy approaches to stimulating innovation.

The model emphasizes how counterfactual policies have different implications for changes

[3]One example of a "failed" drug having important future uses is the COVID-19 drug Paxlovid (nirmatrelvir/ritonavir), which was developed starting in 2020 based on an investigational compound for SARS created in 2003 that never made it to market. See https://cen.acs.org/pharmaceuticals/drug-discovery/How-Pfizer-scientists-transformed-an-old-drug-lead-into-a-COVID-19-antiviral/100/i3.

in market size depending on two dimensions: average market size and revenue timing for each therapeutic area. We consider extending FDA exclusivity terms (akin to the GAIN Act) and price controls (like in the IRA). Comparing outcomes between different counterfactual policies and between therapeutic areas helps to demonstrate that the precise timing of when policy-driven market expansion kicks in matters, even holding discounted lifetime revenue expectations constant.

This paper contributes to our understanding of the economics of antibiotics, adding insights on innovation to a small literature on utilization and diffusion (Adda, 2020; Alsan et al., 2021). A closely related paper, Majewska (2022), also finds large, positive effects of the GAIN Act on clinical trials.[4] Additionally, we offer complementary evidence for effects on patenting and preclinical activity and evidence of heterogeneous effects related to patent exclusivity. Understanding innovation incentives for antibiotics could also translate to other therapeutic areas with tremendous social value and limited private value, like neglected diseases (Gans and Ridley, 2013; Ridley et al., 2021).

On drug innovation more broadly, our paper relates to an extensive prior literature on the effects of expanding expected market size on innovation (Acemoglu and Linn, 2004; Blume-Kohout and Sood, 2013; Dubois et al., 2015; Finkelstein, 2004). Policies that affect market size are important levers for policymakers, though alternative approaches like direct grants for R&D (Howell, 2017) exist. Policies that directly influence expected revenue, such as advance market commitments, are closely related but remain rare in practice (Kremer et al., 2020).

In the U.S. context, the GAIN Act exists alongside a small number of policy interventions that dramatically changed market size for certain types of drugs, including major coverage expansions like the establishment of Medicare Part D in 2003 or the Orphan Drug Act in 1983 (Yin, 2008). The limited number of empirical settings suitable for quasi-experimental approaches motivates our complementary structural analysis that facilitates comparisons of counterfactual policies across a range of therapeutic areas.

Beyond the setting of prescription drugs, our paper relates to classic questions within economics on innovation more generally. Given the importance of innovation in increasing productivity across many industries other than health care, a longstanding question within economics has been the optimal design of intellectual property protection in terms of both patent length (Nordhaus, 1969; Scherer, 1972) and scope (Matutes et al., 1996). In the setting of pharmaceuticals, the FDA influences both length (via market exclusivities) and scope (via different exclusivity categories based on drug characteristics). Innovation effects are

[4]Differences in reduced form analyses between this paper and Majewska (2022) stem from a combination of differences in data sources, construction of the empirical sample, and treatment definition.

also important in other health care settings where prices are wholly or partially regulated. For example, in the market for durable medical equipment, Medicare price reductions led to reductions in innovation that may fully offset savings (Ji and Rogers, 2024).

The rest of the paper proceeds as follows: Section 2 offers relevant background on drug development, policies influencing market size, and antibiotics. Sections 3 and 4 cover our analysis of antibiotics innovation. Section 5 introduces a stylized model of drug development and describes the model estimation procedure, whose results and counterfactual analyses are presented in Section 6.

2 Background

2.1 Drug Development and Protection via Patents and FDA Exclusivity

This paper focuses on the development of pharmaceutical products as regulated by the U.S. Food and Drug Administration (FDA). This process begins with preclinical research, after which the firm can submit an Investigational New Drug application (IND) to the FDA. Once the IND is approved, the firm can commence clinical development, which entails completing a series of clinical trials in order to demonstrate safety and efficacy in human subjects.

Clinical development is a notoriously expensive and risky endeavor. The average length of time from Phase I to completion of Phase III trials is 10-11 years (BIO, 2021), with estimated costs per successfully approve drug ranging widely, but easily exceeding $1 billion (DiMasi et al., 2016; Schlander et al., 2021; Adams and Brantner, 2010), and only 10-15 percent of IND recipients eventually receiving final FDA approval (Schuhmacher et al., 2025).

Given the magnitude of upfront development costs, the high risk of failure, and the relatively low marginal cost for rivals to reproduce newly approved drugs, it must be that private returns to innovation are large enough to encourage entry. Firms heavily rely upon statutory exclusivities that allow monopoly pricing for some period of time before generic or biosimilar competitors are allowed to enter the market. The exact implementations of these exclusivities have important consequences on a drug candidate's market size conditional on approval.

We refer to the two types of exclusivities as "patent" and "market". The lengths of a drug's patent exclusivity and market exclusivity are not dependent on one another, and while two types of exclusivities typically run concurrently for some overlapping period of time, often only one type of exclusivity is needed to preclude entry of perfect substitutes in generic

drugs.[5]

For the purposes of this project, there are two key differences between patent and market exclusivity. First, institutional jurisdiction and term length. Patents are granted by the US Patent and Trademark Office, which oversees patents across a wide variety of industries, and last 20 years. Firms typically receive patents well before FDA approval, leading to heterogeneity across drugs in effective patent life remaining *at the time of approval*. In contrast, market exclusivity is granted by the FDA and begins at the time of FDA approval. New drugs receive five years of market exclusivity, while existing drugs with new clinical applications receive three years of exclusivity. There is limited variation in market exclusivity lengths based on type of drug, with orphan drugs (seven years total), drugs with pediatric indications (additional six months), and QIDPs (additional five years) receiving additional exclusivity.[6]

The second difference is in the robustness of the protection. Patents can be challenged and nullified in court, leading some generics to enter earlier than original patent terms would suggest. Also, many listed patents that do not claim specific products or substances can be circumvented if generic manufacturers can create bioequivalent products without infringing upon active patents. In contrast, FDA exclusivity cannot be shortened through legal challenges from potential rivals. However, firms can strategically patent in order to lengthen the expected length of patent exclusivity, including creation of "patent thickets" to delay competitive entry (Galasso and Schankerman, 2010; Byrski and Wang, 2025). In contrast, firms cannot obtain additional market exclusivities for a drug already approved for a given indication.

In summary, while both patents and market exclusivity establish statutory monopolies key to encouraging private entry, they represent distinct policies. The importance of patent exclusivity for pharmaceutical innovation has often been explored separate from market exclusivity (Budish et al., 2015; Gaessler and Wagner, 2018; Kyle and McGahan, 2012; Wang, 2022; Cockburn et al., 2016; Bloom et al., 2019). However, the interaction between these two forms of protection may dictate how specific policies affect market size.

[5]This section primarily describes small-molecule drugs, as generics are considered perfect substitutes for branded drugs and are treated as such by policies like auto-substitution laws. In contrast, biologic drugs and biosimilars not considered perfect substitutes. The closest analogue would be interchangeable biosimilars, which can be automatically substituted for their branded reference product in only some states. The GAIN Act only applies to small-molecule drugs. https://www.fda.gov/drugs/things-know-about/9-things-know-about-biosimilars-and-interchangeable-biosimilars

[6]Exclusivities protecting newly approved generic therapies also exist, with important implications for drug pricing. As the focus of this project is on innovation in the form of new branded drugs, we only list exclusivities relevant for New Drug Applications.

2.2 Antibiotics Innovation and the GAIN Act

Antibiotics provide a clear example of how policies affecting market exclusivity have been deployed to encourage more innovation in clinical areas where the social value of new drugs may exceed their private value, leading to suboptimal levels of innovation.

In 1900, prior to the advent of antibiotics, infections caused 46% of *all* deaths (Armstrong et al., 1999; Gordon, 1953). By 1996, infectious disease mortality had dropped by 93%, due in part to the discovery and use of penicillin and sulfa antibiotics (Alsan et al., 2021; Armstrong et al., 1999; Jayachandran et al., 2010). Antibiotics have become a staple of modern medicine, but the rise of antibiotic resistance threatens a return to a pre-antibiotic era (Baker, 2015). Each year, antibiotic resistance is associated with 2.8 million infections and over 35,000 deaths in the United States (US Centers for Disease Control and Prevention, 2019) and 1.27 million deaths globally (Murray et al., 2022). The continuous invention of new antibiotics has preserved our ability to treat most infections. Unfortunately, the rate of antibiotic innovation has stagnated in recent decades (Deak et al., 2016; Luepke et al., 2017; Wellcome Trust, 2020).

The simultaneous trends of increasing resistance and declining pharmaceutical investment raise the question of why the pharmaceutical industry develops so few new antibiotics despite high social need (Årdal et al., 2019; Outterson et al., 2015). One likely explanation is a lack of marketability for new antibiotics: novel antibiotics are often kept "in reserve," and many public health guidelines emphasize reductions in "inappropriate" antibiotic use (Centers for Disease Control and Prevention, 2014). These restrictions on use may limit the return on investment for antibiotics (Outterson et al., 2015).

The GAIN Act emerged against the backdrop of many large pharmaceutical firms terminating or withdrawing entire antibiotic pipelines (Koba, 2013; Plackett, 2020). After Pfizer shut down its main antibiotic research facility in 2011, the company's vice president of clinical research cited low financial returns as one of the decisive factors underlying the closure:

> "We were not having scientific success, there was no clear regulatory pathway forward, and the return on any innovation did not appear to be something that would support that program going forward."[7]

To increase incentives to develop new antibiotics, Congress introduced the GAIN Act in September 2010 and signed it into law in July 2012, immediately generating interest among infectious disease physicians (Infectious Diseases Society of America, 2011).

The GAIN Act adds five additional years of market exclusivity for "Qualified Infectious Disease Products," defined as "an antibacterial or antifungal drug for human use intended to

[7] Dr. Charles Knirsch on FRONTLINE (Childress, 2013)

treat serious or life-threatening infections" (U.S. Food and Drug Administration, 2018). The length of this additional exclusivity is significant, doubling the five-year exclusivity period for newly approved drugs.[8] By comparison, the Orphan Drug Act only extended exclusivity by two years. Despite its large effect on exclusivity, the GAIN Act's impact on innovation has not been causally studied.[9]

3 Empirical Approach

To estimate the effect of extending market exclusivity on antibiotics innovation, we take a difference-in-differences approach comparing various outcome measures for antibiotic and antifungal products (treated under the GAIN Act) compared to other infectious disease products (specifically, antivirals and vaccines), before and after the legislation.

Our choice of antiviral and vaccine products as a control group is a natural one, as both antibiotics and antivirals face similar demand shocks: see, for example, the co-occurrence of viral and bacterial pulmonary infections (Hament et al., 1999; Morris et al., 2017). On the other hand, antibiotics and antivirals have distinct scientific development processes, suggesting minimal supply-side spillovers that could bias our estimates: firms are unlikely to conduct both antiviral and antibiotic R&D within a single research group or with the same scientists. In our sample of clinical trials, 87 percent of originating firms are associated with only treatment or only control group drugs, and this increases to 93 percent when conditioning on drugs observed to reach at least phase 2 clinical trials (i.e., drugs observed in phase 2 or phase 3 trials or US launch).[10]

[8]Some drug products cannot qualify as NCEs and instead qualify for a shortened Clinical Investigation Exclusivity (CIE) period of three years based on conducting clinical trials for new indications, dosing regimens, or patient populations. In these cases, the GAIN Act represents an even larger proportional increase in market exclusivity length.

[9]Some descriptive work on the GAIN Act has characterized antibiotics innovation in the years since GAIN's passage as "disappointing" (Darrow and Kesselheim, 2020). The authors' arguments are largely supported by counts of new QIDPs with novel mechanisms of action. We believe that this narrower definition of innovative activity omits important advances like new combination drugs or existing drugs repurposed for new therapeutic indications.

[10]To account for the disproportionate size of a handful of large pharmaceutical companies in our sample relative to smaller biotechnology firms, we also weight by firm portfolio size (i.e., the total number of treatment and control drugs by firm) and find that 74 percent of drug candidates originate within a firm whose portfolio is at least 90 percent concentrated in either treatment or control drugs, also suggesting that any results are unlikely to be primarily driven by substitution between antiviral and antibiotic drug candidates within the same firm.

3.1 Data and Sample Definition

Our primary data source is the *Cortellis* Competitive Intelligence database from Clarivate Analytics (Clarivate Analytics, 2022). *Cortellis* combines information from various public sources (e.g., press releases, financial filings, FDA submissions and approvals, clinical trial registries) to create a database of patents and drug pipelines with a timeline of the clinical trial development history for each drug. Importantly, the data contain non-clinical outcomes like patents and include drug candidates that never advanced beyond preclinical studies, allowing us to calculate a broad range of innovation-related outcome measures even for "unsuccessful" drug candidates.

We systematically extracted the universe of drugs and patents in *Cortellis*. We restrict to patent filings and drugs with any development milestone occurring between 2005 and 2019, allowing us to observe six years of pre-GAIN trends and to exclude the COVID-19 pandemic beginning in 2020. We further restrict to observations with any associated indication under the "Infectious Disease" therapeutic area, which encompasses all bacterial, fungal, and viral infections.[11]

Cortellis contains other patent- and drug-level variables that we use in subsequent analyses, including firm originator name, associated patent identifiers and patent type classifications, and special regulatory designations (including QIDP designation).[12] To measure exclusivity periods for FDA-approved drugs, we use patent and market exclusivity data from the FDA Orange Book database (U.S. Food and Drug Administration, 1996).

3.2 Treatment Assignment and Key Outcome Measures

After extracting all drug candidates and patents within the Infectious Disease therapeutic area, we assign drugs and patents to either the treatment or control group based on medical indications and vaccine/non-vaccine product type. Drug candidates and patents with antibiotic or antifungal indications (eligible for exclusivity extensions through GAIN) form our treatment group, while those with antiviral indications and antibacterial vaccines (non-eligible) form our control group.

We verified that our treatment group of antibiotics[13] includes 110 of the 114 QIDPs in

[11] *Cortellis* classifies each indication attached to a patent or drug candidate into mutually exclusive and exhaustive therapeutic areas (e.g., the indication for "Strep Throat" falls within the Infectious Disease therapeutic area).

[12] The QIDP designation is granted on a case-by-case basis by the FDA, typically before or when a firm submits its drug candidate for final marketing approval. More information on the designation can be found at U.S. Food and Drug Administration (2021).

[13] For simplicity, we henceforth use the term "antibiotics" to refer to all treated indications under the GAIN Act, which includes non-vaccine antibiotics as well as antifungals.

our dataset, compared to only 1 QIDP in our control group (Table 1).[14] This demonstrates that defining treatment and control groups based on indications captures nearly all drug candidates that eventually receive QIDP designation. By not explicitly conditioning on QIDP designation, we avoid confounding from unobservable factors correlated with both receipt of QIDP status (which requires sponsors to provide some initial data demonstrating the drug's ability as an antibacterial or antifungal) and our outcomes. For example, drug candidates with unobservably high quality would be more likely to receive QIDP designation as well as progress through clinical trials.

In *Cortellis*, we observe the exact dates that a drug candidate achieves the following outcomes, which capture innovative activity at different stages of development. Our key outcomes of interest, ordered chronologically from earlier to later in the drug development timeline, are logged counts of: newly filed patents, preclinical studies, clinical trials (separately by phase 1, 2, and 3), and U.S. drug launches. We aggregate these outcomes to the yearly level given typical drug development timelines. The timing of preclinical and clinical outcomes is based on the listed study initiation date. Appendix A contains more details on outcome variables construction.

Drug candidates may accumulate multiple indications, but we count each candidate only once to avoid double counting the same drug. For preclinical and clinical milestones, we take the earliest date within our analysis window that the candidates achieves the milestone across all treatment or control indications. A small number of candidates with both treated and control indications are excluded from analysis.

3.3 Sample Characteristics

Table 1 below shows descriptive statistics for our full sample, which contains N = 1,473 drug candidates in the treatment group and N = 3,485 drug candidates in the control group.[15]

[14] There were 3 QIDPs that had both antibiotic and antiviral indications, which we excluded from our analysis. The single control group QIDP was for baloxavir marboxil, an influenza antiviral.

[15] This is after dropping drugs that can be classified into both groups (76 drugs) and cohorts prior to 1995 (174 drugs).

Table 1. Descriptive Statistics, 2005-2019

	Treatment	Control	Total
Total patent applications	26,589	27,157	53,746
Total unique drug candidates	1,473	3,485	4,958
Drugs with QIDP status	110	1	111
Oral dosage form	20%	16%	17%
Has matched patent	43%	41%	42%
Has product patent	18%	18%	18%
Private firm originator	81%	81%	81%
Orphan drug	9%	7%	7%

Notes: Table shows descriptive statistics for the full drug-level sample from 2005–2019. Treatment indications include antibiotics and antifungal indications, while control indications include antiviral indications and vaccine products.

Treatment drugs are well balanced on their patent-match rate (mitigating concerns that any patenting results may be driven by biased data construction from *Cortellis*), likelihood of having a product patent, and origination in the private sector.

3.4 Difference-in-Differences Specifications

Our main reduced form results use the difference-in-differences event study specification shown below in Equation (1). We consider 2011 as the first treatment year, since the GAIN Act was introduced in Congress in 2010.[16] Because our design has a single treatment timing (2011), our difference-in-difference estimates avoid recent concerns regarding heterogeneous treatment effects that apply to two-way fixed effects estimators (Baker et al., 2022; Roth et al., 2023).

Outcome variables (Y_{gt}) for each group g (treatment versus control) in year t include: ln(patent filings), ln(preclinical studies), and ln(clinical trial initiations) for phase 1, 2, and 3 trials separately.[17]

[16]The GAIN Act was originally introduced as H.R. 6331 on September 29, 2010, and later re-introduced as H.R. 2182 on June 15, 2011, and in the Senate as S. 1734 on October 19, 2011 (Generating Antibiotic Incentives Now Act, 2010, 2011*a*,*b*). Because firms' contemporaneous expectations included the probability that the bill would be passed in the future, we adopt 2011 as the first year that the GAIN Act may have had effects on firm expectations, despite the fact that the official signing of the bill occurred on July 9, 2012. The use of 2011 as our start year is consistent with the existence of policy briefs on the GAIN Act published by the Infectious Disease Society of America as early as February 15, 2011 (Infectious Diseases Society of America, 2011).

[17]Log-transforming outcome measures to express effects in percent terms is preferable given the large difference in pre-period innovation activity between treatment and control groups.

$$Y_{gt} = \sum_t \beta_t \times 1\{treated\}_g + \alpha_t + 1\{treated\}_g + \epsilon_{gt} \tag{1}$$

The coefficients of interest β_t represent the differences in outcome measures between treatment and control groups g in period t. α_t represent year fixed effects, and $1\{treated\}_g$ a pre-period treatment group fixed effect, which normalizes our outcome variables such that the β_t coefficients are calculated by taking the treatment-control difference in each year and further subtracting the average pre-period difference between the two groups. In order to obtain standard errors, we use a bootstrapping procedure.[18]

To compute an average treatment effect, we pool years within the pre- and post-periods, resulting in the Equation (2) specification. Here, the coefficients of interest $\tilde{\beta}$ represents the usual difference-in-differences effect, comparing the post-period of 2011—2019 to the pre-period of 2005—2010 by treatment and control groups.

$$Y_{gt} = \tilde{\beta} \times 1\{treated\}_g \times 1\{\ t \geq 2011\} + 1\{t \geq 2011\} + 1\{treated\}_g + \tilde{\epsilon}_{gt} \tag{2}$$

Phase Transition Specification: An alternative approach to estimating effects on the counts of clinical trial initiations for each phase of clinical trials would be to estimate phase transition rates i.e., the annual probability that a drug candidate already observed in some phase of development initiates a later phase trial, as seen below in Equations (3, event study) and (4, pooled). This outcome variable is frequently used in descriptive analyses of drug development,[19] and we can interpret resulting estimates as effects on the *probability of success* at a given point in the pipeline.

$$Y_{ict}^{k,k'} = \sum_{t \neq 2010} \gamma_t \times 1\{treated\}_i + \pi_c + \pi_c \times 1\{treated\}_i + \delta_i + \alpha_t + \alpha_g + \varepsilon_{it} \tag{3}$$

$$Y_{ict}^{k,k'} = \tilde{\gamma_t} \times 1\{treated\}_i \times 1\{\ t \geq 2011\} + 1\{\ t \geq 2011\} + \pi_c + \pi_c \times 1\{treated\}_i + \delta_i + \tilde{\alpha_t} + \tilde{\alpha_g} + \varepsilon_{it} \tag{4}$$

Here, $Y_{it}^{k,k'}$ is an indicator variable for whether drug i, which has already been observed in phase k of development, initiates phase k' in year t. We control for candidate cohort (π_c), defined as the first year the candidate appears in our sample, and interact cohort with

[18] We use a Bayesian bootstrap with 200 iterations to redraw samples of patent filings and drugs (for preclinical and clinical outcomes). The Bayesian approach (versus standard parametric approach) allows us to resample observations and avoid draws where the counts of patent filings or development milestones equals zero, which would result in an undefined logged value.

[19] See appendix G for examples.

treatment status. This accounts for the evolution of scientific knowledge over time.

The advantage of this approach is that it allows us to control for drug-specific variables or drug fixed effects (δ_i) for greater statistical power and to conduct heterogeneity analyses based on drug characteristics. Year (α_t) and group fixed effects (α_g) are again included.

To estimate heterogeneous treatment effects by drug characteristics, we use H_{it} to encode a dimension of heterogeneity (e.g., patent age). We estimate a version of Equations (3) and (4) where we interact all independent variables with H_{it}. We focus on dimensions of heterogeneity that are pre-determined relative to clinical trial decisions and also affect market expectations, namely patenting variables. We consider a binary indicator for having a product patent (taking these to represent more novel innovation compared to drugs with only non-product patent types)[20] and youngest patent age in year t.[21]

4 Effect of the GAIN Act on Antibiotics Innovation

4.1 Effects on Patenting and Preclinical Activity

Patents have often been used as a proxy for innovation, as firms can only receive patents for "useful, novel, and non-obvious" inventions (Nagaoka et al., 2010). On one hand, increased patenting may reflect more investment in basic science research on antibiotics, which could lead to more new drugs in the long run. On the other hand, firms may simply be patenting a higher fraction of existing ideas. Either way, an increase in antibiotic patents would reflect a higher expected profitability of antibiotics, which would likely induce additional R&D investment in the long run.

We find that the introduction of the GAIN Act is associated with a significant rise in treatment patents compared to control patents. Figure 1 compares the logged number of newly filed patents between the treatment versus control group from 2005 through 2019. Panel A plots raw trends by group, while Panel B plots estimates from Equation (1), with 95% confidence intervals obtained via bootstrapping. Reassuringly, there is no statistically significant pre-trend prior to the introduction of the GAIN Act, supporting the necessary parallel trends assumption. Immediately after the GAIN Act is introduced, we observe a sharp increase in antibiotic (treatment group) patents filings relative to the control group. Even though the treatment group's pre-GAIN patenting level started below that of the control

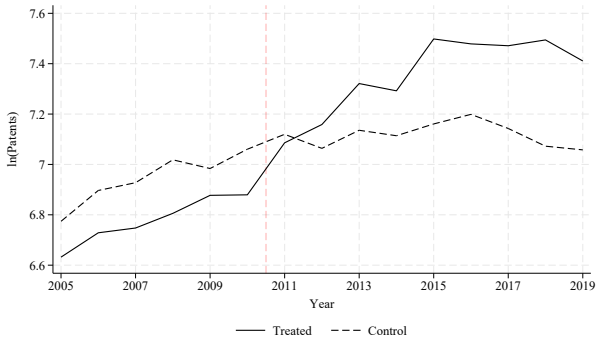
[20]For patent type, we partitioned patents into four categories: product, diagnostic, biologic, and ancillary. The classification of patent types is defined and coded by *Cortellis*. Categories include: product, diagnostic, biologic, combination, formulation, new use, and process. We define ancillary to include combination, formulation, new use, and process patents.

[21]For drugs with multiple associated patents, we consider the age of the youngest patent i.e., the patent with the latest expiration date.

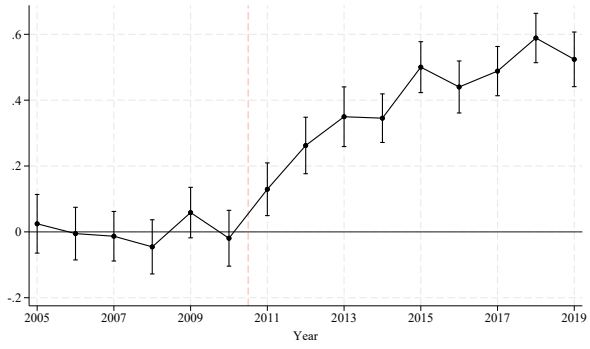
group, it surpassed the control group by 2012. The average effect represents a 47 percent increase in patenting (Appendix Table A2, Column 1). Average effects, effects reported by patent type and patent originator, and a falsification test using patent types unaffected by the GAIN Act's provisions are available in Appendix B.

Figure 1. Effect of the GAIN Act on Patenting Activity

A. Raw Trends in ln(Patent Filings)



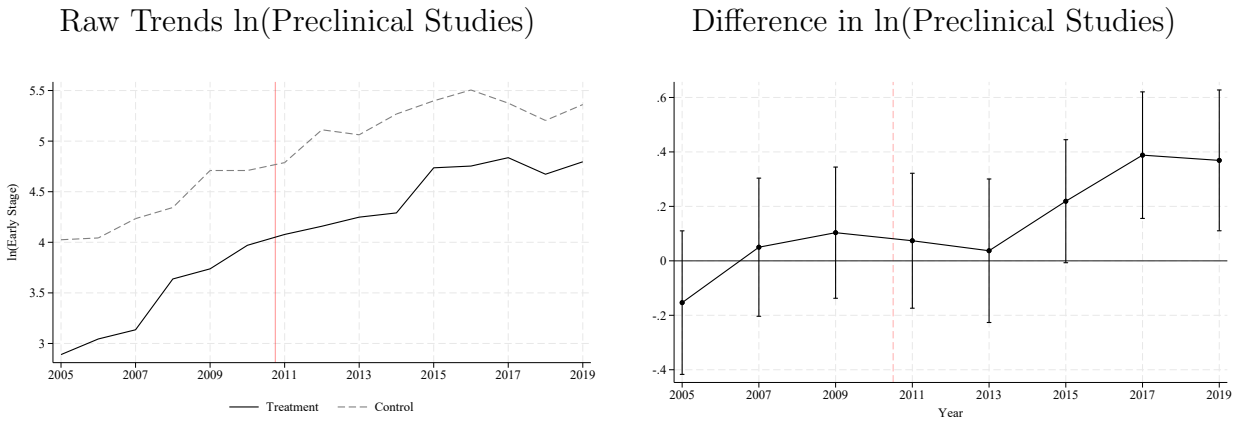
B. Difference in ln(Patent Filings)



Notes: Panel A shows raw trends in the number of patent applications by for both treatment and control groups. Panel B plots the estimated difference (Equation (1)) in the logged number of patents per year between treatment and control groups, with pre-period averages normalized to zero and confidence intervals obtained via Bayesian bootstrap. The timing of GAIN Act introduction is indicated by the dashed vertical line.

After patents, preclinical activity is the earliest indication that a firm is considering development of a new drug product or repurposing an existing product for new indications. Figure 2 below plots the difference in logged preclinical studies between treatment and control, estimated using Equation (1), with 95% confidence intervals obtained via bootstrapping. Again, pre-period trends are quite flat. We observe a delayed uptick in new preclinical studies beginning in 2015 and increasing to about 33 percent in 2019. The delay could be duein part to the time needed for patent application approval if the new preclinical studies stem from discoveries covered by the new patents. Due to the delayed response, the aggregate pre- versus post- comparison is not significant (Appendix Table A6, Column 1).

Figure 2. Effect of the GAIN Act on Patenting Activity



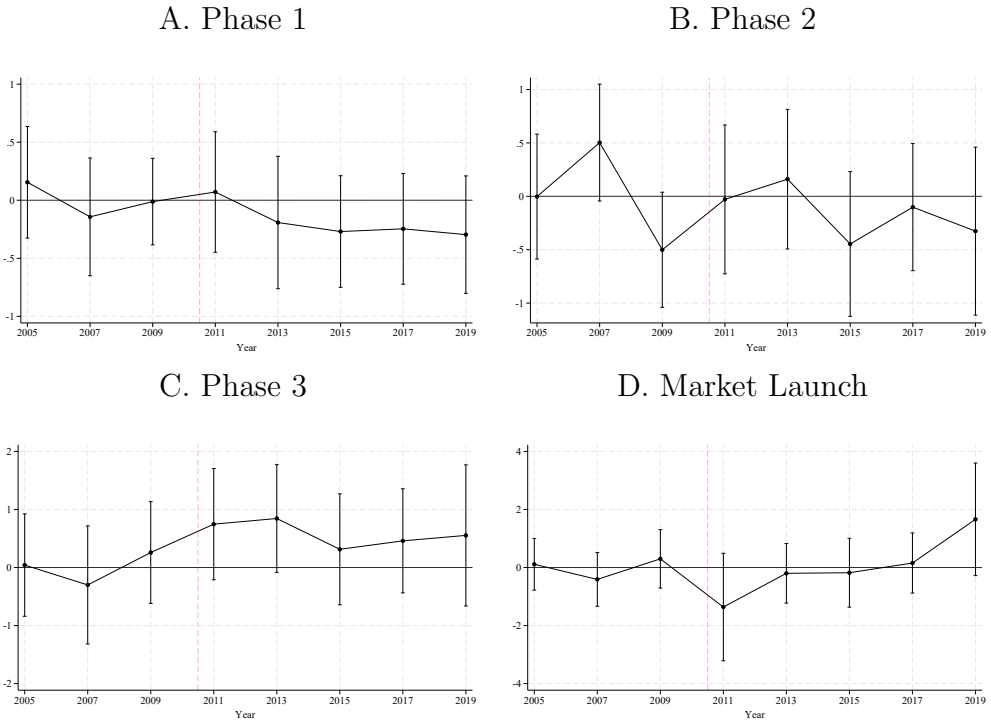
Notes: Panel A shows raw trends in the number of preclinical studies per year for both treatment and control groups. Panel B plots the estimated difference (Equation (1)) in the logged number of patents per year between treatment and control groups, with pre-period averages normalized to zero and confidence intervals obtained via Bayesian bootstrap. The timing of GAIN Act introduction is indicated by the dashed vertical line.

4.2 Effects on Number of Clinical Trial Initiations

Next, we examine effects on clinical trial initiations, separately by phase, and drug launch in the U.S. market. As we progress from phase 1 to launch, outcomes become rarer and more sparse, contributing to the increasing volatility displayed by the raw trends (available in Appendix C) and potentially lower power when it comes to estimating treatment effects. To partly account for this, outcomes are binned into two-year bins except for our final year of 2019.

Figure 3 shows the estimated differences in the logged number of initiations in the treatment versus control group, estimated via Equation (1), with 95% confidence intervals obtained via bootstrap. Though all phases are fairly noisy, most do not have visually appreciable effects, with the exception of an increase in the number of phase 3 trials. We estimate an 85 percent increase (significant at the 0.10 level) in the number of phase 3 trials. Full pooled estimates are reported in Appendix C.

Figure 3. Differences in Log Clinical Trial Initiations by Phase



Notes: Figure shows estimated differences (Equation (1)) in the logged number of trials for treatment versus control groups of drug candidates at each phase transition. Given data quality, sample inclusion is conditional on being observed in the prior phase. (More details available in Appendix C.) The control group average has been normalized to have the same pre-period mean as the treatment group. Confidence intervals obtained via bootstrap. The timing of GAIN Act introduction is indicated by the dashed vertical line. Data are binned into two-year bins except for 2019, which contains one year.

4.3 Heterogeneity by Patent Characteristics

As described in Section 3, taking a drug-level approach and estimating Equation (4) allows us to conduct better powered analyses that can control for or explore drug-level characteristics. Results from the alternative specification using phase transition probabilities as the outcome variable are reported in Appendix C.3. They confirm the results described in the previous section. We find no significant results for all phase transitions except the probability of transitioning into phase 3, where we estimate an average increase of 4.9 pp (significant at the 0.05 level and representing a 94% increase over the pre-period mean) in the probability that a drug advances to phase 3 trials.

To assess what types of drugs appear to respond to the GAIN Act, we examine whether our estimated effects on phase 3 clinical trials differed based on patent characteristics, namely product versus non-product patent type and patent age.[22] We find larger effects from the

[22]Additional heterogeneity analyses by firm type and route of administration are available in Appendix H.

GAIN Act for drugs with product patents (9.8pp, SE=4.8pp) and drugs with patents between 10 and 20 years old, inclusive (18.4pp, SE = 5.8pp).

A major criticism of the GAIN Act and drug innovation policies more generally is that the marginal products may not represent novel or socially valuable innovations (Darrow and Kesselheim, 2020; Dranove et al., 2022). In the context of antibiotic resistance, less novel products may garner less demand. In contrast to the prevailing narrative, we find that drug candidates matched to a product patent (which we consider to be more novel) had larger effects compared to those only matched to new use, combination, reformulation, or process patents. This finding is consistent with our other descriptive evidence on the novelty of recently approved antibiotics (see Appendix D) and with the GAIN Act's stated focus on novel antibiotics.[23]

The larger effects for drugs with patents between 10 and 20 years old suggests an inverted-U shape relating patent age to the value of market exclusivity extensions.[24] We expected smaller responses for drugs with young patents (< 10 years old), as GAIN exclusivity extensions are less likely to extend beyond patent exclusivity expiration for these candidates.

The smaller effects for drugs with expired patents (> 20 years old) may initially be surprising, since these drugs would rely entirely on market exclusivity to limit direct competition. In actuality, this likely reflects a selection process: drugs that do not initiate phase 3 trials within 20 years of patent life likely have limited market potential or other negative attributes (e.g., lackluster phase 1 or phase 2 trial results). Our results suggest that this negative selection effect outweighs the mechanical increase in expected revenue from the GAIN Act for drugs with expired patents.

4.4 Discussion of Empirical Results

We find that the GAIN Act increased patenting (by approximately 47 percent), preclinical studies with a delay (by approximately 33 percent, but confined to the last year of our sample), and phase 3 clinical trial activity (85 percent increase) for antibiotics.

The patenting and preclinical results could precede an increase in projects entering clinical development. However, we do not detect any such increase in phase 1 trials. This could be due to timing: the observed increase in preclinical activity occurs only in the last year of our analysis window. We are wary of extending our analysis past 2019 due to how the Covid-19

[23]Interestingly, while effects are larger for drugs with product patents, effects on product patent filings themselves (Appendix B) are not as large as other patent types. This may reflect firms' desire to focus on novel products already in trials versus those at the patent stage, or it may reflect challenges with generating new product patents.

[24]Only 4.5% of drugs with patent information have multiple patents listed. For these drugs, we select the oldest patent listed.

pandemic in 2020 disrupted pharmaceutical research more generally, but research on viral diseases in our control group in particular.

The quick response of phase 3 trial initiations (beginning in the first year following enactment), combined with no commensurate increases at earlier stages of clinical development suggests a few possible narratives. These phase 3 trials could represent antibiotic projects already in development, but stalled or even previously discontinued around phase 2 trials due to limited market expectations. The GAIN Act then encourages the firm to resume the project. Alternatively, a firm could take a drug already approved for other non-QIDP indications and attempt to repurpose it (typically allowing it to bypass phase 1 and potentially expedite phase 2) for a new indication or reformulate it and and apply for GAIN exclusivity, as was the case with an intravenous version of fosfomycin.[25]

Finally, the drug-level heterogeneity analysis on phase 3 initiations reveals that drugs with product patents (an indicator of novelty and potentially higher market demand) and relatively older patents (indicating shorter potential protection via patents) drive the increase in phase 3 trials. These results provide support for the internal validity of our research design and highlight how FDA and patent policy intersect.

Our estimated effects are meaningfully large. To compare our findings to prior estimates in the literature, we can translate our results into an elasticity of innovation with respect to revenue. For this exercise, we focus on the transition to phase 3 clinical trial results.[26] We compute revenue elasticities in the range of 2.6 to 3.4 (Appendix Section E). These elasticity values are consistent with the prior literature on revenue elasticities of drug innovation, albeit on the larger end of the range. For comparison, Acemoglu and Linn (2004) find elasticities of about 4, Finkelstein (2004) finds elasticities of 2.75 for vaccines, and Dubois et al. (2015) finds an elasticity of 0.23, although this latter estimate is based on new molecular entities, which are a subset of all new drugs. Comparing elasticities across these references is challenging as they span a range of therapeutic areas and time periods.

The limited private incentives to develop antibiotics prior to the GAIN Act may rationalize the larger magnitude of our estimates relative to other therapeutic areas. Antibiotics are

[25]Oral fosfomycin was first approved for use in the U.S. in 1996 to treat urinary tract infections. An intravenous version has been approved in some European countries and Japan since the 1970s, with use against multi-drug resistant bacteria increasing in recent years, but was never developed for the U.S. In 2013, a startup named Zavante began developing an IV fosfomycin product, with the company CEO attributing development to the GAIN Act, saying "Fosfomycin became of interest as antibiotic resistance increased, but it only had three years of patent protection. We saw the opportunity through the GAIN Act, and its incentives, including additional exclusivity, to bring a novel class of drug to patients. Its development wouldn't have been possible without [the GAIN Act]." https://www.biopharmadive.com/news/gain-act-gives-zavante-a-shot-at-new-antibiotic-development/439877/

[26]While this likely underestimates the total effect of the GAIN Act, it avoids assumptions about how to incorporate the earlier-stage effects of additional patents and pre-clinical studies.

unique in that recommended utilization practices, like holding new antibiotics "in reserve," may lead to artificially low private innovation incentives (Hamad, 2010). This lower baseline level of antibiotic innovation might mean that modest additional investment yields a sizable increase in innovative output.

Our results also demonstrate the long timelines of drug development, and the importance of exploring shorter-run outcomes (e.g., patent filings) alongside longer-run outcomes (e.g., phase 3 trials or market launches). In ending our analysis window at 2019 to avoid confounding issues with the Covid-19 pandemic, we are not able to say whether the increases in patent filings and preclinical studies ultimately led to a sustained increased in the number of new antibiotics approved each year.

Taken together, our results offer an optimism about the potential for exclusivity extensions to stimulate innovation in areas where existing private incentives may not be sufficient to generate socially desirable levels of innovation. This success may also translate to other pull mechanisms, including some newer incentive structures that have gained traction in the years since our analysis. For example, England's National Health System in 2019 implemented a subscription-style model (NHS England, n.d.), and legislation outlining a similar model in the United States, the PASTEUR Act, has been proposed multiple times in Congress since 2020 (Doyle, 2020; PASTEUR Act, 2023).[27]

That said, over a decade after the GAIN Act's passage, some industry experts still consider antibiotics as a field to be generally unprofitable, as evidenced by the ongoing bankruptcies of antibiotic developers (Mosbergen, 2023). The challenge of rising antibiotic resistance highlights the importance of further research into what further policies may be able to stimulate the pipeline for new antibiotics.

Next, we introduce a stylized model of drug development that captures the incentives to innovate due to market expansion generated by the GAIN Act and guides the structural analyses and counterfactual policy proposals that follow.

5 Model

5.1 Market Size and Development Decisions

I propose a model where pharmaceutical firms decide whether or not to develop potential preclinical drug candidates based on the candidate's expected development cost and expected

[27] On the push mechanism side, CARB-X, a non-profit funded by various international governments and foundations, selects a group of antibiotics candidates to fund directly (CARB-X, n.d.) and could provide an interesting comparison to the pull mechanisms listed above.

revenue conditional on FDA approval. Revenue is affected in part by policies, like the GAIN Act, that influence when generic competition enters.

An approved drug's lifetime on the market consists of two phases. During the earlier protected phase, the firm's profits are protected by statutory monopolies (patents and market exclusivities) and/or by positioning within a niche in product space. During the latter phase, the profits are competed away by the entrant of perfect substitutes (generics) or near substitutes (competitive obsolescence).

We express drug i's expected lifetime revenue conditional on approval (R_i), discounted relative to its approval date, as

$$R_i = \sum_{t=0}^{G_d-1} \delta^t r_i(t) + \sum_{G_d} \delta^t g_d,$$

where d indexes therapeutic area, t indexes years since approval in $t = 0$, G_d represents the expected length of the protected phase, $r_i(t)$ represents annual revenue as a function of time, and g_d is some constant revenue stream following generic entry or obsolescence of the product. The discount factor, δ, is assumed constant across all firms and all therapeutic areas.

Reflecting what has been consistently observed since the generic approval process was formalized in the 1980s, we assume that $r_i(t) \gg g_d$ for all drugs in all therapeutic areas. Under this assumption, it becomes clear that the bulk of a drug's expected market size accrues during the earlier protected phase, with higher and less heavily discounted revenue streams.[28] Therefore, the value of G_d is an important determinant of a drug's market size.

Firms have some stock of preclinical candidates. They choose to develop a preclinical candidate and initiate clinical trials if and only if the expected NPV of the drug is positive:

$$-C_i + s_d \cdot \underbrace{\left(\sum_{t=0}^{G_d-1} \delta^t r_i(t) + \sum_{G_d} \delta^t g_d \right)}_{R_i} \geq 0. \tag{5}$$

C_i represents a fixed cost of development, which we assume is entirely sunk regardless of whether the drug is eventually approved. The probability of approval conditional on initiating development is given by s_d, which can be thought of as accounting for some exogenous therapeutic area-specific scientific failure rate that halts development for reasons entirely unrelated to cost or revenue expectations.

[28] Some biologics may prove an important exception to this assumption as some biosimilars exhibit much smaller price reductions relative to their reference products compared to generics for small-molecule drugs. For this reason, and certain data limitations specific to biologics, we restrict all further analyses to small-molecule drugs only.

From this simple framework, we can map various policies onto objects in the firm's development condition given by Equation (5). The GAIN Act weakly increases G for antibiotics. R&D subsidies, like the Orphan Drug Act's tax credits, reduce C. Coverage expansions, like Medicare Part D, increase r. Changing regulatory requirements needed for approval could affect both s (e.g., requiring "stronger" evidence to support drug approvals decreases s) and C (e.g., requiring longer trial observation periods increases C).

This model captures the natural intuition that extending market exclusivity (increasing G_d) for certain drugs should, on the margin, weakly increase the number of preclinical candidates entering the development pipeline and thus the number of newly approved therapeutics. However, whether the magnitude of this increase in innovation is economically meaningfully matters on other factors, like the level of pre-extension revenue at the current time of generic entry ($r_i(G_d)$) relative to development costs (C_i) and the riskiness of clinical research (s_d).

5.2 Estimation Overview

The aim of estimating this model is to recover the parameters underlying the distribution of expected revenue and expected development cost. Using these parameters, we can conduct counterfactuals that change market exclusivity terms or affect market size expectations in other ways.

The inherent challenge for calibrating the model is unobserved revenue and cost for the vast majority of drug candidates. Revenue data is necessarily unavailable for drugs that never receive FDA approval and launch in the U.S. market, and no regulation requires firms to report development costs. To surmount this, we impose some distributional assumptions on the revenue and cost distributions and use a simulated method of moments (SMM) approach based on the observed share of preclinical candidates initiating development, observed revenue of approved drugs, and survey data on development costs. This allows us to back out an initial distribution of (revenue, cost) draws that matches the moments observed in our data.

Our approach follows ongoing CBO work (Adams, 2021, 2025), with adaptations to emphasize differences across therapeutic areas and how revenue timing matters for policies affecting when market protections expire.

5.3 Assumptions and Timing of the Model

We assume that expected revenue (R_i) and expected cost (C_i) for candidate i in therapeutic area d are drawn from independent Gamma distributions, F_d^R and F_d^C, respectively. We choose this functional form for its positive support and flexibility in accommodating skewed data, as distributions for both observed revenue and development costs tend to exhibit right

skewness (DiMasi et al., 2016). Due to the limited availability of drug-level development cost data, we fix the shape parameter for F_d^C to be equal to 2, and test the sensitivity of our results against a range of other values.[29]

First, the firm draws expected revenue R_i and cost C_i values for its candidate. Next, it decides whether to initiate clinical development, based on its revenue and cost draws and other inputs listed in Equation (5). Conditional on the firm initiating development, some fraction $(1 - s_d)$ of the projects will fail. The surviving projects launch in the U.S. market and we observe their development costs and annual revenues. For all drugs, we assume that firm expectations are unbiased i.e., that approved drugs actual earn R_i in total discounted lifetime revenue and that development costs actually equal C_i.

For tractability, we collapse all phases of clinical development and do not explicitly model transitions between clinical trials.

5.4 Data Sources

The following data sources help us to calculate moments for our SMM procedure and to calibrate other model inputs (G_d, s_d).

Cortellis, as previously described in Section 3, allows us to identify preclinical candidates by therapeutic area. We follow these candidates over time to calculate the share of candidates that initiate clinical development, as well as the share of drugs initiating development that eventually launch in the U.S. (s_d).[30]

Evaluate Pharma provides annual U.S. sales data (by NDC, which we aggregate by FDA application number) from 1986 through 2024. Data is sourced from a combination of company press releases, presentations, annual reports, and analyst reports. This data is used to calculate the mean and variance of total lifetime sales (discounted relative to approval year) across drugs, by therapeutic area. For the entire analysis, we assume a constant discount rate of 0.086 (Damodaran, n.d.).

Very limited comprehensive drug-level cost data exists that is available to researchers, even in proprietary sources like *Cortellis* and *Evaluate Pharma*. We use available survey data published by the federal government (Office of the Assistant Secretary for Planning and Evaluation, 2014).[31] The report publishes average development costs by phase, originally sourced from *Medidata* around 2004. We inflate these values to 2024 dollars. As with all

[29] A shape parameter $\alpha = 2$ generates a right-skew distribution, with skewness decreasing as α increases.

[30] We restrict to projects that appear in *Cortellis* in 1994 or later to limit variation in regulatory environments.

[31] Other approaches that do not survey pharmaceutical firms have gleaned R&D costs from SEC reports (Wouters et al., 2020). This approach limits the scope to drugs originating from firms without multiple projects in development (typically smaller firms), as reported costs are not reported separately by project.

Summary of Model Inputs and Data Sources

Model Input	Available	Data Source
Pre-clinical ideas (drug-level)	1996-2024	Cortellis
Drugs in development (drug-level)	1996-2024	Cortellis
Revenue (drug-level)	1986-2024	Evaluate Pharma
Cost (therapeutic area-level)	Collected approx. 2004	ASPE survey
Drug characteristics and exclusivity	1938-2024	FDA

surveys, selective survey inclusion may limit generalizability. We use this data to construct mean development cost by therapeutic area.

Finally, publicly available data from the FDA allows us to merge on drug-level information, namely FDA approval date and expiration dates for all patent and market exclusivities attached to the drug application. Exclusivity expiration data come from the FDA Orange Book (which covers small-molecule products), but equivalent information is not available from the Purple Book (covering biologic products) for most of our study window.[32] As such, this portion of the analysis is restricted to small-molecule drugs, which still represent the majority share of new drug approvals, prescriptions, and (until 2023) drug expenditures in the United States (IQVIA, 2018, 2024).

5.5 Estimation Approach

Estimation involves two components. First, to estimate parameters underlying the expected revenue and expected development cost distributions, which sets the distribution of preclinical ideas in (revenue, cost) space. Second, to estimate annual revenue as a function of time on the market, which helps us calculate the predicted effect on lifetime revenue from changing exclusivity terms.

5.5.1 Estimating Expected Revenue and Cost Distribution Parameters

We take a simulated method of moments approach, where each of 2,000 simulations, in each therapeutic area d, draws N_d (determined from *Cortellis* data) preclinical candidates from initial distributions $F_d^R(\theta_0^R)$ and $F_d^C(\theta_0^C)$, and then simulates the firm development decisions and clinical development successes. The following moments are calculated for each simulation: (1) average revenue of approved drugs, (2) variance in revenue of approved drugs, (3) average cost to develop approved drugs, and (4) share of preclinical candidates initiating development.

[32]The Purple Book began listing patent data in 2021.

The simulated moment averages are compared to observed moments from data, and the optimization routine iterates.

5.5.2 Estimating Shape of Annual Revenue

Whereas the previous section helped us to calibrate distributions for R_i, now we look within that term and take a spline-based approach to estimating trends in annual revenue as a function of time ($r_i(t)$) using panel data of annual sales from *Evaluate Pharma*, as shown in Equation (6).

$$r_{idt} = f_d(t) + \beta^m 1\{t > E_i^m\} + \beta^p 1\{t > E_i^p\} + \alpha \cdot nrival_{it} + \epsilon_{idt}. \tag{6}$$

Our outcome variable, r_{idt}, has been normalized such that revenue in a drug's first full year on the market equals 100. This strips out level differences in market size in any given year across drugs, and helps us to isolate just the rate at which revenue is increasing or decreasing over time. We use a natural cubic spline specification and allow the spline to be estimated separately by therapeutic area ($f_d(t)$).

Two indicator variables, $1\{t > E_i^m\}$ and $1\{t > E_i^p\}$, capture when market exclusivity and patent exclusivity expire for a given drug, with E representing the year of expiration. Products can have multiple concurrent exclusivities (e.g., 5-year NCE exclusivity for initial FDA approval and 3-year NCI exclusuvity for follow-on indication approval, OR multiple patents), so we only use the latest expiration date.

We observe in the Orange Book data that many listed patents claim neither the drug substance nor the drug product. These likely represent "weaker" patents, or patents less likely to stand up to legal challenges from potential generic entrants. The phenomenon of firms choosing to list "junk" patents has been widely documented,[33] and we frequently observe generic entry prior to expiration of *all* listed patents. As such, we restrict our observations to only consider substance or product patents when constructing E_i^p.

To account for competition, we control for the number of other drugs (defined based on unique combinations of active ingredients) with the same ATC2 designation in that year ($nrival_{it}$). This helps account for how competition between different drugs may affect revenue.

5.5.3 Total Revenue Versus Revenue Timing

The distinction between the two estimation components (total revenue R_i and revenue timing $r_i(t)$) particularly matters when we consider policies that affect revenues at a particular point

[33] https://www.ftc.gov/news-events/news/press-releases/2024/04/ftc-expands-patent-listing-challenges-targeting-more-300-junk-listings-diabetes-weight-loss-asthma

in a drug's lifetime, as an exclusivity extension does. For example, the magnitude of incentive to develop a preclinical candidate under a new policy that extends exclusivity from five to ten years depends on how much revenue the candidate expects to earn between years 6 and 10 after market launch.

Many factors affect how a drug's lifetime revenue is distributed over time, like anticipated disease prevalence over time. Drugs to treat emergent conditions with expected declining incidence over time, like an infectious disease outbreak, will earn a larger share of their total revenues well before exclusivity expires, rendering exclusivity extensions less effective policy options to encourage more innovation. In contrast, a drug to treat a chronic autoimmune condition may have very stable sales over time, perhaps even increasing over time if the drug becomes approved for additional indications. More examples that compare and contrast drugs by total revenue and revenue timing are available in Appendix I.

6 Estimation Results and Counterfactuals

6.1 Estimates for Expected Revenue and Cost Distributions

Summary statistics on our expected revenue and cost distributions by therapeutic area as implied by our parameter estimates are presented in table 2, in descending order of mean revenue.

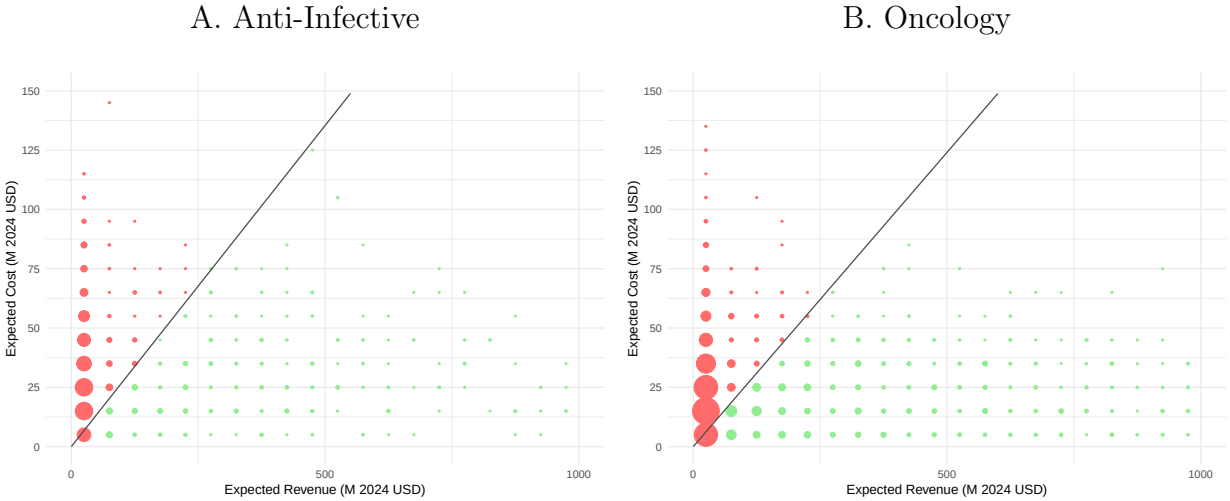
Table 2. Estimated Summary Statistics, by Therapeutic Area

Therapeutic Area	**Avg Revenue** *(std dev)* *M 2024 USD*	**Avg Cost** *M 2024 USD*
Hematology	228 (381)	62.5
Oncology	195 (417)	24.0
Immunomodulation	194 (530)	87.2
Central Nervous System	180 (399)	48.0
Endocrine	177 (394)	47.1
Gastrointestinal	174 (389)	16.2
Cardiovascular	166 (387)	24.1
Anti-Infective	155 (373)	32.5
Respiratory	149 (370)	19.6

A visual representation of the distribution of preclinical candidates in (revenue, cost) space demonstrates the high skewness of the revenue distribution. Figure 4 shows that the majority of ideas are located about the origin. While some of these ideas do get developed (due to very low development costs), the majority of developed drugs reside in the lower-right corner (higher revenue, lower cost) of the space.

Superimposing the firm's decision onto this space shows the threshold defining the marginally developed drugs. Extending exclusivity or implementing other policies that expand a firms' market size expectations will shift the distributions of preclinical candidates rightward, pushing more over candidates over the development threshold. Subsequently, the effect on innovation depends on the density of preclinical candidates to the left of the line.

Figure 4. Distribution of Preclinical Ideas Across Expected Revenue and Development Costs



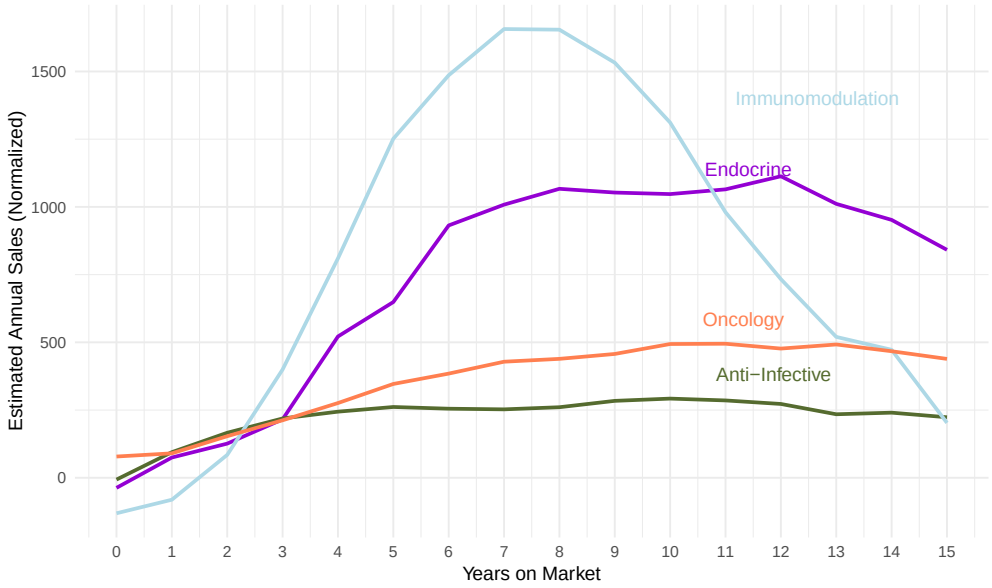
Notes: Each panel plots a binned distribution of preclinical candidates by expected revenue (x-axis) and expected development costs (y-axis) for separate therapeutic areas. Axes have been truncated for visual ease. Points are sized to reflect the number of preclinical candidates represented, and color coded according to the firm's development decision (green = develop, red = don't develop.) The threshold for development is superimiposed in black.

The next sections combine these results with the revenue timing estimates, allowing us to predict how much lifetime revenue changes with market exclusivity terms or other related policies and how much new drug development firms initiate as a result.

6.2 Estimates for Shape of Annual Revenue

Figure 5 plots average predicted revenue as a function of time from Equation (6) for each therapeutic area, normalized such that revenue in the drug's first full year on the market equals 100. We censor the plot at 15 years on the market due to sparsity of data past that point. We can see heterogeneity in how quickly annual revenues rise, peak annual revenues proportional to earlier years, and the speed of decline. We can also see similarities where large differences existed before: mean expected revenue for oncology preclinical candidates is 26 percent higher than for anti-infective candidates, but the two therapeutic areas exhibit similar trends in annual revenue.

Figure 5. Predicted (Normalized) Annual Revenue as Function of Time



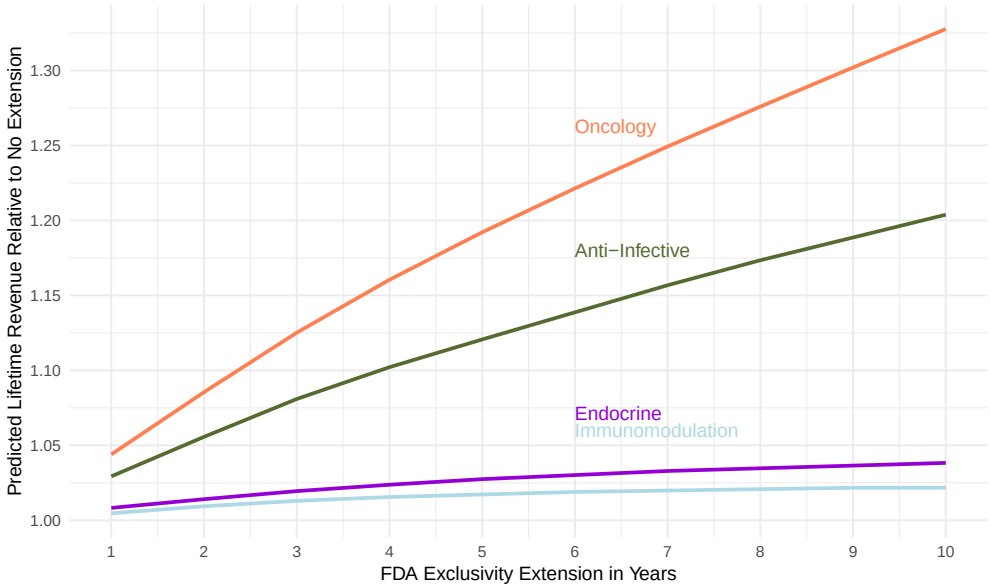
Notes: Figure plots average predicted annual revenue as a function of years on the market, separately by therapeutic areas. Values are normalized such a value of 100 represents revenue in a drug's first full year on the market. Predicted values below 100, especially in the early years, reflect boundary effects that remain after fixing end conditions to try to mitigate the phenomenon for a natural spline.

6.3 Counterfactual Exercises

6.3.1 Extending Market Exclusivity

Using estimates from Section 6.2, we calculate the change in predicted lifetime revenue from extending each drug's market exclusivity expiration by a fixed number of years. Predicted lifetime revenue with extended exclusivity (relative to predicted revenue with no extension) as a function of exclusivity extension length is plotted in Figure 6. An outcome value of 1 represents no change in predicted revenue.

Figure 6. Change in Predicted Revenue as Function of Market Exclusivity Extension



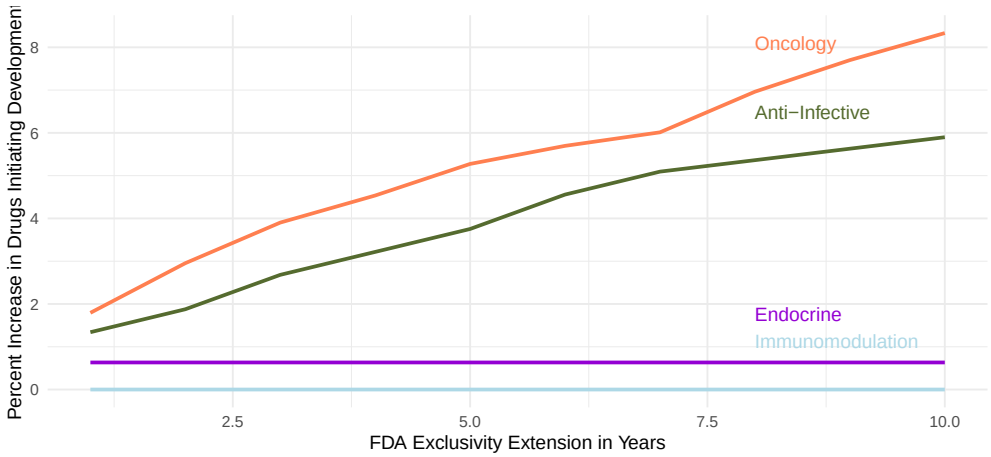
Notes: Figure plots average predicted lifetime revenue from a given market exclusivity extension (x-axis) relative to predicted revenue with no extension. An outcome value of 1 represents no change in predicted revenue.

As we expect, changes in predicted revenue move positively with exclusivity extension length. However, certain therapeutic areas benefit far more from each additional year of exclusivity. At just one additional year of market exclusivity, we predict oncology drugs to increase lifetime revenue by close to 5 percent. By five years (the length of the GAIN Act extension), we predict an approximately 12 percent increase in anti-infective revenues, nearly 20 percent for oncology, yet less than 4 percent for endocrine and immunomodulation drugs.

We combine these predictions with the estimated revenue and cost distribution parameters under the status quo. If we assume that all preclinical candidates would uniformly benefit from the average revenue increase following an X year market exclusivity extension, we can count the number or share of preclinical candidates on the margin of development that respond to the extension.

Figure 7 plots the percentage increase in number of preclinical candidates initiating clinical development as we add on additional years of market exclusivity. The percentage increases in oncology and anti-infective drugs entering clinical development imply rather large elasticities of innovation with respect to revenue. At the GAIN Act's five year extension mark, we estimate an elasticity around 3.3, in line with our back-of-the-envelope calculations using the reduced form results (Appendix E).

Figure 7. Predicted Increase in Drug Development Following Exclusivity Extension



Notes: Figure plots predicted percentage increase in number of preclinical ideas entering clinical development (relative to no exclusivity extension) as a function of exclusivity extensions.

We have assumed that preclinical candidates arrive exogenously i.e., that expanded market size does not induce discovery of more preclinical candidates. This assumption could be relaxed by introducing some correlation between market size and the number of preclinical discoveries made. This analysis, in treating the pool of preclinical candidates as fixed in relation to market expectations, would likely underestimate the effect of market expanding policies on innovation without accounting for the positive feedback between market expansion and discovery.

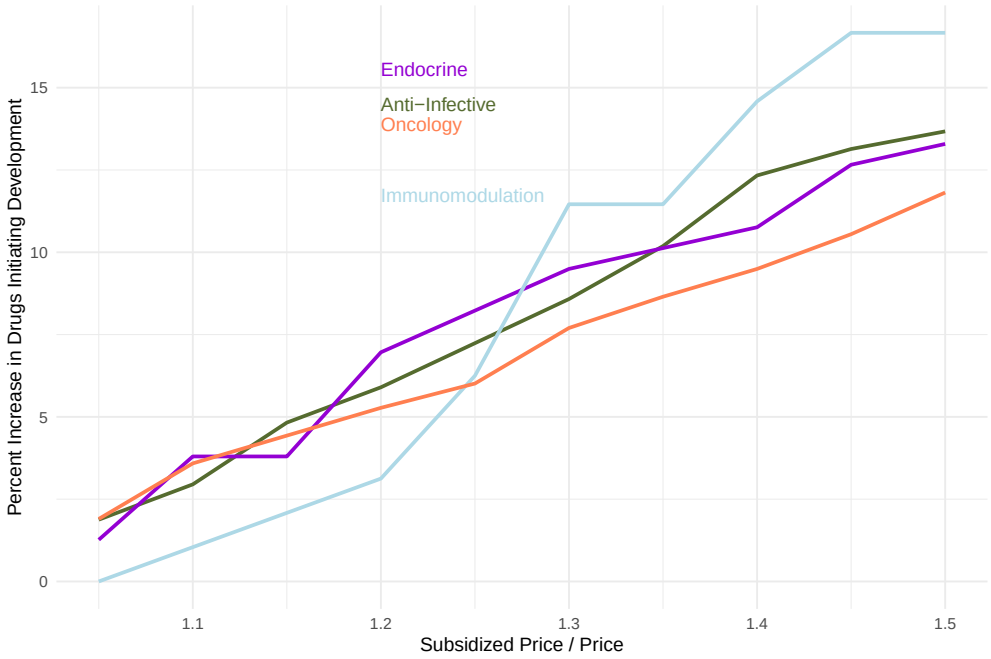
6.3.2 Price Controls

Direct price controls have been less common historically in U.S. drug policy, though have been incorporated as components of other policies intended to stimulate innovation. For example, advance purchase agreements or advance market commitments typically fix prices alongside volume guarantees. This was a component of the U.S. Covid-19 vaccine development response and has also been used to incentivize innovation or scale production in lower-income markets (Kremer et al., 2020; Socal and Anderson, 2021).

We consider two versions of a price control policy. The first is a price premium active from the drug's first year on the market, which we operationalize as increasing revenue each year by a certain fixed percentage. Unlike the market exclusivity extension, price premiums lead to a uniform increase in lifetime revenue across all drugs in all therapeutic areas. Japan's drug pricing system is a more targeted analog to this policy: certain drugs are awarded price premiums based on clinical value (e.g., high efficacy), local development (e.g., first launch in Japan), and indication type (e.g., orphan disease) (Trinity Life Sciences, 2024; Sun

et al., 2014). Compared to the exclusivity extension predictions, the predicted increase in development is more similar across all therapeutic areas with the uniform increase in lifetime revenue. This leads to more similar innovation responses across therapeutic areas, as seen in Figure 8.

Figure 8. Predicted Increase in Drug Development Under Price Premium



Notes: Figure plots predicted percentage increase in number of preclinical candidates (relative to zero price premium) entering clinical development as a function of price premium.

The second type of price control is an implicit tax for a set of high lifetime revenue drugs, a policy that weakens incentives to innovate but lowers drug expenditures. For this counterfactual, we loosely follow the structure of the price negotiation provisions for small-molecule drugs in the Inflation Reduction Act of 2022. All drug prices are freely determined for the drug's first nine years on the market. Beginning in year 10, drugs in the top decile of revenue, are subject to a 60 percent reduction in annual revenues.[34]

Using our shape of revenue estimates, we calculate (by therapeutic area), the share of discounted lifetime revenue earned in the first nine years on the market, on average 71 percent (median 73 percent) for drugs with sufficient observations in *Evaluate Pharma*.[35] Using the estimates from Section 6.1, we simulate draws of preclinical candidates and identify which

[34]In practice, negotiated prices would only apply until generic entry. In our stylized model, we have assumed that revenue after generic entry (g_d) is very low, so assuming some percentage reduction on the post-generic revenues leads us to negligibly overstate the effect of the policy on lifetime revenue.

[35]We restrict our sample to drugs with at least 15 years of revenue data in *Evaluate Pharma*.

candidates are in the top decile of lifetime revenue. These drugs disproportionately fall within the higher revenue therapeutic areas, like Hematology and Oncology. For those candidates, we reduce revenue after nine years by 60 percent.[36] The average change in lifetime revenue for the top decile drugs is an 18 percent decline.

We then compare development decisions before and after the implicit revenue tax. We predict that fewer than 1 percent of preclinical candidates would change development decisions because of the policy. The limited impact on innovation stems from a combination of factors. First, discounted lifetime revenue is disproportionately distributed over time, with on average only 29 percent of discounted revenue incurred in Year 10 or later. Second, 90 percent of candidates are entirely unaffected by the policy. Finally, many of the affected candidates appear to be "blockbuster" drugs where lifetime revenue far surpasses development costs. In other words, the drugs affected by the policy are unlikely to be the same drugs on the margin of development before the policy change, though these conclusions would change as the share of drugs subject to the policy or the magnitude of price reductions changed (Vogel et al., 2024).

7 Discussion

As opposed to innovation grants or prizes, exclusivity extensions preserve positive selection based on private willingness to pay: drugs with higher commercial value are more likely to be developed (Weyl and Tirole, 2012). If private returns are positively correlated with social value, then marginal innovations should also improve social welfare. For drug categories for which private and social values clearly diverge, variations in market exclusivity could be employed as a kind of "Pigouvian tax or subsidy" to correct for these differences. Exclusivity extensions do not require governments to raise funds or decide which drug candidates to reward (Dubois et al., 2022), though as with the GAIN Act, policymakers could still decide to only reward certain *types* of drug candidates. These features may distinguish market exclusivity extensions from other policies affecting expected profits, such as pricing regulation, subscription models,[37] and direct grants.[38]

However, we see that the effective impact of an exclusivity extension on revenue depends heavily on revenue timing, which is influenced by patenting patterns or competitive obsoles-

[36]The first round of negotiated prices yielded average discounts of approximately 60 percent off of list prices (Centers for Medicare & Medicaid Services, 2024). In reality, the negotiated price would likely represent a smaller discount relative to the price *net of rebate*.

[37]Examples include England's National Health System subscription and the PASTEUR Act proposed in the US (NHS England, n.d.; Doyle, 2020; PASTEUR Act, 2023).

[38]Example includes CARB-X (CARB-X, n.d.).

cence, neither of which are necessarily correlated with the social value of a drug candidate. As we saw in the reduced form results (Section **??**), responses to the GAIN Act were not uniform across drugs by patent age.

Similar to an exclusivity extension, a price premium increases the monopoly rents accruing to a newly approved drug. In contrast, these increased rents occur immediately once the drug enters the market, and the effect on revenue does not interact with other factors like remaining patent life. This limits variation in the predicted effects of the policy on lifetime revenue, and subsequently the predicted effects on drug development.

However, alongside concerns about underinvestment in certain therapeutic areas like antibiotics, recent drug policy discussions have also included concerns about the affordability and access to drugs before generic entry, especially when few substitutes exist. This motivated policies like the IRA's drug price negotiations, which could be viewed as a cap on exclusivity that only applies to the highest revenue drugs. The tradeoff is reduced incentives to innovate, though as we and other papers have suggested, the aggregate impact on innovation is likely to be quite modest given revenue timing and policy scope.[39]

8 Conclusion

In this paper, we find that a policy (the GAIN Act) extending market exclusivity for antibiotics by five years increased innovation as measured by patent filings, preclinical studies, and progression to phase 3 trials. We then expand our scope to consider the effect of extending exclusivity, alongside price premiums and implicit revenue taxes as other policies affecting incentives to innovate, on a broader range of therapeutic areas. Our structural analyses highlight how a policy's effect on innovation depends on the number of candidates on the margin of development and on the interaction between the timing of when the policy affects revenue and the distribution of revenue over time.

Priorities for drug innovation change over time in response to emergent health needs. Careful attention to how public policies affect incentives to innovate in particular therapeutic classes or for particular types of drugs will be crucial for determining whether society obtains essential new drugs, including antibiotics, in the future.

[39] See Appendix F for a back-of-the-envelope exercise using our reduced form results to extrapolate to how the IRA could decrease overall drug innovation.

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Online Appendix
Policy Incentives for Pharmaceutical Innovation

Edward Kong and Olivia Zhao

A Construction of Key Outcome Measures for Antibiotics Case Study

In *Cortellis*, we observe the exact dates that a drug candidate achieves the following outcomes, which capture innovative activity at different stages of development. Our key outcomes of interest, ordered chronologically from earlier to later in the drug development life cycle, are:

- *Newly filed patents: Cortellis* maintains a repository of patents linked to medical indications, allowing us to categorize patents into our treatment and control groups. *Cortellis* also classifies patents by type: "product" (referring to a new drug or therapeutic compound), "diagnostic" (related to methods or tests to diagnose diseases or conditions), and "ancillary" (a category we define to include combination, formulation, new use, and process patents). These categories allow us to assess whether certain types of inventions are more or less responsive to exclusivity incentives. We separately consider biologic patents (products or processes related to biologic drugs) in a falsification or "placebo" test, as biologics were explicitly exempt from the GAIN Act. We did not analyze transitions between patents and clinical trials, because reliable linkages between patents and individual drug candidates do not exist.

- *Preclinical activity ("phase 0"):* This stage represents new drug candidates that have entered into the first step of the development pipeline, but have not yet initiated human trials.[40]

- *Initiation of phase 1, phase 2, or phase 3 clinical trials:* Initiations of subsequent phases of clinical trials represent forward progress through the pipeline. Considering each of these phases separately allows us to identify which stage(s) are most responsive to exclusivity extensions and which stages appear to be bottlenecks. This information could inform policies targeted at specific stages. In addition, because clinical trials are initiated earlier and more frequently than drug launches (which may take many years),

[40] *Cortellis* contains 2 different designations for preclinical work: "preclinical" and "discovery." We combine these two categories into a single "preclinical" stage.

using trial initiations allows us to detect smaller, more rapid responses to new policies such as the GAIN Act.

- *Drug launches*: While drugs may be launched in separate countries at different times, we focus on U.S. drug launches because GAIN Act incentives apply only to that market.

B Pooled Estimates and Heterogeneity Analyses For Patenting Activity

The effects of the GAIN Act on patenting varied by patent and owner types. Table A1 shows how patenting effects varied by patent type, with the largest increases among diagnostic, combination, formulation, new use, and process patents. Product patents exhibited a significant, but smaller, increase. As a placebo test, we show that patents for biologics (which were not eligible for GAIN Act exclusivity) did not significantly increase.

Appendix Table A1. Effects on log Patents, by Patent Type

Patent type	(1) Aggregate	(2) Product	(3) Diagnostic	(4) Ancillary	(5) Biologics
Treatment X Post GAIN	0.387**	0.117**	0.392**	0.231**	0.123
SE	(0.018)	(0.035)	(0.050)	(0.028)	(0.079)
N (patents)	53,746	15,524	8,507	30,267	3,653

$^{+}p < 0.1, ^{*}p < 0.05, ^{**}p < 0.01$

NOTES: Table shows results comparing treatment and control groups before vs. after the GAIN Act, separately by patent type. The Ancillary patent type is defined to include combination, formulation, new use, and process patents. Biologics were not covered by the GAIN Act and can therefore be considered a negative control or placebo outcome.

Table A2 shows how effects varied by owner type, comparing estimates for all companies (Column 1), for-profit pharmaceutical firms (Column 2), and non-pharmaceutical entities (Column 3). Non-pharmaceutical companies exhibited larger relative increases, but account for fewer patents overall. Table A3 shows that effects on product patents were primarily driven by non-pharmaceutical firms.

Appendix Table A2. Effects on log Patents, by Owner Type

Patent owner type	(1) Aggregate	(2) Pharmaceutical	(3) Non-pharmaceutical
Treatment X Post GAIN	0.387**	0.341**	0.464**
SE	(0.018)	(0.023)	(0.035)
N (patents)	53,746	32,328	17,619

$^{+}p < 0.1, ^{*}p < 0.05, ^{**}p < 0.01$

NOTES: Table shows results comparing treatment and control groups before vs. after the GAIN Act, separately by the type of patent owner. Non-pharmaceutical owners are primarily comprised of universities, hospitals, and non-profit institutes.

Appendix Table A3. Effects on log Product Patents, by Owner Type

	(1) Pharmaceutical	(2) Non-pharmaceutical
Treatment X Post GAIN	-0.048	0.346**
	(0.048)	(0.064)
N (patents)	10,371	5,241

$^{+}p < 0.1, ^{*}p < 0.05, ^{**}p < 0.01$

NOTES: Table shows results comparing treatment and control groups before vs. after the GAIN Act, limiting to product patents, separately by the type of patent owner. Non-pharmaceutical owners are primarily comprised of universities, hospitals, and non-profit institutes.

Heterogeneity by Patent Type: Product patenting, which in our setting is especially socially valuable regarding combating resistance and in pharmaceutical R&D in general represents more innovative or novel developments, increased by 12%.

Diagnostics-related patents, which were QIDP-eligible under the GAIN Act, increased by 48%. Earlier versions of the GAIN Act (Generating Antibiotic Incentives Now Act, 2011*b*) explicitly included a provision to add 6 months of exclusivity for "companion diagnostic" tests, but this provision was not included in the version of the GAIN Act that was eventually passed (Food and Drug Administration Safety and Innovation Act, 2012). In 2021, FDA guidance clarified that the agency considers products intended to diagnose infections to be eligible for QIDP status, citing FDA precedent dating back to 1998 (U.S. Food and Drug Administration, 2021). Although we cannot determine the extent to which innovators believed that new diagnostics would directly benefit from the GAIN Act, our results are robust to the exclusion of diagnostic patents, which comprise a relatively small share of antibiotic patents overall (Appendix Table A1).

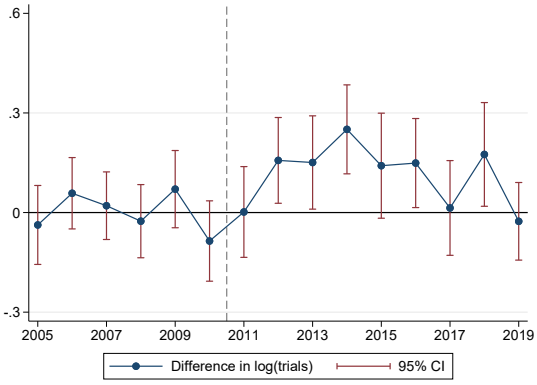
Even if firms did not believe that diagnostics could receive QIDP status, diagnostic patents could complement development or marketing efforts for antibiotic products. In terms of development, diagnostics can expedite clinical trials by improving screening and enrollment of patients into trials, potentially saving time and money by ensuring that only patients most likely to benefit from therapy are enrolled (Trevas et al., 2021). In terms of marketing, companion diagnostics could be used to drive demand for their associated antibiotic (Morel et al., 2016).

Ancillary patents exhibited a robust increase after the GAIN Act (Figure A1, Panel (c)), with an aggregate effect of 23% (Appendix Table A1, Column 4). Although typically considered less novel, these patents (which include combination, formulation, new use, and process patents) can still be socially valuable. In the context of antibiotics, combination

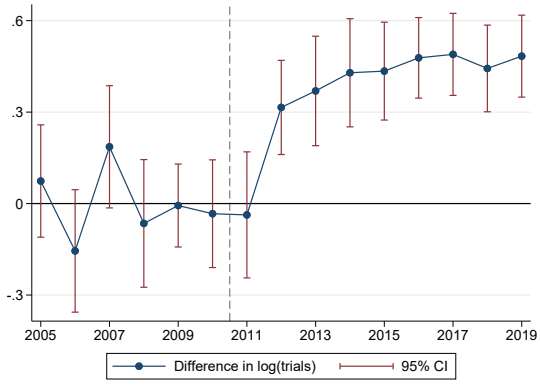
therapies are important for overcoming resistance.[41]

Appendix Figure A1. Heterogeneity in Patenting Effects by Patent Type

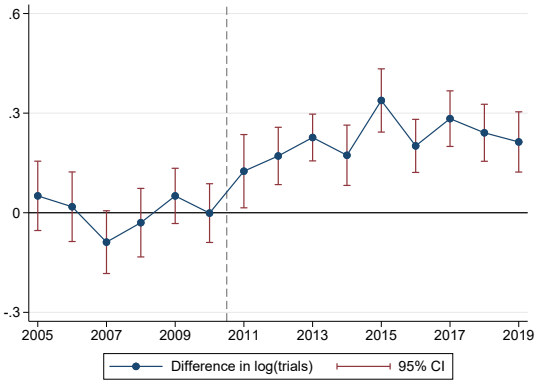
(a) Product Patents (most innovative)



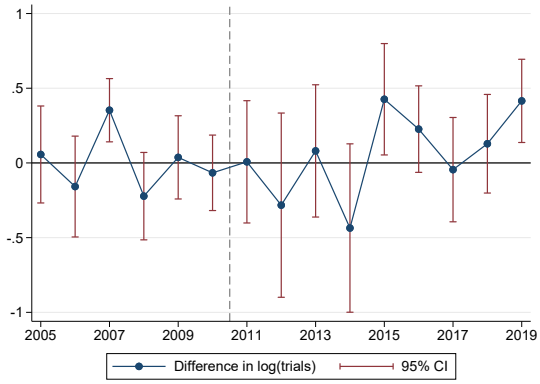
(b) Diagnostic Patents



(c) Ancillary Patents



(d) Biologic Patents (placebo outcome)



Notes: Each panel plots the difference in patenting between treatment and control indications for a different type of patent: product patents in Panel (a), diagnostic patents in Panel (b), ancillary patents (combination, formulation, new use, and process patents) in Panel (c), and biologic patents in Panel (d). Pre-period averages are normalized to zero and confidence intervals are obtained via Bayesian bootstrap. GAIN Act introduction is indicated by the dashed vertical line.

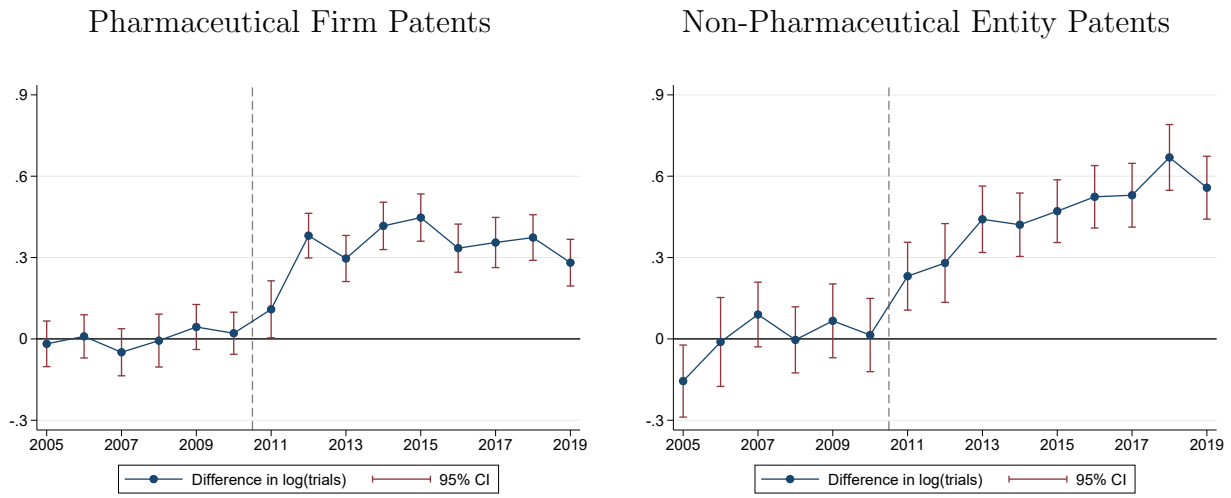
Biologic patents as a placebo outcome: Biologics are explicitly excluded from QIDP eligibility, as they are not approved under Section 505 of the FD&C Act (U.S. Food and Drug Administration, 2018). Thus, this category of patents serves as a placebo or falsification test. Reassuringly, we do not observe any effect of the GAIN Act on biologic patents (Figure A1, Panel (d)). This lack of an effect on patents for an excluded subcategory of antibiotic drugs (biologics) lends strong support to our parallel trends assumption and choice of control group.

[41] Antibiotic combinations often take the form of an antibiotic combined with a compound that inhibits a resistant bacteria's evolved defenses against that antibiotic. One example of this is the antibiotic Avycaz (ceftazidime-avibactam).

Heterogeneity by Pharmaceutical firms versus Non-Pharmaceutical entities: The majority of patents are owned by pharmaceutical firms, but around one-third are owned by non-pharmaceutical entities such as universities, hospitals, and non-profit institutes (e.g., the National Institutes of Health). Our data include 32,328 pharmaceutical patents versus 17,619 non-pharmaceutical patents.

We find that non-pharmaceutical owned patents exhibited a stronger *relative* increase in patenting compared to pharmaceutical/biotech company owned patents, 59% versus 41% (Appendix Table A2). This highlights the importance of public institutions in generating the basic research that feeds into later stages of drug development (Li et al., 2017). These results also suggest that economic incentives matter even for public entities, likely because subsequent development efforts (i.e., clinical trials) are driven by or in partnership with pharmaceutical firms. That said, because private firms conduct the bulk of patenting overall, private patents represent a larger share of the *absolute* increase in antibiotic patents induced by the GAIN Act.

Appendix Figure A2. Heterogeneity in Patenting Effects by Owner Type



Notes: Figures show the effect of the GAIN Act on the number of patent applications per year for treatment versus control indications estimated through Equation (**??**), separately for pharmaceutical owners (left) and non-pharmaceutical entities including universities, hospitals, and non-profit institutes (right). Pre-period averages are normalized to zero and confidence intervals are obtained via Bayesian bootstrap. The timing of GAIN Act introduction is indicated by the dashed vertical line.

Of note, we find that product patents increased by 40% among non-pharmaceutical entities, but did not change among pharmaceutical firms (Appendix Table A3). The increase in patents owned by pharmaceutical firms was driven by non-product patents. In Section **??**, we show that pharmaceutical firms also played an important role in advancing existing drug candidates through phase 3 clinical trials.

Taken together, our findings suggest that public entities took the lead on early-stage product innovation, which may later be acquired by larger firms with more clinical trials expertise. Meanwhile, pharmaceutical firms focused their efforts on non-product patents and advancing existing products through later development stages. This aligns with documented trends of public versus private innovation activities in the pharmaceutical industry (Cockburn and Henderson, 2003).

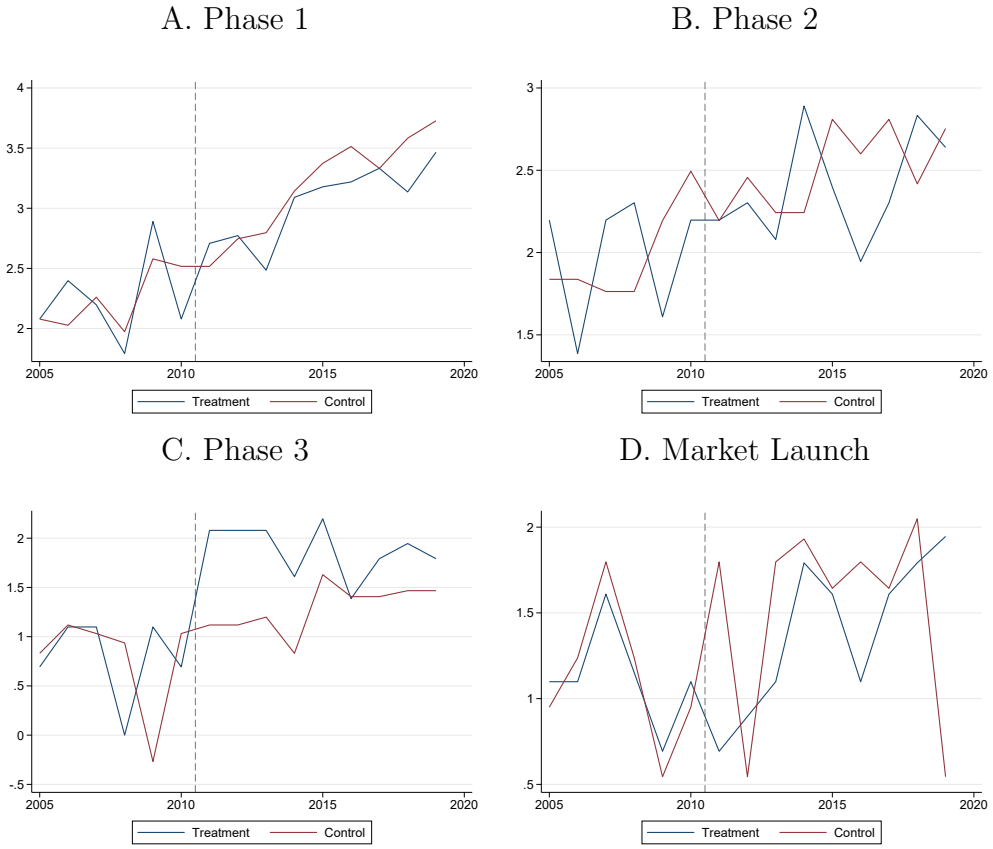
Importantly, although we find evidence that public and private entities specialize on different stages of antibiotic innovation, both sectors responded to economic incentives. Put another way, public sector innovation is not completely immune to policies that primarily affect the private profitability of novel drugs.

C Additional Results for Preclinical, Clinical, and Market Launch Outcomes

C.1 Preclinical Outcomes

C.2 Raw Trends for Clinical Outcomes

Appendix Figure A3. Raw Trends in ln(Clinical Trial Initiations) by Phase and Market Launch

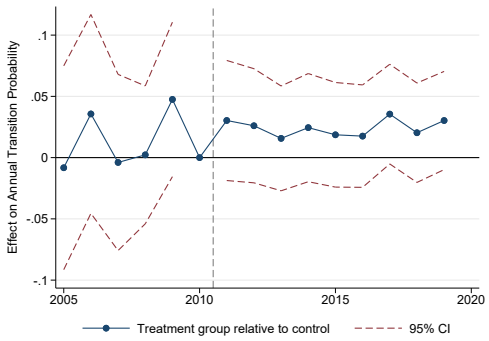


Notes: Figure shows the logged number of first trial initiations or market launches for treatment versus control groups of drug candidates at successive points of the development pipeline. Given data quality, counts are conditional on being observed in the prior phase. (More details available in appendix **??**.) The control group average has been normalized to have the same pre-period mean as the treatment group. The timing of GAIN Act introduction is indicated by the dashed vertical line. Data are binned into two-year bins except for 2019, which contains one year.

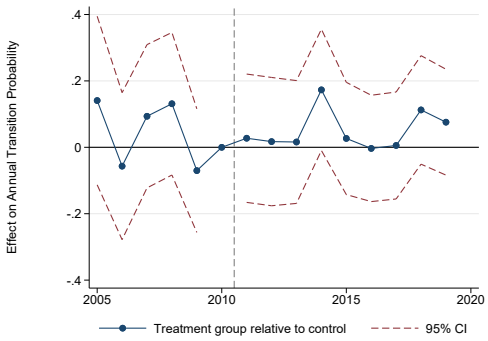
C.3 Phase Transition Event Studies for All Adjacent Phases

Appendix Figure A4. Event studies by phase

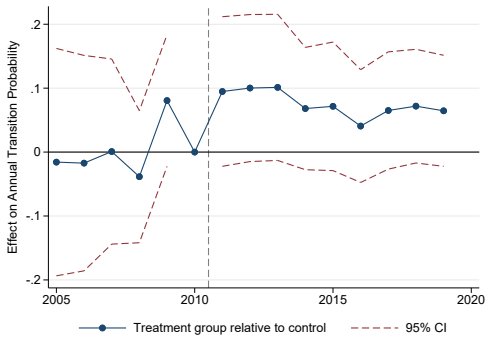
(a) Early stage to phase 1



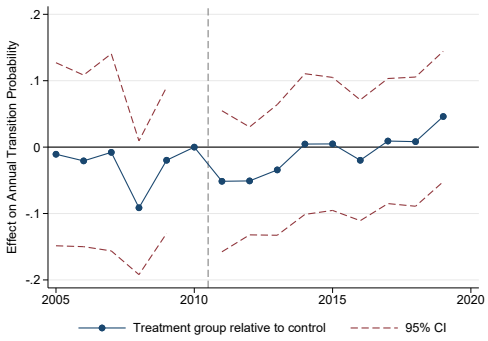
(b) Phase 1 to phase 2



(c) Phase 2 to phase 3



(d) Phase 3 to launch



Notes: Figure shows the baseline event study specification for adjacent phase transitions. The Y-axis shows the probability of advancing to a later phase for drug candidates with treated indications (antibiotics) versus control indications (antivirals and antibacterial vaccines). The dashed gray vertical line indicates the timing of the GAIN Act; 2011 is the first post-period year. The control group average has been normalized to have the same pre-period mean as the treatment group.

Table A4 below shows the full set of pooled difference-in-difference results for all adjacent phase pairs estimated through Equation (3). Effects are concentrated on the phase 2 to 3 transition. With drug fixed effects (Column 4), we also see modest effects for phase 1 to 2.

Appendix Table A4. Pooled Difference-in-Differences Results for Adjacent Phase Transitions

	(1) Baseline	(2) Dose X Treatment	(3) Biologic X Treatment	(4) Drug FE
Panel (a): Phase 0 to phase 1				
Post X Treatment	0.010	0.003	0.003	-0.021+
	(0.012)	(0.012)	(0.012)	(0.011)
Pre-period mean				
Treatment	0.070	0.070	0.070	0.070
Control	0.041	0.041	0.041	0.041
N unique drugs	3,352	3,352	3,352	2,802
N	17,163	17,163	17,163	16,613
Panel (b): Phase 1 to phase 2				
Post X Treatment	0.017	0.007	0.008	0.125*
	(0.043)	(0.043)	(0.043)	(0.058)
Pre-period mean				
Treatment	0.225	0.225	0.225	0.225
Control	0.146	0.146	0.146	0.146
N unique drugs	1,027	1,027	1,027	806
N	4,005	4,005	4,005	3,784
Panel (c): Phase 2 to phase 3				
Post X Treatment	0.069*	0.060*	0.064*	0.100**
	(0.028)	(0.028)	(0.028)	(0.038)
Pre-period mean				
Treatment	0.068	0.068	0.068	0.068
Control	0.077	0.077	0.077	0.077
N unique drugs	741	741	741	633
N	3,897	3,897	3,897	3,789
Phase (d): Phase 3 to launch				
Post X Treatment	0.015	0.018	0.020	-0.008
	(0.021)	(0.021)	(0.021)	(0.022)
Pre-period mean				
Treatment	0.065	0.065	0.065	0.065
Control	0.054	0.054	0.054	0.054
N unique drugs	504	504	504	455
N	3,177	3,177	3,177	3,128

$^{+}p < 0.1,^{*}p < 0.05,^{**}p < 0.01$

NOTES: Table shows pooled event study estimates of yearly phase transition rates from Equation (**??**), separately for each pair of adjacent phases. The coefficient of interest, Post X Treatment, reflects the effect of the GAIN Act on the transition rate of antibiotics versus a control group comprised of antivirals and vaccines. Column 1 shows our baseline specification. Column 2 adds dosage form indicators and interactions with the treatment group. Column 3 adds a biologic indicator and interaction with the treatment group. Column 4 controls for drug fixed effects.

Appendix Table A5. Effect of the GAIN Act on Advancement to Phase 3 Clinical Trials

	Baseline	Dose X Treatment	Biologic X Treatment	Drug Fixed Effects
Post X Treatment	0.0486	0.0460	0.0469	0.0640
	(0.019)	(0.019)	(0.019)	(0.023)
Pre-period mean				
Treatment group	0.052	0.052	0.052	0.052
Control group	0.056	0.056	0.056	0.056
N unique drugs	1,336	1,336	1,336	1,133
N	7,403	7,403	7,403	7,200

Notes: Table shows pooled event study estimates from Equation (**??**) of the annual phase transition rate of drugs observed to enter phase 1 or 2 that initiate phase 3 trials. The coefficient of interest, Post X Treatment, reflects the effect of the GAIN Act on the transition rate of antibiotics (the treatment group) versus a control group comprised of antivirals and vaccines, which are not eligible for GAIN Act benefits. Column 1 shows our baseline specification, which includes fixed effects for the treatment group, year, cohort (the year a drug candidate is first observed in our dataset), and cohort X treatment (which adjusts for differences in cohort effects between treatment versus control groups). Column 2 also includes dosage form indicators and interactions with the treatment group. Column 3 adds a biologic indicator and interaction with the treatment group. Column 4 controls for drug fixed effects, where observations are dropped for drugs that are only observed once. Standard errors (in parentheses) are clustered at the drug level.

We do not find statistically significant changes in clinical trial activity for other phase transition pairs, and our confidence intervals allow us to rule out large effects (Appendix Table A4). For the phase 0 (preclinical) to phase 1 transition, our 95% confidence intervals rule out effects outside of -19% to +49% of the pre-period mean for the treatment group. For phase 1 to 2, we can rule out effects outside of -30% to +45%. This suggests that the increase in phase 3 trials was not offset by declines in phase 1 or 2 trials.

For drug candidates reaching phase 3, we do not find significant changes in the probability of launch. This suggests that the increase in new phase 3 candidates did not offset efforts to bring existing phase 3 candidates to market. Towards the end of our sample window, this also suggests that the additional phase 3 candidates induced by the GAIN Act were likely to be of similar quality to pre-existing phase 3 candidates. One caveat is that, given the small number of these drug candidates, we are only able to rule out effects on launch rates outside of -40 to +86% of the pre-period mean.

C.4 Pooled Estimates

Table A6 below quantifies the log-initiation results by pooling data in the pre- and post-periods. Panel (a) quantifies the results shown above in Appendix Figure A4. Panel (b) adjusts for cohort X treatment group interactions by summing up initiations separately by cohort (defined as the first year a drug appears in our dataset at any phase) and including cohort X treatment fixed effects. Overall, the results from this alternative specification are consistent with our baseline results in the main text, but with less statistical power. Column 6 of Panel (a) shows that, among all drugs reaching phase 1 or 2, the GAIN Act was associated with an approximately 40% increase in phase 3 (or higher) trial initiations. After adjusting for cohort-treatment group interactions (Panel b), the magnitude of the phase 1-3 estimate increases and is statistically significant (P = 0.019). Consistent with our analysis in the main text, the largest effects were driven by the phase 2-3 transition, with smaller, null effects for other phases.

In general, we view these log-initiation results as broadly consistent with our main text results on transition rates. The log-initiation specifications are less well-powered for two reasons. First, the results in Panels (b) – (f) do not account for the denominator: the number of drugs "at-risk" that are available to transition to the next phase in each year. Second, the log-initiation specifications do not allow for adding detailed controls, since this requires dividing the data into smaller bins. Because the outcome is the log of the number of initiations, bins that happen to contain zero initiations are undefined.

Appendix Table A6. Aggregate DID Estimates for the ln(initiation) Specification

	(1) Phase 0	(2) Phase 0-1	(3) Phase 1-2	(4) Phase 2-3	(5) Phase 3-L	(6) Phase 1-3
Panel (a) Without controls						
Treatment X Post GAIN	0.143	-0.215	-0.099	0.614+	-0.015	0.442
SE	(0.096)	(0.162)	(0.208)	(0.318)	(0.374)	(0.292)
Panel (b) With adjustment for cohort X treatment group						
Treatment X Post GAIN	-1.227	0.092	-0.096	0.978+	-0.327	1.230*
SE	(0.933)	(0.453)	(0.354)	(0.580)	(0.693)	(0.523)
N (drug-years)	7,876	17,124	4,002	3,895	3,177	7,398

$^{+}p < 0.1$,$^{*}p < 0.05$,$^{**}p < 0.01$

NOTES: Table shows results from difference-in-differences comparisons regressing log trials on a treatment group indicator, post GAIN Act (year $\geq$ 2011) indicator, and their interaction. Reported effects are for the treatment X Post-GAIN interaction term. Panel (a) does not include any controls and thus reflects the graphical results shown in Appendix Figure **??**, whereas Panel (b) controls for cohort (the first year a drug candidate is observed in the dataset at any phase) and treatment group interactions. Standard errors are obtained via bootstrap at the drug candidate level with 200 re-sampling draws; Panel (b) uses a Bayesian bootstrap to avoid cases where re-sampling draws contain no observations for particular cells.

D Descriptives on Approved Antibiotics

Beyond the *number* of new antibiotics approved, policymakers also care about quality, in particular whether new antibiotics are novel, as novelty may correlate with social value in the antibiotics setting.[42] In Section 4.3, we showed that drugs with more novel product patents drive our GAIN Act effects. Here, we present a descriptive analysis that examines other measures of novelty, comparing the 67 antibiotics launched before and after GAIN during our study window. We abandon our control group for this analysis, since characteristics reflecting novelty in antibiotics (e.g., whether the antibiotic is a new dosage form of an old active ingredient) are not relevant for antivirals or vaccines.

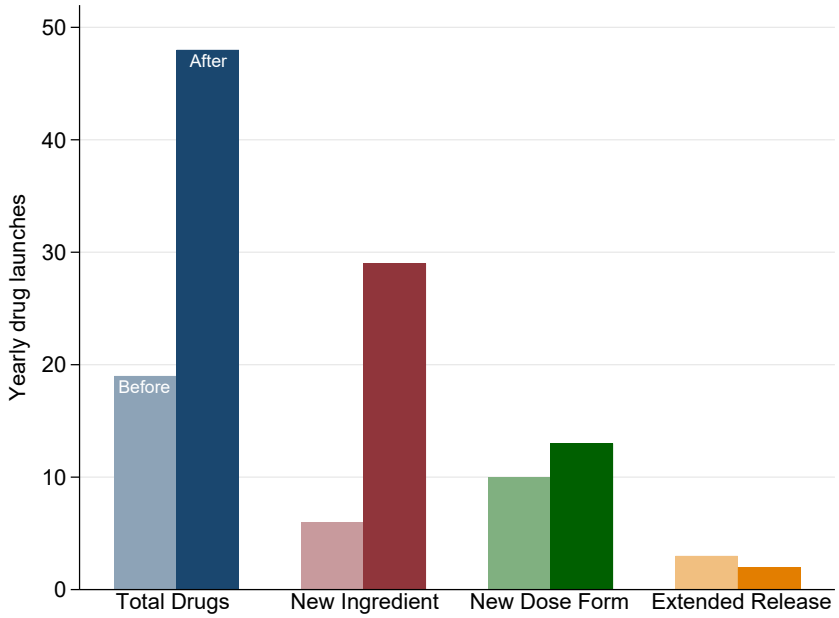
For this descriptive exercise, we manually coded whether each new antibiotic includes a novel active ingredient, a new dosage form or route of administration,[43] or was simply an extended-release version of an existing drug. One antibiotic (lefamulin) represented an entirely new class.

Figure A5 below shows that antibiotics launched after the GAIN Act appear somewhat *more* novel than antibiotics launched prior. After the GAIN Act, the launch rate of antibiotics increased (from 3.3 per year to 4.8 per year). A larger percentage of these drugs contained novel active ingredients (increasing from 30% to 60%), and a lower percentage represented new dosage forms (declining from 55% to 27%) or extended-release formulations of existing drugs (declining from 15% to 4%). In sum, after the GAIN Act, antibiotics launched at a faster rate, with a larger share featuring novel active ingredients.

[42] Social value is also derived from policies that induce innovation in areas where social need is higher. In theory, all QIDPs should satisfy this criterion, as QIDPs are required to address "life-threatening conditions."

[43] New dosage forms and delivery routes be valuable to treat specific clinical syndromes; for example, inhaled versus intravenous tobramycin for lung infections.

Appendix Figure A5. Characteristics of New Antibiotics Before and After GAIN



Notes: Figure shows characteristics of N=67 treatment-group drugs that were first launched in the 6 years prior to GAIN (2005-2010) or after the GAIN Act was announced (2011-2020). The first bar in each group represents 2005-2010; the second bar in each group represents 2011-2020. The Y-axis reports the yearly rate of new drug launches in each category-by-time period. Group definitions are as follows: Total Drugs (yearly average number of all new antibiotic launches), New Ingredient (antibiotics with a novel active primary ingredient), New Dose Form (antibiotics with a previously approved active ingredient in a novel dosage form), and Extended Release (new antibiotics whose main novelty is an extended-release formulation). The sample of treatment group drugs also includes some antifungals and protein-based therapies, such as monoclonal antibodies.

Both the difference-in-differences estimates and these descriptive facts help to highlight the conceptual distinction between innovation "quality" and marketability: many antibiotics that yield modest private returns may nonetheless be socially valuable.

E Revenue Elasticity Calculations

We use two approaches to approximate the average increase in exclusivity for antibiotics after GAIN. Both methods assume for simplicity that revenues arrive at a constant rate over the drug's exclusivity period and fall to zero after the drug goes generic.

The first (simpler) approach only considers GAIN's effect on market exclusivity for all antibiotics launched between 2005 and 2020. Using FDA Orange Book data, we calculate the increase in market exclusivity across all antibiotics, only some of which are approved with QIDP status and receive the GAIN exclusivity extension. This yields an increase in market exclusivity of 36% for the average antibiotic.

The second approach accounts for the fact that patent and market exclusivities run concurrently, and the total exclusivity of a drug is the maximum of the two types of exclusivities. Because the GAIN Act only increased market exclusivity, understanding its effect on total exclusivity requires accounting for the effect of patents. Below, we explain how accounting for patents decreases this increase to +28%.

Patents are valid for up to 20 years, and each antibiotic may have multiple patents. However, unlike market exclusivity, patent exclusivity can be challenged in court. However, patent challenges are difficult to predict. Thus, to assess the effect of GAIN on total (patent + market exclusivity), we use the empirical distribution of total exclusivity for antibiotics approved prior to the July 2012 (when the GAIN Act went into effect).

We define total exclusivity as the difference between the FDA approval date of the first generic and the FDA approval date of the branded antibiotic. Of 19 antibiotics approved prior to GAIN, we observe total exclusivity for 8 of them, which averaged 10.54 years, but with a large standard deviation of 5.76 years. To assess the effect of GAIN, we conducted a simulation to compare this pre-GAIN total exclusivity distribution with the post-GAIN market exclusivity distribution, which conferred an average of 10.0 years of market exclusivity (SD = 1.5 years). We simulated 10,000 draws from both distributions (assumed to be normally distributed with the above means and standard deviations) and applied the restrictions that (1) baseline exclusivity cannot be negative, and (2) GAIN can only add at most 5 years of additional exclusivity.

While the average post-GAIN market exclusivity is less than the average pre-GAIN total exclusivity (10.0 years versus 10.5 years), the large standard deviations mean that many drugs do benefit from additional GAIN exclusivity. Assuming that new drugs draw pre- and post-GAIN exclusivities independently, we find that 46% of drugs would benefit from GAIN exclusivity, with an average benefit of 3.3 years for these drugs. Including the 54% of drugs that would not benefit, we calculate that GAIN adds an average of 1.6 years of exclusivity in

this scenario. The benefits of GAIN are heavily skewed toward drugs with low pre-GAIN total exclusivities, such that the average percent increase in exclusivity in the simulation exercise is +58%. As 48% of the drugs in our treatment group received GAIN exclusivity after 2012, we calculate that the GAIN Act increased total exclusivity by $58\% \times 48\% = 28\%$.

Combining these estimates with our baseline DID estimates from Table 2 yields revenue elasticities in the range of $0.94/0.36 = 2.6$ to $0.94/0.28 = 3.4$.

F Impact of the Inflation Reduction Act on Innovation

Using the FDA Orange Book data, we compute that an average of 83.5 small-molecule branded drugs were approved each year from 2005 through 2019. The Inflation Reduction Act (IRA) allows the government to negotiate Medicare prices for up to 20 additional drugs each year, with the set of price-negotiated drugs expanding over time. However, due to eligibility criteria, negotiations may apply to fewer than 20 drugs.[44]. Estimates by Vogel et al. (2024) suggest that on average, negotiation may apply to 7.4 new drugs per year. In the long run, this implies that a randomly chosen new drug has a $7.4/83.5 = 8.9\%$ probability of being subject to price negotiation.

To model the effects of the IRA as a cap on market exclusivity, we use the same distribution of pre-GAIN total exclusivity as in Appendix Section E. Because the IRA allows for price negotiation to occur after 9 years of market exclusivity for small molecule drugs, we simulate a 9-year exclusivity cap, which reduces the total exclusivity of affected drugs (those who would have had > 9 years of exclusivity) by an average of 5.2 years, or an average percent decline of 33%. We make the conservative assumption that all drugs are equally likely to be negotiated, implying an expected percent decline in total exclusivity of $8.9\% \times 33\% = 3.0\%$. In Appendix Section E, we computed that the GAIN Act increased total exclusivity by 28%. Hence, we infer that the relative effect of the IRA on expected exclusivity is 3.0% / 28% = 0.107.

The next step requires estimating the reduction in a drug's U.S. revenue that results from negotiation, compared to the effect of generic entry, which we conservatively assume is a 100% reduction in revenue. This is a function of (1) the revenue decrease negotiated by Medicare and (2) the share of a drug's U.S. revenue that derives from Medicare. For (1), Hernandez et al. (2024) use the actual, newly negotiated maximum fair prices for the first 10 drugs subject to the IRA and find a 22% savings to Medicare on these drugs. For (2), we use the facts that Medicare accounted for $256 billion (42%) of the $603 billion in total U.S. drug spending in 2021 through Part B and Part D (Parasrampuria and Murphy, 2022; Kaiser Family Foundation, 2023). Thus, we estimate that Medicare price negotiation results in a $0.22 \times 0.42 = 9.2\%$ decrease in U.S. revenues.

Recall our main estimates that the GAIN Act increased antibiotic preclinical studies by 33% by the end of our sample window and phase 3 trials by 94%, for a total effect of 127%.[45] From this, we can infer that the IRA will lower drug innovation by approximately

[44]For more details on the drug negotiation program, see https://www.kff.org/medicare/issue-brief/faqs-about-the-inflation-reduction-acts-medicare-drug-price-negotiation-program/

[45]We assume that the increase we estimate for in antibiotic patenting is subsumed in the effect on preclinical studies, rather than additive.

$0.107 \times 9.2\% \times 127\% = 1.3\%$, or a loss of $1.3\% \times 83.5 = 1.05$ drugs per year.

Effects may be much larger for drugs that are mainly used for elderly patients on Medicare. The maximum impact of negotiation on U.S. revenues, assuming a 100% Medicare share, would be 22%, implying a larger $0.107 \times 22\% \times 127\% = 3.0\%$ decline.

Our calculation may be too conservative for several reasons. First and foremost, the IRA is specifically targeted towards drugs with the highest Medicare revenues, whereas our estimates for the GAIN Act pertain to the average antibiotic. The targeting of the IRA toward drugs that (ex-post) generate the highest revenues magnifies its effect on total profits for the industry as a whole, compared to policies like the GAIN Act that are not targeted based on ex-post revenues. Moreover, the IRA will also likely induce shifts in innovation away from drugs treating conditions of the elderly. Second, we did not include our estimated 47% increase in antibiotic patenting. Although some of this effect is likely subsumed in the 33% increase in preclinical studies observed by 2019, it may also lead to greater extensive-margin increases in innovation in the long-run. Lastly, antibiotics may be less responsive to exclusivity changes compared to other drugs, especially if new antibiotics are mostly held in reserve and annual revenues are low at baseline. This would imply larger innovation effects of the IRA for non-antibiotics.

Antibiotics may be more responsive to exclusivity changes compared to other drugs. For instance, profitability may be a more significant barrier for antibiotic innovation, compared to other areas where scientific considerations constitute the primary barriers. If this is the case, then our estimate for IRA innovation effects would be too large.

For comparison, the Congressional Budget Office estimated that the IRA would reduce drug innovation by about 1.1% over the next 30 years.[46]

While this calculation involves many assumptions, our hope is that it provides a useful framework for translating our results to other settings. One could modify each of the above assumptions to reach alternative estimates of the effect of the IRA. For example, if one believed that the innovation elasticity for antibiotics was two times *larger* than that of drugs affected by the IRA, this would cut the inferred IRA innovation effect in half.

[46]This is based on a decline of 15 drugs out of 1300 drugs approved over the next 30 years. See p. 5 of https://www.cbo.gov/system/files/2022-07/senSubtitle1_Finance.pdf

G Phase Advancement Probabilities

Table A7 below reports phase-specific advancement probabilities, computed for each phase k, k' pair as the share of drug candidates observed to reach phase k by 2018 that are also observed to have a subsequent phase k' trial.[47]

Appendix Table A7. Phase Advancement Probabilities

	Treatment	Control	Total
preclinical to phase 1			
N preclinical	1,096	2,169	3,265
Share advancing to phase 1	26%	31%	29%
Phase 1 to 2			
N phase 1	292	770	1,062
Share advancing to phase 2	61%	51%	54%
Phase 2 to 3			
N phase 2	240	576	816
Share advancing to phase 3	50%	46%	47%
Phase 3 to U.S. launch			
N phase 3	174	396	570
Share launched	51%	32%	38%
Phase 1 to 3			
N phase 1 or 2	368	1,008	1,376
Share advancing to phase 3	40%	33%	35%

NOTES: For the "Phase 1 to 3" transition, reported probabilities are calculated using the sample of drugs that we observe in either phase 1 or phase 2 clinical trials by 2018. Drugs with both phase 1 and phase 2 activity observed by 2018 only enter the sample once (they are not "double counted"). Sample sizes reflect the number of unique drug candidates (compounds), aggregating over all of the indications of each drug.

On average across both treatment and control, 29% of drugs observed in preclinical studies progress to at least phase 1 trials, 54% of phase 1 drugs progress to at least phase 2, 47% of phase 2 drugs progress to phase 3, and 38% of phase 3 drugs are launched in the U.S.. We can see that antibiotics have somewhat lower rates of progression from preclinical to phase 1. However, conditional on reaching phase 1, a similar share of antibiotics progress to phase 2 (61% versus 51% of controls) and from phase 2 to phase 3 (50 versus 46%). Conditional on reaching phase 3, a larger share of antibiotics is launched (51% versus 32%).

[47]We require that phase k begins by 2018 because our data only extend through 2021. This allows each drug candidate at least three years to advance to phase k'

Overall success rates: To get an overall launch rate using the full sample of drugs (as opposed to just the drugs observed going from preclinical to launch), we use the individual transition probabilities and assume independent transition probabilities. Thus, the overall launch rate of a preclinical antibiotic is $26\% \times 61\% \times 50\% \times 51\% = 4.0\%$ and the overall launch rate of a preclinical antiviral drug is 2.3%. An antibiotic that reaches phase 1 has a 16% probability of being launched, compared to an 8% probability for control group drugs, with most of the difference accounted for by a smaller launch probability for control drugs.

Comparisons of success rates to the literature: Table A8 below provides estimates of conditional transition probabilities in the existing literature that are specific to antibiotics or infectious disease drugs more broadly.

Our values are roughly similar for the transitions from phase 1 through phase 3 trials. Our estimates of transitions between preclinical to phase 1 trials are higher. One possible reason is that reporting of preclinical activity (which tend to be less publicized compared to clinical trials and drug approvals) likely exhibits the most variance across data sources and that Cortellis might be selectively reporting preclinical activity that leads to phase 1 trials.

Relative to the literature (Appendix Table A8), the drugs in our sample are less likely to launch in the U.S. after initiating phase 3 trials. One reason for the discrepancy may be the types of firms and drug products included in our sample compared to the literature. Our sample of antibiotics, antivirals, and vaccines may be less commercializable than the average infectious disease drug in the literature. In addition, our success probabilities only count U.S. launches associated with a treatment or control indication: drugs that have a treatment or control indication in phase 3, but are launched under other indications, are not coded as successes in our analysis. Reassuringly, we are able to closely match overall success rates from Aryal et al. (2023), which also uses the Cortellis dataset.

Appendix Table A8. Probability of Success Estimates from the Literature

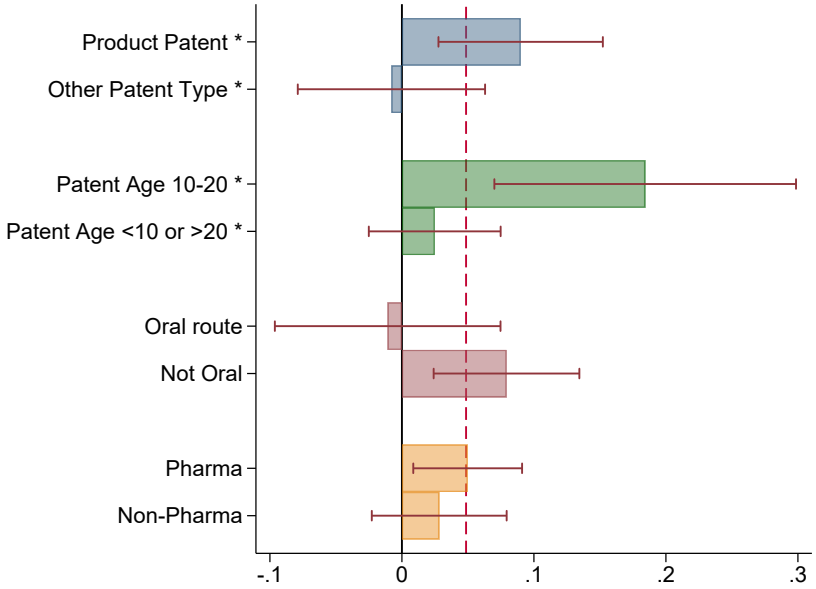
Paper	preclinical to Phase 1	Phase 1 to 2	Phase 2 to 3	Phase 3 [a] to Launch
Dowden and Munro (2019)		0.59	0.38	0.71
Wong et al. (2019)		0.70	0.58	0.75
Stephens (2015)	0.09	0.33	0.75	0.64
Hay et al. (2014)		0.67	0.46	0.63
Thomas et al. (2016)		0.70	0.43	0.73
Payne et al. (2007)	0.26	0.25	0.5	0.50
DiMasi et al. (2010)		0.58	0.52	0.79
DiMasi et al. (2020)[b]		0.76	0.53	0.78
Range across above papers	0.09–0.26	0.25–0.76	0.35–0.75	0.50–0.79
Average in our sample	0.29	0.54	0.47	0.38
Aryal et al. (2023)[c,d]	preclinical to launch for infectious diseases: 0.16			

NOTES: Table shows transition probability estimates from the literature. Other than Aryal et al. (2023), the included papers satisfy the following criteria: (1) cited in the literature review of a model of antibiotic value developed by researchers at Boston University (Outterson, 2021) (2) report estimates based on authors' own analysis of data (3) published as institutional report or in peer-reviewed academic journals.
[a] Most studies usually decompose the "phase 3 to launch" transition into at least two discrete steps, with intermediate milestones of FDA application submission and FDA approval. We have collapsed these steps into one transition, and the values in this column are found by assuming independence and multiplying all relevant conditional transition probabilities.
[b] Study uses regulatory approval in other countries around the world, not just FDA approval and launch in the U.S. market.
[c] Study also uses *Cortellis* as a data source.
[d] Conditional transitional probabilities calculated at the drug-indication level. Parameters from all other papers calculated at the drug-level or only for a drug's lead indication.

Other studies that use the *Cortellis* data: Aryal et al. (2023) also uses *Cortellis* data to estimate conditional transition probabilities. The authors use a sample constructed at the firm-drug-indication-level and report a success rate of 72.3% in transitioning from phase 3 to FDA application and success rate of 89.0% in transitioning from FDA application to approval, so we infer a phase 3 to approval success rate of $72.3\% \times 89.0\% = 64\%$. Specific to infectious disease products, the authors report that 16% of drugs with preclinical activity eventually go to market. Using a drug-indication version of our sample, we find a conditional transition probability of 62% between phase 3 and launch and 19% between preclinical and U.S. launch, which closely match the other *Cortellis* estimates in Aryal et al. (2023).

H Other Heterogeneity Analyses for Antibiotics Phase Transition Difference-in-Differences Specification

Appendix Figure A6. Effect on Advancement to Phase 3 Trials: Drug-Level Heterogeneity



Notes: Figure shows effect heterogeneity across drug characteristics for the phase 1 to phase 3 transition estimated through a versions of Equation (4) that interacts the difference-in-differences independent variables with each dimension of heterogeneity. The vertical dashed line represents the average treatment effect from our baseline specification without heterogeneity. Color-coded groups reflect binary characteristics: each bar represents the effect of the GAIN Act for a single group. Error bars represent 95% confidence intervals for each group-specific effect. The (*) indicates $p < 0.05$ for the between-group difference in treatment effects (i.e., the interaction term between the binary characteristic and Post X Treatment). Sample for "Product Patent" and "Patent Age 10-20" is restricted to observations with a matched patent. Sample for "Oral route" is restricted to observations with route of administration information.

Pharmaceutical firms versus non-pharmaceutical entities: Effects on phase 3 clinical trials appear to be larger for traditional pharmaceutical firms, although we are not powered to detect significant differences between pharmaceutical firms and non-pharmaceutical entities. Pharmaceutical firms almost exclusively develop products in the later stages of development, so would be most directly affected by the incentives in the GAIN Act. However, many non-pharmaceutical entities conduct early stage R&D in antibiotics in the hopes of selling the project or licensing technology to a pharmaceutical firm. In that way, even upstream actors in the development process could rationally respond to the GAIN Act, and we do see a positive (but noisily estimated) response from non-pharmaceutical entities.

Oral versus non-oral drugs: Our results are primarily driven by drug candidates with

non-oral dosage forms, which are primarily intravenous (IV) medications.[48] Although the interaction term is not significant, the larger point estimate for IV drugs is consistent with the stated focus of GAIN that QIDP status should be awarded for "serious and life-threatening infections," which typically require intravenous antibiotics (Darrow and Kesselheim, 2020).

[48]Non-oral drugs also include other routes of administration, such as inhalation.

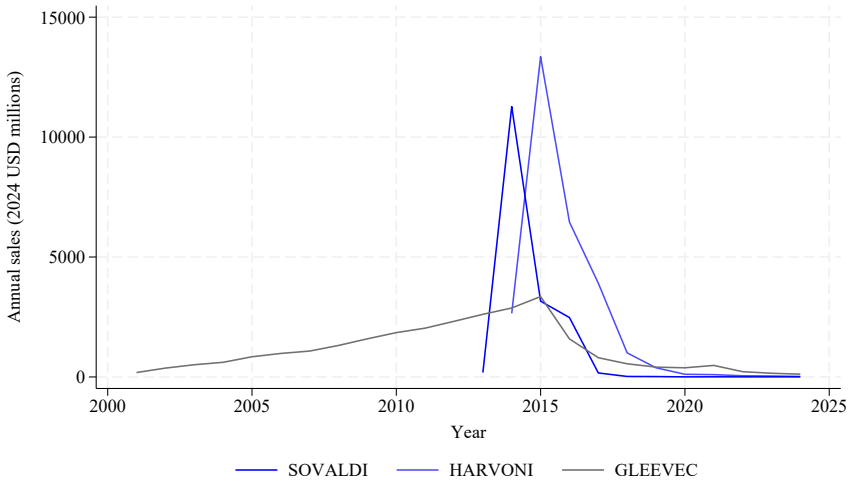
I Comparing and Contrasting Examples of Drugs by Total Revenue and Revenue Dynamics

A stark example of drugs with "extreme" revenue timing profiles are Sovaldi (sofosbuvir) and Harvoni (ledipasvir/sofosbuvir), two drugs approved to treat Hepatitis C in 2013 and 2014, respectively. These were ground-breaking treatments that not only dramatically decreased side effects typical of existing HepC treatments, but also dramatically increased treatment success rates. These drugs are considered cures for many common types of HepC.

The nature of a cure, compared to treatment for a chronic disease, is that the size of the population eligible to receive the drug shrinks over time as utilization increases. For Sovaldi and Harvoni, this dynamic combined with later entry of rival products and market saturation (due in part to very high prices), led the two drugs to have very "front-loaded" revenues. Sales peaked in each drug's first year on the market, and had functionally collapsed by year 5 on the market, well before its market exclusivity expiration (see figure below).

In contrast, take another blockbuster drug in Gleevec (imatinib). The figure below shows that Gleevec had similar *lifetime* revenue to the HepC drugs i.e., the area under each drug's curve is roughly similar. However, we can see that Gleevec does not reach peak sales until 2015, more than a decade after its initial FDA approval. The drop in Gleevec's revenue corresponds to generic entry. The comparison of these two drugs demonstrates the intuition that market exclusivity expiration is much more valuable for drugs like Gleevec. Were its generic entry to be delayed by just one more year, we could extrapolate and assume that Gleevec likely could have earned in the neighborhood of an additional $3 to 5 billion dollars.

Appendix Figure A7. Annual Revenue of HepC drugs (Sovaldi/Harvoni) Versus Gleevec



Another way of demonstrating this phenomenon is looking at how quickly drugs accrue some X% of their lifetime revenue. The graph below plots the cumulative share of lifetime revenue incurred as a function of years on the market. Drugs like Sovaldi/Harvoni (blue) have very concave shapes, quickly reaching a plateau near 1 and with the bulk of revenue already earned by the time exclusivities expire. TNF inhibitors (green) represent the opposite: "back-loaded" drugs are likely protected by patents to allow for the long lifetime of steady sales, and the convexity of the shape could indicate that the drugs are accumulating new indications and diffusion across more patient populations is actually accelerating over time. For these drugs, we infer that market exclusivity was not very important in protecting revenue streams, as annual revenue continues to increase well after initial market exclusivity expires.

This implies that there exists some Goldilocks zone of drugs that benefit most from extending market exclusivity: those still earning meaningful revenue when original exclusivity expires and where marginal market exclusivity would "dominate" whatever patents protect the product.

Appendix Figure A8. Cumulative Lifetime Revenue Share Over Time (select Drug Classes)