# Beyond the Label: Regulatory Arbitrage in Pharmaceutical Market Entry*

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**Abstract**

In regulated markets, high entry barriers can create incentives for firms to circumvent regulation or selectively avoid approval for certain products. We provide evidence consistent with such regulatory arbitrage in U.S. pharmaceuticals: Firms conduct clinical trials in large patient populations but initially seek approval in smaller, lower-risk markets to reduce regulatory burden. Firms then rely on off-label drug use to expand demand beyond approved uses. While this approach expedites market entry, it raises policy concerns about treatment adoption without strong supporting evidence. Our findings highlight how regulatory design may induce strategic entry by firms and alter the diffusion of new technologies.

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## 1 Introduction

In many industries, government regulation determines which products may enter the market and under what conditions (Dranove et al., 2022; Joskow, 2005; Maini and Pammolli, 2023; Mulligan, 2022; Olson, 2002; Peltzman, 1973; Vives, 2019). While such entry regulation is intended to ensure product safety and efficacy, it can also create incentives for firms to respond strategically to circumvent regulatory requirements. For instance, ride-sharing apps such as Uber and Lyft have been able to bypass city taxicab regulations by arguing that they are technology platforms and not transportation providers (Posen, 2015). Similarly, financial technology ("fintech") companies like PayPal refrain from certain activities, including holding customer funds or making loans, to avoid being regulated as banks (Douglas, 2016).

The decision to circumvent regulatory approval is particularly salient in health care, where entry regulation by the U.S. Food and Drug Administration (FDA) creates a unique set of incentives and disincentives for manufacturers to seek regulatory approval for new uses of approved products (Friedman, 1996).[1] Firms must obtain separate FDA approval to legally market a drug for each distinct disease market. Although this structure incentivizes firms to pursue supplemental approvals for a drug's additional therapeutic uses, the high costs and risks of conducting rigorous clinical trials necessary for approval may deter them. Further, an alternative, non-regulatory pathway exists where approved drugs can be used by consumers for unapproved ("off-label") uses (Eisenberg, 2005).

In this paper, we provide new empirical evidence consistent with the view that pharmaceutical firms engage in regulatory arbitrage—the practice of exploiting gaps or differences in regulation across jurisdictions or within a single regulatory framework—in their market entry strategies. Rather than seek approval in the largest potential disease market (or indication), firms may initially pursue approval in smaller, more favorable indications with lower regulatory risks. Once approved, firms can rely on off-label use to access broader patient populations without incurring the full costs of formal approval across all indications.

[1] Another health care setting where regulatory loopholes have been documented is hospital upcoding, where hospitals reclassify patients into diagnosis codes that lead to greater reimbursement (Dafny and Dranove, 2009; Dafny, 2005).

In choosing to engage in regulatory arbitrage, firms face a central trade-off between regulatory risk and market reach: On the one hand, initial approvals in narrow indications can lower the upfront risk of market entry. For instance, trials for smaller indications require fewer participants (Sertkaya et al., 2016), and advances in genetic sequencing and biomarker testing allow firms to selectively enroll patients with higher treatment responsiveness, thereby increasing the probability of approval (Chandra et al., 2019; Michaeli et al., 2023). On the other hand, expanding demand later through supplemental approvals or off-label use introduces other costs and uncertainties. Off-label indications cannot be directly promoted, potentially limiting uptake, and their use may expose firms to reputational or legal risks. As a result, the prevalence of off-label use—and thus regulatory arbitrage—is likely to vary across contexts.

The potential for regulatory arbitrage to shift firms' decisions, while conceptually clear, is difficult to study empirically for two main reasons. First, variation in regulation requirements is rare, with regulatory changes typically anticipated and similar across product markets. As a result, traditional empirical methods—which typically rely on exogenous changes over time or across product markets—are ill-suited to assess how regulatory design may shift firms' approval decisions. Second, to understand how regulation shapes these decisions, it is necessary to identify the benchmark set of indications in which a firm has conducted clinical trials for a drug and might plausibly seek regulatory approval. In most industries, the set of plausible markets a firm might have entered (but chose not to) is unobserved, limiting researchers' ability to characterize how firms alter their entry strategies in response to regulation.

Our empirical focus on drug development allows us to make progress on both of these issues. To address the first concern, identifying meaningful variation in regulation, we build on prior work that leverages unique features of the health care sector to identify useful variation (see, e.g., Budish et al., 2015; Chandra et al., 2016; Cohen et al., 2021; Stern, 2017). In particular, we exploit variation across disease indications in both the likelihood of regulatory approval and the potential to expand demand through off-label prescribing. These differences across indications create scope for regulatory arbitrage. To address the second challenge, we construct a comprehensive dataset linking a drug's

regulatory approvals to its full set of clinical trials. These data allow us to distinguish between disease indications in which a firm invests through clinical testing (the benchmark) and those in which it ultimately seeks FDA approval.

To illustrate, Figure 1 explores market entry decisions across a drug's lifecycle, plotting mean market size by indication order—defined as the sequence of disease indications in which a given drug is clinically tested or approved—for cancer drugs first approved from 1978 to 2016. Panel A indicates that firms prioritize large indications for their clinical trial testing, consistent with incentives to gather information about larger market sizes. However, Panel B indicates that firms prioritize smaller indications for regulatory approval.[2] While such patterns could be due to differences in scientific opportunities (Kao, 2025), market conditions (Acemoglu and Linn, 2004), or intellectual property (IP) protection (Budish et al., 2015), the indication order-market size relationships persist even after controlling for these factors.

Motivated by this finding, we examine how approval sequencing varies with the total market size a drug can access, including both approved *and* off-label indications. We conduct two complementary empirical tests. In our first empirical test, we document evidence that expected off-label drug use is incorporated into firms' market entry decisions. Although off-label use is not directly observable ex ante, we exploit two features of the cancer market—the largest pharmaceutical market in terms of spending (IQVIA Institute, 2018)—for these analyses. First, multiple uses are common, and estimates of off-label use range from 50 to 75 percent (Pfister, 2012).[3] Second, the rise of cancer genome sequencing enables us to use genetic data to identify biologically-likely off-label disease indications. We use these data to construct a novel genomic similarity index between cancer sites, allowing us to approximate each drug's total potential market size, including both approved and off-label uses. After accounting for off-label potential, we uncover a meaningful reversal in the relationship between approval order and market size: Indications that receive earlier approval

[2]These patterns are not simply driven by variation in indication labeling (e.g., "cancer") or trial phase: Our trial data are specific to the cancer site (e.g., "ovarian cancer"), and analyses restricted to phase III trials yield similar results (Appendix Figure A1).

[3]This is due to favorable off-label reimbursement policies in cancer treatment, as well as other factors (e.g., high disease severity and fewer treatments for rare cancers) encouraging physicians to experiment beyond formally approved uses.

are often linked to larger total potential market sizes. This pattern is consistent with regulatory arbitrage—firms seek initial approval in smaller indications that offer a lower-risk path to market, while delaying approval in broader markets or relying on off-label diffusion to expand demand without formal approval.

In our second empirical test, we exploit cross-disease heterogeneity in the propensity for *actual* off-label drug use. Using therapeutic-level off-label prescribing rates from the medical literature, we show that the negative relationship between indication order and market size differs across two groups: The decline is substantially steeper for drugs in low off-label therapeutic areas than for drugs in high off-label areas. These results are consistent with the hypothesis that regulatory arbitrage is particularly prevalent among firms developing drugs with high off-label potential. These firms can pursue initial approval in smaller markets, anticipating later expansion through off-label prescribing. In contrast, firms whose drugs have low off-label potential face fewer opportunities for informal diffusion of their pharmaceuticals and therefore have stronger incentives to prioritize larger markets in initial approval decisions. We consider alternative explanations—such as differences in trial duration, regulatory review times, and firm selection—and show that they are unlikely to explain our results.

Finally, we examine the policy implications of our findings. Back-of-the-envelope calculations suggest that seeking initial approval in a smaller indication shortens time to market by approximately 7.9 months, yielding an estimated $99.6 million in value to firms through earlier revenues and reduced trial costs. Thus, regulatory arbitrage by pharmaceutical firms may speed market entry and expand patient access to promising treatments. However, this acceleration comes with a potential cost: Off-label uses are often not backed by randomized or high-quality evidence and are associated with higher rates of adverse events (Eguale et al., 2016; Richardson, 2016; Wittich et al., 2012). Our findings underscore the importance of understanding how firms respond to the structure of regulatory incentives—and raise questions about whether existing approval pathways strike the appropriate balance between speed and quality.

This paper makes multiple contributions to the literature. First, a growing body of research has examined the relationship between regulation and innovation incentives, particularly in the context of medical technologies (Acemoglu and Linn, 2004; Berger et al., 2021; Blume-Kohout and Sood, 2013; Danzon and Keuffel, 2014; Dubois et al., 2015, 2025; Galasso and Luo, 2017; Grennan and Town, 2020; Maini and Pammolli, 2023; Malani and Philipson, 2012; Stern, 2017). Our paper adds to understanding of the consequences of entry regulation, both intended and unintended. We highlight how regulation affects not only whether a drug is approved, but also how firms prioritize among multiple potential markets. When firms can access broader markets through off-label prescribing, regulation creates incentives to pursue approval in smaller indications, while avoiding or deferring approval in larger ones. This dynamic has important implications for how policymakers allocate oversight and set evidentiary standards across therapeutic areas.

Second, this paper contributes to a growing set of papers on the measurement (Radley et al., 2006; Stafford, 2008), drivers (Dubois et al., 2025; Larkin et al., 2014; McKibbin, 2023; Shapiro, 2018), and consequences of off-label drug use (Bradford et al., 2018; Tunçel, 2025). Most closely related to our research, Dubois et al. (2025) show how policy changes on off-label promotion and prescribing influence firms' decisions to submit drug uses for formal approval. We build on this research by introducing a novel, ex ante measure of off-label market potential—one that does not require access to health care claims data but instead leverages biologically-based measures of similarity across disease indications to identify functional similarities.

Third, prior research has documented regulatory arbitrage in various contexts, such as in the choice of bankruptcy filing jurisdictions (Ellias, 2018), states of incorporation (Bebchuk and Cohen, 2003; Cain and Davidoff, 2012), litigation courts (Cohen et al., 2019; Sytch and Kim, 2021), global sourcing (Berry et al., 2021), and store locations (Holmes, 1998; Rao et al., 2011). However, despite growing policy attention to its implications for consumer welfare and drug access (Congressional Research Service, 2021), empirical evidence on regulatory arbitrage in the pharmaceutical sector remains limited. The prior work generally focuses on how firms selectively choose among different jurisdictions, with different regulations, for their activities (also called forum shopping). We add to

the existing literature by demonstrating that, even when governed by a single regulatory framework, pharmaceutical firms strategically circumvent this regulation by selectively choosing therapeutic uses for formal approval.

The paper proceeds as follows. Section 2 describes the institutional background. Section 3 presents a stylized model of indication choice. Section 4 outlines the data, including construction of our novel disease similarity index, and provides summary statistics. Section 5 explains our research design and gives the empirical results. Section 6 discusses the firm and policy implications of regulatory arbitrage. Section 7 concludes.

## 2 Background

### 2.1 Pharmaceutical Development and Entry Regulation

The development and approval process for a novel drug is long, costly, and risky. Drug development typically begins with preclinical testing in animals and human cells. If successful, the manufacturer submits an Investigational New Drug (IND) application to the FDA and begins the most expensive aspect of drug development: clinical trials. These trials advance through three primary phases, with costs increasing at each subsequent phase. Phase I trials assess safety and dosage in healthy volunteers; phase II trials examine safety and efficacy in 100 to 300 patients; and phase III trials test the drug in larger populations of 300 to 3,000 patients (FDA, 2024). Upon successful completion of phase III trials, the sponsor submits a New Drug Application (NDA) for FDA review. The full process typically spans 8 to 12 years, with estimated costs ranging from $300 million to over $2.6 billion and a success rate of only 9 percent for drugs that enter clinical testing (Adams and Brantner, 2006; Aryal et al., 2024; CSDD, 2014; Danzon and Keuffel, 2014; DiMasi, 2001; DiMasi et al., 2003; Wouters et al., 2020).

Importantly, FDA approval is indication-specific, meaning a drug receives regulatory approval to treat a specific disease in a specific patient population. To gain approval for an additional use, the manufacturer must submit a new IND, conduct supporting clinical trials, and file a supplemental New Drug Application (sNDA). The cost and duration of this process depend on the similarity

between the original and new indications (FDA, 1998a). For example, if the original and new uses are closely related, manufacturers seeking approval for the new use may skip phase I trials and conduct fewer phase II trials.[4] While some drug uses are discovered after the drug is first approved, others are known prior to approval. Indeed, industry reports highlight that "indication sequencing"—including the choice of a drug's "lead" indication—is an important decision for pharmaceutical firms (IQVIA, 2023). Beyond resource and time costs, there can be additional risks to the firm associated with seeking supplemental approvals, for instance, if subsequent clinical trials threaten the evidence base for approved indications or lead to the discovery of significant adverse events.

### 2.2 Off-Label Drug Use

The practice of using approved health care technologies for unapproved uses is legal and common, particularly among treatments for cancer, cardiovascular diseases, and psychiatric diseases (Stafford, 2008). An estimated 90 percent of approved drugs have multiple therapeutic uses (Gelijns et al., 1998). Off-label use occurs for a variety of reasons, including the lack of FDA-approved therapies for specific populations, the practice of using the same treatment for different but similar conditions, and insurance coverage (Wittich et al., 2012). For example, off-label use of psychiatric medicines is common in children because children are rarely included in clinical trials for drug approval (Lee et al., 2012). Many mental illnesses share the same or similar symptoms, motivating physicians to use a drug approved for one condition to treat another.[5]

The FDA recognizes that off-label use can be clinically appropriate under some circumstances, but it has expressed concern about its widespread adoption without rigorous supporting evidence (FDA, 2014). Indeed, prior research has found that off-label use is associated with higher rates of adverse events (Eguale et al., 2016). To mitigate potential public health risks, the FDA prohibits the direct promotion of off-label uses to physicians and patients. Nevertheless, evidence suggests that

[4] Examples include a new stage of the same disease or the same disease in a new population.

[5] The prevalence of off-label use depends on a physician's propensity to prescribe a drug with limited evidence of safety and efficacy. In practice, physicians who engage in off-label use are rarely accused of medical malpractice, and the process of informed consent does not require physicians to disclose that a drug is being used off-label. Further, off-label use is not necessarily negligent if the off-label use is included in the current standard of care.

manufacturers still generate clinical evidence to encourage off-label use.[6,7] Additionally, the FDA's policies towards forbidding off-label advertising has gradually loosened and been challenged over time (Avorn et al., 2015; FDA, 2014). For example, the Food and Drug Administration Modernization Act (FDAMA) of 1997 first permitted manufacturers to distribute peer-reviewed articles about off-label uses. In 2009, the FDA issued new guidance on reprint distribution that further eased restrictions. The Second Circuit's 2012 decision in *United States v. Caronia* held that the government could not criminally prosecute truthful, non-misleading off-label promotion.[8] Given this regulatory landscape, firms may strategically rely on off-label use—rather than pursue the costly, risky, and time-intensive process of formal approval for supplemental indications—to expand demand for their drugs.

### 2.3 Regulatory Arbitrage in the Pharmaceutical Industry

Regulatory arbitrage has been defined as "structuring activity to take advantage of gaps or differences in regulations or laws" (Pollman, 2019, p. 567). Since FDA approval is specific to a given use, firms developing drugs with multiple uses face variation in the likelihood of approval across indications. At the same time, off-label prescribing provides a mechanism for market diffusion beyond formally approved uses. This regulatory structure allows firms to respond strategically: They can pursue initial approval in small, lower-risk indications to minimize regulatory burden and expedite market entry, while relying on off-label drug use to access larger markets without formal approval.

The approach presents both advantages and disadvantages for pharmaceutical firms. On the one hand, obtaining approval in smaller disease indications is often less costly than in larger markets (Jayasundara et al., 2019). Trials for smaller indications typically require fewer participants, reducing recruitment costs (Sertkaya et al., 2016). Moreover, advances in genetic sequencing and biomarker testing allow firms to target patient subgroups with higher treatment responsiveness, further increasing the likelihood of approval (Chandra et al., 2019; Michaeli et al., 2023). Consistent with

[6]The U.S. Department of Justice has charged and fined several major companies with illegal off-label promotion, including Eli Lilly ($1.4 billion in 2009), Pfizer ($2.3 billion in 2009), GlaxoSmithKline ($3 billion in 2012), and Abbott ($1.6 billion in 2012).

[7]Off-label drug use could still occur without supporting clinical evidence, driven instead by physician experience and experimentation.

[8]Note that the staggered nature of these policy changes and the fact that they affected all disease areas simultaneously makes traditional difference-in-differences approaches difficult to implement in this setting.

this view, Appendix Figure A2 shows that drugs tested in smaller indications are associated with higher FDA approval rates and faster regulatory review times (i.e., the number of months between application submission and approval). Additionally, because drug prices in the U.S. are typically not indication-specific (Chandra and Garthwaite, 2017), firms can set higher prices based on inelastic demand in the small indication and apply the same price for its broader (off-label) use.

On the other hand, smaller indications often have limited patient populations, which can slow enrollment and restrict early revenues. Relying on off-label use for market expansion introduces uncertainty, as insurers may decline coverage and physician adoption can be uneven or unpredictable (Shapiro, 2018). Regulatory risk also remains as off-label promotion is restricted and enforcement has varied over time. Further, these off-label uses will typically be supported by weaker scientific evidence, and new adverse events may be discovered among patient populations not formally approved for the drug, threatening existing approved uses.

Taken together, FDA regulation creates asymmetric incentives across therapeutic markets. Regulatory arbitrage by pharmaceutical firms reflects a deliberate trade-off between regulatory risk and market reach. The extent to which firms pursue this strategy in practice is an empirical question we examine in the remainder of the paper.

## 3 A Model of Indication Choice

In this section, we provide a stylized theoretical model of how a pharmaceutical firm chooses among disease indications when seeking FDA regulatory approval. The model formalizes the central trade-off in our setting: Firms balance the regulatory costs and risks of approval in each indication against the potential to expand demand through off-label prescribing in related disease markets. Our key insight is that when off-label potential is high, firms may seek initial approval in smaller, lower-risk indications rather than in the largest available market. This response to the structure of regulation is what we characterize as regulatory arbitrage.

### 3.1 Preliminaries

We consider a drug manufacturer deciding whether to apply for FDA approval for a candidate molecule. The manufacturer can choose to apply for approval for an indication $i$ from a set $I = \{1, \ldots, N\}$ of $N$ possible disease indications. Each indication is defined as a quintet $(M_i, K_i, p_i, \mathcal{O}_i, T_i)$ where $M_i$ is the indication's focal market size (or, more accurately, the expected financial returns from that indication conditional on approval), $K_i$ is the cost of applying for approval (e.g., running clinical trials and going through FDA review processes), $p_i$ is the probability of receiving approval, $\mathcal{O}_i$ is indication $i$'s potential set of off-label indications, and $T_i$ is the indication's total market size (or the expected financial returns from that indication *plus* all its potential off-label uses).

*Timing.* The framework has two periods, after which the product goes generic and revenue goes to zero. We assume that because of some (unmodeled) capacity constraint, manufacturers can only apply for one indication in each period.

*Indication choice set.* We assume that the choice set of potential indications for approval is known and fixed prior to the time of the drug's initial approval; i.e., we abstract away from the situation where learning about additional indications may occur after the drug's initial approval. This is consistent with the growth of large-scale screening methods to identify new indications early in a drug candidate's life, such as in silico screens (Cha et al., 2018). We consider the choice set to correspond to indications in which the firm has already conducted early-stage clinical trials. If an indication is chosen for initial approval, it is no longer available for supplemental approval. For simplicity, we assume the firm's choice set consists of two indications, $I = \{A, B\}$, where $A$ denotes a large-market indication and $B$ a small-market one, i.e., $M_A > M_B$.

*Cost of regulatory approval.* Consistent with existing evidence on the costs of clinical trials, we consider the costs of regulatory approval to be greater for indications of larger market size, i.e., $K_A > K_B$.[9]

[9] We set per-period variable costs to be zero.

*Probability of regulatory approval.* We assume that the probability of approval is greater for smaller indications, i.e., $p_A < p_B$. This is plausible due to selective patient enrollment for smaller indications.

*Off-label markets.* Each indication has a corresponding set of potential off-label indications, denoted by $\mathcal{O}_i$. If a drug receives regulatory approval for indication $i$, then $\mathcal{O}_i$ is the set of all indications $j$ for which doctors may choose to prescribe the drug off-label (i.e., indications in $\mathcal{O}_i$ exceed some threshold of known relatedness to indication $i$). We assume that $A$ is in $\mathcal{O}_B$ and $B$ is in $\mathcal{O}_\mathcal{A}$. For simplicity, we consider all other potential off-label indications for $A$ to be captured by representative indication $A'$ and similarly for $B$. That is, $\mathcal{O}_A = \{B, A'\}$ and $\mathcal{O}_B = \{A, B'\}$.

*Off-label diffusion rate.* The rate of off-label diffusion is $d_{i,j} \in [0, 1]$, which is known to the firm and gives the proportion of the market for indication $j$ that will actually use the drug off-label following regulatory approval for indication $i$. For example, a diffusion rate of 0 would imply that, following initial regulatory approval for $i$, the drug is not used at all off-label for indication $j$, and a diffusion rate of 1 would imply that it is used by $j$'s entire expected market. Note that these diffusion rates are symmetric such that $d_{i,j} = d_{j,i}$.

*Total market size.* Total market size $T_i$ for a given indication is the sum of its focal market size plus its potential off-label markets, which are given by the market size of each off-label indication weighted by its diffusion rate: i.e., $T_i = M_i + \sum_{j \in \mathcal{O}_i} d_{i,j} M_j$. We consider $T_i$ to be the total expected financial returns a firm receives from indication $i$'s approval, including from all its off-label uses. Given the assumptions above on $M_A > M_B$, whether $T_A$ is greater than $T_B$ or vice versa will depend on off-label diffusion rates and market sizes. We hold market sizes as fixed over the two periods.

The profit-maximizing pharmaceutical firm will seek to enter the market with its drug in period 1 if and only if the expected return from the initial indication exceeds its fixed cost of regulatory approval. Similarly, the firm will seek a supplemental regulatory approval if and only if the expected return from the supplemental indication exceeds its fixed cost. We make the simplifying assumption that entry in at least the first period is optimal. Conditional on entry, the firm chooses an order of

indications for its drug that maximizes the expected stream of total profits over the two periods (i.e., the drug's on-patent life). The firm's decision tree is given in Figure 2.

### 3.2 Firm Incentives to Seek Regulatory Approval

This framework produces four potential strategies for the firm: (1) enter with $A$ in period 1, enter with $B$ in period 2; (2) enter with $A$, no entry; (3) enter with $B$, enter with $A$; and (4) enter with $B$, no entry. We consider the expected value from each strategy in turn.

The expected value of seeking regulatory approval for indication $A$ in period 1 and for indication $B$ in period 2 is:

$$EV_{A,B} = 2p_A T_A + p_B[(1 - d_{A,B})M_B + \sum_{\substack{k \in \mathcal{O}_B \\ k \neq A}} d_{B,k}(1 - d_{A,k})M_k] - K_A - K_B \tag{1}$$

Note that with regulatory approval for $A$ in period 1, the firm penetrates a portion $d_{A,B}$ of the market for $B$ via off-label use. This leaves $(1 - d_{A,B})$ of the market for $B$ that can be gained via regulatory approval for $B$ in period 2. Note also that while $A \in \mathcal{O}_B$ initially, since the drug receives regulatory approval for $A$ in period 1, it is no longer included among $B$'s potential off-label markets at period 2. For any indication $k \in (O_A \cap O_B)$, the firm penetrates a portion $d_{A,k}$ of the market for $k$ via off-label use in period 1, leaving $d_{B,k}(1 - d_{A,k})$ of the market for $k$ to be gained via off-label use in period 2.

The expected value of seeking regulatory approval for indication A in the first period and not entering in the second is:

$$EV_{A,no\ entry} = 2p_A T_A - K_A \tag{2}$$

Similarly, the expected value of seeking regulatory approval first for B and second for A is:

$$EV_{B,A} = 2p_B T_B + p_A[(1 - d_{A,B})M_A + \sum_{\substack{j \in \mathcal{O}_A \\ j \neq B}} d_{A,j}(1 - d_{B,j})M_j] - K_B - K_A \tag{3}$$

And the expected value of seeking regulatory approval for B in the first period and not entering in the second is:

$$EV_{B,no\ entry} = 2p_B T_B - K_B \tag{4}$$

The firm chooses the strategy (indication choice in the first period and whether to seek regulatory approval in the second for the remaining indication) that maximizes its expected value.

### 3.3 Model Predictions

We aim to understand how market size relates to regulatory approval decisions in settings where off-label use is more or less common. In the subsections that follow, we consider three separate scenarios: (1) where off-label use is prohibited, (2) where complete off-label diffusion occurs following a drug's regulatory approval in a given indication, and (3) where off-label diffusion is intermediate, varying across indication pairs.

#### 3.3.1 Off-Label Use is Prohibited

First, we consider the scenario where off-label use is prohibited ($d_{A,j} = d_{B,k} = 0\,\forall j, k$). In that case, the expected value in equation (1) simplifies to $2p_A M_A + p_B M_B - K_A - K_B$ and the expected value in equation (2) simplifies to $2p_A M_A - K_A$. Equations (3) and (4) simplify similarly. Conditional on $2p_A M_A - K_A > 0$ and $p_B M_B - K_B > 0$, and given our initial assumptions on market size $M_A > M_B$ and the probabilities of approval $p_A < p_B$, the firm will select indication $A$ for regulatory approval in period 1 and indication $B$ for approval in period 2 if and only if:

$$2p_A M_A + p_B M_B - K_A - K_B > 2p_B M_B + p_A M_A - K_B - K_A, \text{ or} \tag{5}$$

$$M_A > \frac{p_B}{p_A} M_B \tag{6}$$

The condition in (6) shows that provided $M_A$ is large relative to $M_B$, then the firm selects $A$ for regulatory approval in settings where off-label use is prohibited. This leads us to the following proposition:

PROPOSITION 1. *In the absence of off-label use, firms will prioritize the larger indication for initial regulatory approval provided that indication's market size is sufficiently large.*

### 3.3.2 Complete off-label diffusion

Second, we consider the scenario where regulatory approval for an indication leads to complete off-label diffusion, i.e., the total off-label population for that indication also uses the drug ($d_{A,j} = d_{B,k} = 1 \, \forall j, k$).

Here, the expected value in equation (1) simplifies to $2p_A T_A + p_B \sum_{\substack{k \in \mathcal{O}_B \setminus \mathcal{O}_A \\ k \neq A}} M_k - K_A - K_B$ and the expected value in equation (2) simplifies to $2p_A T_A - K_A$. Again, equations (3) and (4) simplify similarly.

The firm's optimal strategy will differ depending on the nature of $\mathcal{O}_A$ and $\mathcal{O}_B$ and the relative market sizes of their associated indications. We consider the following two scenarios:

**Scenario 1:** $A$ and $B$ have the same potential off-label markets ($A' = B'$). In this scenario, under complete diffusion, the firm has no incentive to seek regulatory approval in the second period because it is already reaching all potential markets, including off-label ones, with regulatory approval in the first period. Conditional on $2p_B T_B - K_B > 0$ and given our initial assumptions on the probability of regulatory approval $p_A < p_B$ and fixed costs of approval $K_A > K_B$, the firm will select indication $B$ for regulatory approval in period 1 and seek no approval in period 2.

PROPOSITION 2. *Under complete diffusion and the same potential off-label markets, firms will enter the smaller indication first and seek no entry in the second period.*

**Scenario 2:** $A$ and $B$ have no potential off-label markets in common ($\mathcal{O}_\mathcal{A} \cap \mathcal{O}_\mathcal{B} = \emptyset$). Conditional on $2p_B T_B - K_B > 0$ and $p_A M_{A'} - K_A > 0$, the firm will select indication $B$ for regulatory approval in period 1 and indication $A$ for approval in period 2 if and only if:

$$\begin{aligned} 2p_B[M_B + M_A] + 3p_B M_{B'} > \\ 2p_A[M_A + M_B] + 3p_A M_{A'} \end{aligned} \tag{7}$$

See Appendix B for the proof. Given our initial assumption of $p_B > p_A$, a sufficient condition for this inequality to hold is $M_{B'} > M_{A'}$, i.e., that $B$'s off-label markets are larger than $A$'s off-label markets.

In the event that entry in the second period is not profitable, the firm will select indication $B$ for regulatory approval in period 1 and seek no approval in period 2 if and only if:

$$\begin{aligned} 2p_B[M_B + M_A + M_{B'}] - K_B > \\ 2p_A[M_A + M_B + M_{A'}] - K_A \end{aligned} \tag{8}$$

As in the case of inequality (7), a sufficient condition for inequality (8) to hold is $M_{B'} > M_{A'}$. We thus have the following proposition:

> PROPOSITION 3. *Under complete diffusion and no off-label markets in common, firms will enter the smaller indication first provided its off-label market sizes exceed those of the larger indication.*

### 3.3.3 Intermediate Off-Label Diffusion

Finally, we consider the scenario of intermediate off-label diffusion, where diffusion rates vary across indication pairs and fall between 0 and 1. In particular, we demonstrate when a firm may strategically choose to seek initial regulatory approval in a smaller market instead of a larger one. Conditional on entry in both periods, the firm will select indication $B$ for regulatory approval in period 1 and indication $A$ for approval in period 2 if:

$$\begin{aligned} p_B[\sum_{k\in\mathcal{O}_B} d_{B,k}M_k + d_{A,B}(M_A + M_B) + \sum_{\substack{k\in\mathcal{O}_B \\ k\neq A}} d_{B,k}d_{A,k}M_k] > \\ p_A[\sum_{j\in\mathcal{O}_A} d_{A,j}M_j + d_{A,B}(M_A + M_B) + \sum_{\substack{j\in\mathcal{O}_A \\ j\neq B}} d_{A,j}d_{B,j}M_j] \end{aligned} \tag{9}$$

See Appendix B for the proof. This inequality will be satisfied if $p_B$ is sufficiently large relative to $p_A$ and/or if $B$'s off-label market reach is sufficiently large (which may occur with either high

off-label diffusion rates or high focal market sizes for those potential off-label indications.) This gives us the following proposition:

> PROPOSITION 4. *Under intermediate off-label diffusion, firms will prioritize a smaller indication for initial regulatory approval provided that indication's probability of approval or the off-label markets it penetrates through regulatory approval are sufficiently large.*

While we do not aim to test each proposition, taken together, they suggest instances where a firm would engage in regulatory arbitrage by choosing initial entry in a smaller indication rather than a larger one. We now take this theoretical prediction to the data.

## 4 Data

To empirically investigate whether pharmaceutical firms engage in regulatory arbitrage when making market entry decisions, we construct a novel dataset combining regulatory approvals, clinical trials, market size, and genetic similarity across cancer indications. Our main analytic dataset consists of 129 cancer drugs first approved by the FDA between 1978 and 2016. We consider two types of market entry decisions: regulatory approvals and clinical trials. We obtain regulatory approval data from the Clarivate Cortellis Competitive Intelligence Global database and the FDA's Drugs@FDA database, which together provide information on both original NDAs and sNDAs. We classify approved indications at the cancer site-stage level (e.g., "breast–metastatic").[10] We link these regulatory data to clinical trial records from the Clarivate Cortellis Clinical Trials Intelligence database.[11] Data limitations prevent us from categorizing clinical trial indications to the cancer stage level; as a result, our clinical trial analyses are conducted at the drug-cancer site level.

To proxy for market size, we collect data on the number of new diagnoses associated with each cancer's site and stage (Budish et al., 2015). These data come from the Surveillance, Epidemiology,

[10] FDA-approved indications are typically more granular than our site-stage coding. For instance, letrozole was initially approved for "advanced breast cancer in postmenopausal women with disease progression following anti-estrogen therapy," and later for "first-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor-unknown locally advanced or metastatic breast cancer." Both approvals are classified as "breast–metastatic."

[11] The clinical trials used in our main analyses consist of those linked to an approved drug. In robustness checks, we confirm that our results are robust to including all clinical trials, regardless of whether they are linked to an approved or unapproved drug.

and End Results (SEER) database, available from the National Cancer Institute (NCI). We focus on five-year lagged averages of market size, where we calculate these lags relative to either the year of indication approval (for regulatory approval analyses) or trial start (for clinical trial analyses).

### 4.1 Cancer Genome Mapping Data

To capture the potential for regulatory arbitrage, we construct a novel proxy for each drug's off-label market size using data from large-scale cancer genome mapping studies. Cancer genome sequencing is an advance in medical technology that systematically catalogs the genetic mutations underlying different cancer types. Genome sequencing compares the DNA sequences of cancer cells to those of normal tissue, so that researchers can determine the mutations behind specific cancers and understand similarities across different cancer types (Weinstein et al., 2013). Using genetic sequencing data, we characterize the similarity between different diseases to define a drug's expected off-label cancer sites. For instance, cancer mapping efforts have revealed the occurrence of the same genetic mutations underlying both ovarian and breast cancer (TCGA Research Network, 2011). This suggests that ovarian cancer may be an off-label site for a drug approved for breast cancer (Pleasance et al., 2022).

We obtain information on gene-cancer pairings uncovered in large-scale cancer mapping efforts from the publicly accessible Catalogue of Somatic Mutations in Cancer (COSMIC) and cBioPortal for Cancer Genomics (cBioPortal) databases (Cerami et al., 2012; Sondka et al., 2018; Tate et al., 2018). Both databases contain a curated set of cancer genome data from hundreds of genetic sequencing studies and catalog the set of genes (e.g., BRCA1) containing mutations that are causally associated with cancer (e.g., breast and ovarian cancers). We follow the bioinformatics literature in focusing on high-frequency mutations within each cancer site, and define "high frequency" as the top 10 percent of mutations identified in large-scale sequencing studies.[12]

Our use of genome mapping data to quantify biologically-driven off-label potential is conceptually related to recent efforts in the bioinformatics literature to use molecular and genomic similarity

[12] In robustness checks, we show that our findings are robust to alternative thresholds.

to guide drug repurposing and discovery (Cheng et al., 2019; Tanoli et al., 2021). This includes leveraging data from disease-specific sequencing efforts (e.g., the Cancer Genome Atlas) and genome-wide association studies (GWAS) to uncover biological linkages across diseases that are then used to identify new uses for existing drugs (Uffelmann et al., 2021). As a point of validation, genetically similar cancer sites are likely to be treated with the same drugs (Chakravarty et al., 2017; Suehnholz et al., 2024).

We build on these insights by exploiting genetic similarity to study how regulation shapes firms' innovation and entry decisions, using it to estimate the ex ante set of disease markets where a drug may plausibly be used off-label.[13] Before proceeding, we note that the use of cancer genome mapping data to construct the similarity index raises a question about whether firms would have had access to this genetic information at the time of their R&D and market entry decisions. While our genomic similarity measure likely captures some relationships that were revealed to firms only through large-scale sequencing efforts Kao (2025), it also reflects longstanding biological relationships between cancer sites that were at least partially understood through firms' prior research experiences. In light of this, our genomic similarity-based measure of off-label market size is best interpreted as an upper bound on the set of biologically-linked off-label markets available to firms and unlikely to be entirely unrelated from their available information at the time of entry decisions.

#### 4.1.1 Gene-Based Disease Similarity

Using the cancer genome mapping data, we then estimate the similarity between cancer sites using the extent of overlap between sets of genetic mutations associated with each cancer type. In the spirit of Krieger et al. (2022), we quantify the similarity between two different cancer sites by calculating the Tanimoto distance (Jaccard coefficient). This measure calculates the distance between each set of genetic mutations associated with each cancer site. For example, the similarity index $s$ between cancer sites A and B is the intersection of A and B's genetic mutations divided by the union of

[13] We are unable to exploit the staggered release of information from large-scale cancer genome mapping studies (as in Kao (2025)) because that information disclosure occurs at the gene-cancer site level, which is too granular to generate meaningful variation in our setting.

these mutations:

$$s_{A,B} \equiv \frac{|A \cap B|}{|A \cup B|} = \frac{|A \cap B|}{|A| + |B| - |A \cap B|} \tag{10}$$

A similarity index of 0 implies that a pair of cancer sites are not closely related and have no common mutations, while a measure of 1 implies that they are closely related and have exactly the same set of mutations. Figure 3 provides a heat map of our similarity index across all cancer sites. The mean index across these cancer sites is 0.207 (SD = 0.263).

#### 4.1.2 Calculating Expected Off-Label Market Size

We use the similarity index to determine the expected off-label market size for each indication. This calculation is based on the market size for cancer sites related to indication $i$ and the corresponding similarity indices:

$$\textit{Off-Label Market Size}_{i,t} = \sum_{j \neq i} s_{i,j} \textit{Market Size}_{j,t} \tag{11}$$

Here, indication $i$ has an off-label market size at time $t$ that is defined as the weighted sum of the market sizes of all other cancer sites $j$ ($j \neq i$) at time $t$, where the weight is the similarity index between cancer sites $i$ and $j$. To illustrate, consider a simple example between three cancer sites, A, B, and C. Assume that cancer site B has a similarity with cancer site A ($s_{A,B} = 0.09$) and a similarity with cancer site C ($s_{B,C} = 0.01$). Suppose that at time $t$, the market size for cancer site A is 100 and the market size for cancer site C is 20. At time $t$, the off-label market size for a drug initially approved in cancer site B is $(0.09 \times 100) + (0.01 \times 20) = 9.2$. Intuitively, the similarity index $s_{i,j}$ is an empirical proxy for the off-label diffusion rate $d_{i,j}$ in the conceptual framework: A higher genetic similarity between cancer sites $i$ and $j$ implies a greater likelihood that a drug approved for one site will be used off-label in the other.

Before continuing, we note some limitations of this measure. First, our similarity measure may not fully capture the true level of overlap across cancer sites. In particular, the data we use may reflect both false positives and false negatives. On the one hand, not all shared genetic mutations between cancer sites necessarily imply a therapeutically meaningful linkage; some mutations may be common across many cancers without indicating that a drug effective in one site would be useful

in another. To address this concern, we construct an alternative similarity measure that restricts attention to genes found in the COSMIC Cancer Gene Census, a curated, expert-reviewed catalog of genes for which mutations have been causally implicated in cancer.[14] By limiting the set of mutations to those with stronger evidence of a causal role in cancer development, this measure reduces the likelihood that our index captures biologically spurious overlap. On the other hand, our baseline restriction to the top 10 percent of most frequently occurring mutations within each cancer site may exclude relevant but lower-frequency mutations, potentially understating the true level of similarity between cancer sites. To address this, we gradually broaden the frequency threshold to include the top 20 percent and top 30 percent of mutations. We show that our results are robust to both of these alternative similarity measures. Second, our gene-based similarity measure is aimed at reflecting off-label drug use that is supported by scientific evidence. Since off-label drug use can be driven by other factors, such as costs and drug side effects (Stafford, 2008), it is likely to be an underestimate of the overall off-label market size (Radley et al., 2006). To address this, we conduct an analysis where we directly incorporate *actual* measures of off-label drug use.

### 4.2 Controls

We collect data on multiple control variables to mitigate the concern that the relationship between indication order and market size may be confounded by factors unrelated to the practice of regulatory arbitrage. As a proxy for the level of competition faced by each drug in a given indication, we count the cumulative number of drug approvals in the same indication in the year prior to the indication approval year (for regulatory approval analyses) or the trial start year (for clinical trial analyses). To capture regulatory incentives associated with subsequent market entry decisions, we compile data on whether the drug ever received an orphan drug designation or accelerated approval. Established in 1983, the Orphan Drug Act (ODA) offers targeted regulatory incentives (e.g., tax benefits and regulatory exclusivities) to firms developing drugs for "orphan" diseases (i.e., rare diseases affecting less than 200,000 individuals).[15] Since the passage of the ODA, there has been a significant increase

[14] The CGC's cancer experts apply strict criteria when determining the set of gene-cancer associations to include in the database. For more information, see `https://www.sanger.ac.uk/data/cancer-gene-census/`.

[15] For more details, see `https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products`.

in the number of approved orphan drugs (from 10 in 1990 to 77 in 2017) (Miller and Lanthier, 2018). Since orphan designation increases firm incentives for entry in small indications, failing to control for it may conflate entry decisions that are driven by targeted regulatory incentives, rather than firms' decisions to engage in regulatory arbitrage. Separately, the FDA implemented the Accelerated Approval program in 2012 as a way to allow drugs that filled an unmet medical need to be approved more quickly on the basis of a surrogate endpoint rather than a direct measure of clinical benefit.[16] Smaller indications may be more likely to qualify for accelerated approval because they are more likely to represent areas of serious unmet need with few existing treatment options. If accelerated approval disproportionately lowers the regulatory requirements for smaller indications, the patterns we document could partly reflect the availability of this expedited pathway rather than strategic sequencing by firms. Controlling for accelerated approval status allows us to distinguish entry decisions shaped by this regulatory pathway from those more consistent with regulatory arbitrage.

Next, we construct controls for intellectual property protection, which may also influence the relationship between indication order and market size. For instance, Budish et al. (2015) show that firms have reduced incentives to pursue research for early-stage cancers relative to late-stage ones because of the former's longer development times and shorter resulting patent terms post-launch. If early-stage cancers tend to have larger market sizes, then observed patterns in indication order may partly reflect patent-related incentives rather than strategic regulatory behavior. In light of this, we combine information on pharmaceutical IP protection from the United States Patent and Trademark Office (USPTO) and the FDA's Orange Book.[17] We create two controls for IP protection: *Primary IP protection* measures the months from each indication approval (or trial start) date to when the drug's primary IP expires. We consider the primary IP expiration to be the latter of either the molecule patent or the new chemical entity exclusivity expiration. Primary IP protection is generally considered the strongest form of IP protection, with almost certain enforcement.[18] *Potential IP*

[16] For more details, see `https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval`.

[17] Drugs are protected by two types of IP rights: patents granted by the USPTO and regulatory exclusivities granted by the FDA.

[18] For those trials taking place before a drug's initial launch, we assume the firms have an ex ante expectation of what this primary IP expiration will be. For trials or approvals taking place after the primary IP has expired, we consider this measure to be zero.

*protection* gives the maximum possible term of monopoly protection, if all IP on a drug were upheld. It measures the months from each indication approval (or trial start) to when the final IP on the drug expires.[19]

Table 1 presents descriptive statistics for our sample of oncology drugs first approved between 1978 and 2016. The average drug is tested in 47 different trial indications (cancer sites) and receives FDA approval in 4 unique approval indications (cancer site-stage observations).[20] Within our sample, 56 percent of drugs receive an orphan drug designation and 34 percent have an accelerated approval. Across all drug-indications, the mean primary IP protection remaining at the time of approval is 124 months (10.3 years) and mean potential IP protection is 174 months (14.5 years). The maximum primary IP protection remaining is 277 months (23.1 years) and maximum potential IP protection is 346 months (28.8 years). Mean off-label market size (36,632 diagnoses) is 37 times the mean market size of approval indications (985 diagnoses). Appendix Figure A4 shows that there are meaningful time lags between indications: The average time between trial indications is more than 1 year and the average time between approval indications is nearly 3 years.

## 5 Empirical Approach and Results

We next systematically examine whether firms sequence clinical trials and regulatory approvals in ways consistent with regulatory arbitrage. While Figure 1 provides descriptive evidence of how average market size varies with indication order, our estimations mirror firms' sequencing decisions: When a firm has several potential indications, firms must decide the order in which to pursue their indications. We aggregate our data on market entry decisions, market size, and drug characteristics into drug-indication order (e.g., letrozole-first indication) observations, where indication order is defined as the sequence of indications in which a given drug is clinically tested (or approved).[21] For

[19] For trials occurring before a drug's initial launch, we consider the patents and exclusivities in effect at launch to calculate this measure. For all trials after launch, we consider the patents and exclusivities in effect at the trial start date.

[20] Appendix Figure A3 shows the complete distribution of trial and approval indications per drug.

[21] When a single indication order corresponds to multiple indications (e.g., a drug is initially clinically tested in both breast and ovarian cancers in trials starting on the same date), we take the average of their market sizes.

drug $d$ and indication order $i$, we estimate the following:

$$IndicationOrder_{d,i} = \alpha + \beta_1 MarketSize_{d,i} + \gamma X_{d,i} + \epsilon_{d,i} \tag{12}$$

Our main estimate of interest is the coefficient on $MarketSize$, the natural log of the lagged five-year average market size associated with indication order $i$ for drug $d$. An estimate of $\beta_1 < 0$ suggests that larger markets are prioritized earlier (lower indication order), whereas $\beta_1 > 0$ suggests that smaller markets are prioritized earlier. We include a comprehensive set of controls $X$ to account for observable factors that may influence firms' indication order decisions, including detailed measures of intellectual property protection (i.e., primary and potential IP); the drug's initial approval year; its cancer group (e.g., stomach and esophageal cancers would belong to the "digestive system" cancer group); the level of competition (i.e., the cumulative number of drug approvals in the same indication as of the prior year); and regulatory incentives (i.e., whether it has an orphan designation or accelerated approval). All estimates are from ordinary least squares (OLS) regressions with robust standard errors.

### 5.1 Trends in Market Entry Decisions

We begin by examining descriptive trends in firms' market entry decisions. Figure 4 plots the relationship between indication order and market size for our sample of drugs, separately for clinical trials (Panel A) and regulatory approvals (Panel B). Consistent with Figure 1, Panels A and B illustrate key differences between the order of clinical trials and regulatory approvals. Panel A shows a strong negative correlation between trial indication order and market size: Earlier indications are associated with larger potential markets. In contrast, Panel B reveals no discernible relationship between approval indication order and market size, suggesting that firms do not systematically prioritize larger markets when seeking FDA approval. These patterns indicate the presence of regulatory arbitrage—firms may initially target smaller, more favorable indications for formal approval while using off-label pathways to access larger markets.

Importantly, the fact that firms tend to initiate trials in larger potential markets but seek initial FDA approval in smaller markets suggests that scientific and logistical constraints, such as availability of technological resources and trial participants, are unlikely to be driving the observed patterns. For example, if firms' market entry decisions were primarily driven by patient availability, we would expect similar patterns across both trials and approvals. Instead, the divergence suggests that firms may delay approval in larger markets, despite having trial data, to reduce their regulatory burden.

Appendix Table C1 formalizes these relationships. Column 1 reports the raw correlation between trial indication order and market size. The estimated coefficient implies that a 10-percent increase in market size is associated with a 0.22-unit ($\approx -2.315 \times \ln(1.10)$) decrease in indication order. Column 2 shows that this negative relationship between trial indication order and market size persists once all controls are included, and the relationship remains significant at the 1-percent level. Columns 3 and 4 repeat these same regressions for approvals instead of trials. Column 3 confirms that approval indication order has no significant relationship with market size. Once all controls are included in Column 4, the relationship remains quantitatively small and insignificant. These findings suggest that observable firm and market characteristics do not explain the gap between the ordering of clinical trials and regulatory approvals.[22]

While our setting does not allow for identification of the direct effects of regulatory structure on entry behavior—these results provide novel descriptive evidence consistent with regulatory arbitrage. Specifically, the findings suggest that firms may strategically pursue approval in smaller disease markets where entry barriers are lower, relying on off-label use to access larger markets. In the sections that follow, we conduct two empirical tests to assess this hypothesis more directly by incorporating measures of off-label market potential into our analyses.

[22] Appendix Table D1 shows that we observe similar trends when expanding our set of trials to include those associated with both approved and unapproved cancer drugs with a first trial between 1998 and 2001, corresponding to the most complete coverage of our trials dataset.

### 5.2 Incorporating Off-Label Market Potential

In our first empirical test to determine whether the patterns we observe above are consistent with regulatory arbitrage, we incorporate our measure of total market size—defined as the sum of the focal indication's market size and its genetically similar off-label markets. Table 2 presents results using this expanded outcome measure. For reference, Columns 1 and 3 repeat the baseline specifications of Appendix Table C1, where the primary explanatory variable is the market size of the focal indication only and all controls are included. Column 1 shows the clinical trial specification, and Column 3 shows the approval specification. Columns 2 and 4 replace the primary explanatory variable with total market size, incorporating potential off-label opportunities based on disease similarity. Column 2 shows that for clinical trials, the negative relationship between indication order and market size persists even when off-label potential is included: A 10-percent increase in total market size is associated with a 0.11-unit ($\approx -1.110 \times \ln(1.10)$) decrease in indication order. Column 4 reveals a noticeable shift in approvals. Whereas Column 3 showed no relationship between approval indication order and focal market size, Column 4 shows that when total market size is used as the explanatory variable, the relationship becomes negative and statistically significant. A 10-percent increase in approval indication order is associated with a 0.014-unit ($\approx -0.146 \times \ln(1.10)$) decline in indication order.

As a robustness check, we construct alternative measures of total market size based on broader gene-cancer similarity thresholds. Specifically, we define "high frequency" as the top 20 percent or 30 percent of mutations identified in large-scale sequencing studies. We also construct measures that restrict attention to frequently occurring mutations among genes found in the COSMIC Cancer Gene Census. Table 3 shows that the main results are robust to these alternative definitions of genetic similarity, supporting our findings across a range of biologically-linked off-label markets. Under these alternative definitions, we find that a 10-percent increase in total market size is associated with a decline in indication order of between 0.014 ($\approx -0.145 \times \ln(1.10)$) and 0.016 ($\approx 0.164 \times \ln(1.10)$) units.

These results are consistent with the view that firms systematically prioritize larger markets when conducting clinical trials, but seek initial FDA approval in smaller focal indications. In other words, firms may enter through smaller, more favorable regulatory pathways while anticipating subsequent expansion into biologically-similar markets via off-label use. We note that the total market size and approval indication order estimates in Table C1 and Table 3 are marginally significant and so we interpret them with caution. However, the stability of the sign, magnitude, and significance across all alternative similarity specifications in Table 3 increases our confidence in these patterns. Further, in the subsequent section, we provide complementary evidence by exploiting variation in actual off-label prescribing rates across disease categories.

### 5.3 Differences in Actual Off-Label Drug Use

In the prior analyses, we estimated off-label market potential by linking our cancer dataset to cancer genome mapping information. This allowed us to approximate a drug's *expected* off-label market size as supported by scientific evidence. In practice, off-label use may occur in the absence of supporting scientific evidence (e.g., due to physician experience, experimentation, the lack of FDA-approved treatments, or reimbursement policies). To complement our previous approach, we conduct a second empirical test incorporating measures of *actual* off-label drug use. One challenge is that available measures of actual off-label drug use are generally restricted to survey and health insurance claims data that cover specific patient populations (e.g., Medicare enrollees), limiting our ability to capture total off-label drug use. We use therapeutic-level off-label prescribing rates from Radley et al. (2006), who estimate these rates based on physician surveys, as a proxy for actual off-label activity.

For this empirical test, we extend our analyses beyond cancer by using a cross-disease dataset consisting of cancer and non-cancer drugs first approved between 1998 and 2021. We categorize approved indications using International Classification of Disease (ICD-9) codes. As a proxy for the market size of drugs in this dataset, we use the number of diagnoses from the Medical Expenditure Panel Survey (MEPS). We calculate yearly average market size at the ICD-9 level, using data from 1996 to 1997. We distinguish disease categories with high versus low opportunities

for regulatory arbitrage, as measured by their off-label propensity. Diseases with low off-label propensity (low opportunities for regulatory arbitrage) include antidiabetics, antihypertensives, and antihyperlipidemics; those with high off-label propensity (high opportunities for regulatory arbitrage) include oncology, anticonvulsants, psychiatry, and antiasthmatics (Radley et al., 2006). Our final cross-disease sample includes 615 drugs (of which 482 drugs are initially approved in diseases with high off-label propensity and 133 drugs in diseases with low propensity) mapped into 802 drug-indication observations.

Figure 5 shows that drugs in disease categories with high off-label propensity receive more total approvals, on average, than those in low-propensity categories. Notably, the relationship between indication order and market size differs across the two groups. For high off-label drugs, each 10-percent increase in market size is associated with a 0.008-unit ($\approx$ -0.081 $\times$ ln(1.10)) decrease in indication order. For low off-label drugs, the decline is steeper—a 0.026-unit ($\approx$ -0.277 $\times$ ln(1.10)) decrease in indication order. These results are in line with the hypothesis that firms in high off-label areas are more willing to pursue initial approval in smaller markets, anticipating later expansion through off-label prescribing. In contrast, firms in low off-label areas face fewer opportunities for informal diffusion of their pharmaceuticals and therefore have stronger incentives to prioritize larger markets in their initial approval decisions.

We supplement these cross-disease findings with several robustness checks. First, we control for observable drug and market characteristics (Appendix Table D2). Second, we include controls for alternative disease measures (Anatomical Therapeutic Chemical (ATC) classifications) in Appendix Table D3.[23] Finally, we verify the robustness of our categorization using an alternative measure of off-label use derived from IMS prescribing data (Appendix Table D4).

### 5.4 Alternative Explanations

Our findings provide evidence of regulatory arbitrage in pharmaceutical firms' entry decisions. Through the inclusion of various controls, we have addressed multiple alternative explanations.

[23] We are grateful for the ATC-drug crosswalk provided by the authors of Kakani et al. (2022).

For instance, one concern may be that the indication sequencing choices we observe reflect firms' abilities to obtain regulatory incentives or exclusivities for more narrow indications; our controls for orphan drug designation, accelerated approval, intellectual property protection, and indication group account for such opportunities. In this section, we consider several alternative explanations for the patterns we observe.

### 5.4.1 Differences in Expected Trial Duration

One alternative explanation is that firms sequence their clinical trials based on expected trial duration rather than market size. For example, firms may give priority to indications with longer anticipated trials if these involve more complex diseases requiring extended trial periods and closer monitoring. If this were the case, the negative relationship between trial indication order and market size, as well as the absence of a corresponding relationship for approvals, could be explained by variation in trial length rather than by regulatory arbitrage.

To evaluate this potential alternative explanation, we return to the cancer dataset used in our prior analyses and redefine trial indication order using trial end dates rather than start dates. As shown in Appendix Figure D1, the strong negative relationship between trial order and market size remains. This result suggests that the observed patterns are unlikely to be driven by differences in trial duration.

### 5.4.2 Differential FDA Review Times

A second alternative explanation is that the absence of a strong relationship between approval indication order and market size could be driven by differential FDA review times. If firms tend to submit applications for larger markets earlier, but those applications are subject to longer regulatory review periods, then the approval order we observe may reflect agency timing rather than firm strategy. To address this, we collect original application submission dates from FDA review letters and redefine approval indication order using submission rather than approval timing. As shown in Appendix Figure D2, the relationship between approval order and market size remains statistically insignificant, suggesting that variation in FDA review times does not explain our findings.

### 5.4.3 FDA Selection

A third alternative explanation is that the observed approval patterns reflect direct FDA selection rather than firm strategy. Because publicly available FDA data include only successful approvals, it is possible that we observe more approvals in smaller markets simply because applications for larger indications are more likely to be rejected or delayed. If so, the lack of a strong relationship between approval order and market size could reflect FDA selection (e.g., where the FDA systematically denies or slows approval for drugs targeting larger indications) rather than firms' indication order decisions.

Although we cannot directly observe unsubmitted or rejected applications, multiple factors suggest this explanation is unlikely to account for our findings. First, our results are robust to controls for regulatory incentives, such as orphan drug designation and accelerated approval, which are closely linked to approval likelihood. Second, the costs associated with filing an FDA application are substantial, making it unlikely that firms would routinely submit applications they expect to be denied. Taken together, these considerations support the interpretation that the observed sequencing of approvals reflects firm strategy (which may be informed by regulatory expectations) rather than a pattern driven primarily by FDA selection.

### 5.4.4 Firm selection

Finally, a separate concern is that these patterns are driven not by strategic rationales but by firm selection (e.g., an sNDA is not sought since the drug is found to be unsafe or ineffective). In Section 6.1, we assess the clinical trial quality of a drug's indications for which the firm seeks regulatory approval and those for which it does not. If differences in the pattern of clinical trials and regulatory approvals were primarily due to scientific rationales, we would expect to see little variation in trial quality between indications with and without regulatory approval. Contrary to this expectation, we find statistically significant differences, suggesting that firm selection is not a primary factor behind the sequencing of indications that we observe.

## 6 Firm and Policy Implications

Our results suggest that firms engage in regulatory arbitrage by initially seeking approval in smaller, more favorable markets and relying on off-label use to expand into others. In considering the effects of regulatory design, prior papers have examined how regulation affects R&D costs through changes in trial design and time to market (Berndt et al., 2005; Chandra et al., 2026), as well as how it shapes the number of markets firms choose to enter (Dubois et al., 2025; Maini and Pammolli, 2023). Building on this work, this section presents a set of back-of-the-envelope calculations to assess how regulatory arbitrage affects three outcomes: firms' trial design choices, the speed of market entry, and the number of markets entered. Our findings raise important questions for regulators, who must weigh the benefits of accelerated access to new treatments against the need for sufficient evidence on drug safety and efficacy. While our calculations are intentionally simple (e.g., they do not account for the actual uptake or costs of promoting off-label use, payer coverage, or legal risks), they offer insight into the trade-offs that arise when regulatory structure shapes firm incentives.

### 6.1 Impact on Clinical Trial Design Quality

Given the structure of FDA regulation, a key question is whether firms respond to less stringent regulatory requirements by relying on weaker forms of evidence when expanding off-label use. To assess this, we examine the design quality of clinical trials that have a primary purpose to increase off-label use (e.g., through dissemination of results in scientific publications) and not to support a future sNDA. For firms, a key advantage of such "non-regulatory" trials is that they, by definition, do not require the high costs or rigor associated with trials supporting regulatory approval. For example, the FDA considers randomized controlled trials the "gold standard," but such trials are typically more costly to conduct. Although publicly available cost estimates are limited, Moore et al. (2018) find that pivotal trials with a placebo or active comparator cost between $28.8 and $48.9 million, on average, while those without a comparator cost $13.5 million.[24] However, trials aimed at expanding off-label use often do not use randomized controlled designs (Bothwell et al.,

[24] Pivotal trials are trials of safety and/or efficacy used to support regulatory approval.

2016). As a result, we compare the quality of trials likely conducted for regulatory purposes with those likely conducted for non-regulatory purposes.

For each drug in our sample, we classify the indications tested in clinical trials as either "regulatory" (for which the firm eventually receives FDA approval) or "non-regulatory" (for which the firm does not seek approval). Figure 6 compares the share of high-quality trials for regulatory and non-regulatory indications, with quality defined as trials that are randomized and controlled. Looking at all trials, we find a significantly higher share of high-quality trials for regulatory indications than for non-regulatory indications (48 percent versus 39 percent, respectively; $p < 0.01$).

The likelihood of high trial quality is likely to vary across different trial phases, which vary in length and cost. Firms are less likely to conduct late-stage clinical trials (i.e., phases II/III and III) that are high quality if they do not intend to pursue regulatory approval. In accordance with this view, we find little difference in trial quality among late-stage trials. In contrast, we find these differences are driven by early-stage trials (i.e., phases I and II), with a higher share of high-quality early-stage trials among regulatory indications than among non-regulatory indications (35 percent versus 31 percent, respectively; $p < 0.01$). Overall, through this exercise, we see that the ability to engage in regulatory arbitrage appears to shift the quality of firms' clinical trials.

### 6.2 Impact on the Speed of Entry Into New Markets

Long development timelines are a major driver of high drug development costs (Wong et al., 2014). By seeking initial regulatory approval in smaller indications, firms can potentially bring a drug to market more quickly by conducting smaller clinical trials with a segment of participants more likely to respond to treatment (Chandra et al., 2019). In this section, we carry out a back-of-the-envelope calculation to quantify the dollar value to firms of expediting market entry, focusing specifically on the speed with which cancer drugs enter the market when pursuing initial approval in small versus large indications.

We restrict our sample to each drug's first approval and consider "small" indications as those within the lowest quartile of market size (e.g., soft tissue including heart cancer) and "large" indications as

the rest (e.g., breast cancer). Measuring from pivotal trial start date to approval date, drugs with small initial indications reach the market in 44.8 months on average, while those with large initial indications reach the market in 52.7 months, for a difference of 7.9 months. To translate these time savings into dollar savings, we make use of a recent study of clinical trial costs, which finds that each additional month in late-stage trials amounts to a median $671,000 spent (Martin et al., 2017). Multiplying this figure by 7.9 months suggests that pharmaceutical firms can save more than $5.3 million in trial costs alone by engaging in regulatory arbitrage and seeking initial approval in a smaller market.

In addition to trial cost savings, firms also benefit from revenues obtained earlier. To determine per-drug revenues over this time, we turn to Schuhmacher et al. (2022), who examine new drugs launched and their total sales from 2011 to 2020. Given that we are considering drugs launched in small indications, we take a conservative approach by excluding blockbusters (with mean annual sales of >$1 billion) and high-selling ($0.5–0.999 billion) drugs from our revenue calculations. Looking only at low- (<$0.1 billion) and medium-selling ($0.1–0.499 billion) drugs, we determine these drugs have an average annual revenue of $143.2 million, equating to $94.3 million over 7.9 months.[25] We consider this to be a conservative estimate of total revenues because drugs initially launched in small indications may still generate large or even blockbuster-level sales, due to both the potential for off-label use and competitive factors allowing monopoly pricing to be high.

Summing the costs saved from clinical trials and the revenues obtained via earlier market entry, we obtain a total value to firms of $5.3 million + $94.3 million = $99.6 million per drug from seeking initial approval in a small market relative to a large one. While these calculations are purposefully simple (e.g., they do not take into account variation in clinical trial costs or the costs and uncertainty associated with off-label promotion), they do provide insight into the potential financial incentives firms face when selecting initial markets for approval.

[25] We calculate annual revenues from Figure 1 of Schuhmacher et al. (2022) as follows: ($82.1 billion total revenues for medium-selling drugs + $4.7 billion for low-selling drugs)/(51 medium-selling drugs + 50 low-selling drugs)/6 years average commercialization period over 2011 to 2020 = $143.2 million annual per-drug revenue.

### 6.3 Impact on the Number of Markets Entered

For policymakers, an important issue is how regulatory policy influences the amount of innovation developed. Here, we analyze how regulatory arbitrage in the pharmaceutical industry affects the number of markets a firm enters for a single drug. The high barriers to entry associated with regulatory approval for larger markets suggest that if off-label use were banned, we might expect firms to pursue regulatory approval for a portion of these indications, provided the market expansion benefits exceed the costs of obtaining sufficient scientific evidence for approval. For the remaining indications, for which the benefits of formal approval do not exceed the costs, these drug-indication pairs would become "missing" in the sense that firms would no longer pursue them. As such, a natural question is, how many "additional" indications do firms explore because of the regulatory structure that allows them to enter new markets through off-label drug use? Stated differently, how many off-label indications are associated with a given drug?[26]

To determine this, we begin with each drug's set of non-regulatory indications (i.e., those tested in clinical trials but never submitted for formal approval). Non-regulatory indications include both ones pursued for off-label purposes and ones discontinued for scientific reasons. To isolate "off-label" indications, we use two methods to remove indications likely discontinued due to scientific concerns. Our first method is based on the idea that firms typically terminate trials early when they encounter safety or efficacy issues, making it unlikely they will seek regulatory approval for the indication or disclose trial outcomes to facilitate off-label drug use (Cook et al., 2014). We therefore exclude unapproved indications with an above-median share of early trial terminations, suggesting negative findings. Our second method is motivated by the idea that firms conducting high-quality (i.e., randomized controlled) trials without seeking regulatory approval likely do so because of inadequate safety or efficacy findings. We therefore also exclude indications with an above-median share of high-quality trials that did not lead to approval, reflecting potentially unfavorable results. The remaining non-regulatory indications are classified as off-label.

[26] For simplicity, this exercise does not consider the "size" of the associated indications.

Using these data, we document the total number of regulatory and off-label indications associated with a drug. The average drug is associated with a total of 9.7 such indications, of which only 3 are approved and a mean of 6.7 are off-label.[27] Figure 7 gives the full distribution of off-label indications across our sample. Our findings support the notion that the opportunity for regulatory arbitrage likely increases the overall number of indications that firms focus on in their clinical trial efforts. A key caveat to interpreting these results is that we are examining equilibrium outcomes. If off-label drug use were banned, the total number of indications tested in clinical trials may decline. However, it is not clear that the average number of indications for a given drug would fall to 3, as firms might pursue regulatory approval for some indications initially intended for off-label use. Therefore, we consider the mean number of off-label indications (6.7) as an upper bound on the number of additional indications that firms may still pursue for a given drug if off-label use were prohibited.

## 7 Discussion and Conclusion

This paper provides new evidence on how pharmaceutical firms engage in regulatory arbitrage in their market entry decisions. Using comprehensive data on clinical trials and regulatory approvals, combined with large-scale genomic mapping information, we show that firms often seek initial approval in smaller disease indications—where the likelihood of approval is higher—before expanding into larger, related areas through off-label prescribing. These relationships hold even after accounting for key drug and market characteristics, such as regulatory incentives targeted towards rare diseases or intellectual property protections. The patterns are most pronounced for drugs with a high propensity for off-label prescribing.

Our results offer several important insights for future research. First, we provide evidence consistent with the view that differences in regulatory burden (e.g., approval rates) may drive the observed patterns (e.g., Appendix Figure A2). However, other explanations remain possible. For example,

[27] Our main analyses consider trial indications at the site level and approval indications, for which we have more granular data, at the site-stage level. For this analysis of the number of markets, because we explicitly match trial to approval indications, all indications are at the site level. As such, we have a mean of 3 approval indications per drug at the site level versus, as indicated in Table 1, 4 approval indications per drug at the site-stage level.

one alternative explanation is that firms learn over time where a drug is most effective and pursue approval wherever the clinical signal is strongest. While learning certainly plays a role in drug development, a pure learning effect does not suggest that genetically-linked off-label markets should affect which indication receives earlier approval (Table 2) or that approval sequencing should differ across high and low off-label propensity diseases (Figure 5). Both patterns suggest the presence of regulatory arbitrage and are unlikely to be driven by learning alone. Separating strategic sequencing from learning remains an important area for future work. Another explanation is that smaller indications may allow firms to set higher prices due to reduced levels of competition (Chandra and Garthwaite, 2017) or involve lower commercialization, marketing, and manufacturing costs. Initial approval in such markets may enable firms to generate revenue to finance the production and sale of additional indications. Future research may investigate these mechanisms using detailed data on pricing and drug costs.

Second, we document a new fact about the order in which drug applications are obtained. Like many studies on the pharmaceutical industry (see, e.g., Acemoglu and Linn, 2004; Ellison and Ellison, 2011), our analysis is limited to successful regulatory applications (i.e., approved NDAs and sNDAs). This restricts our ability to fully characterize firms' strategic entry decisions. This concern is mitigated by the fact that firms generally do not submit applications to the FDA that they anticipate will be rejected. However, researchers with access to such rejected application data may aim to more precisely identify the set of indications for which firms are likely to seek regulatory approval. This will broaden our understanding of how regulatory incentives shape firms' market entry strategies.

Third, our findings not only speak to how regulatory design shapes a firm's approval sequencing for an individual product, but also raise questions about the broader—often unintended—effects of that design. For example, the potential for regulatory arbitrage may shift the types of drugs a firm chooses to develop in the first place. It may encourage investment in drugs that target small indications with relatively little patient burden, potentially at the expense of drugs aimed at larger, unmet needs. Similarly, understanding how off-label expansion compares to formal supplemental

approvals, in terms of prescribing behavior and patient outcomes, is critical for evaluating the welfare implications of these market entry strategies.

Nevertheless, our findings provide new empirical evidence on an understudied dimension of regulatory design in shaping the diffusion of new medical technologies. Rather than treating approval as a one-time decision, FDA regulation requires firms to navigate a sequence of market entry choices, each with its own regulatory burden. The ability to rely on off-label use introduces an informal, lower-risk pathway to market expansion, fundamentally altering firm incentives regarding where and when to seek formal approval. Our work suggests that regulatory flexibility can promote earlier access to new therapies but may also lead to uneven evidence generation across patient populations. These trade-offs raise important policy questions about how to structure pre-market approval regulation and post-market surveillance in a way that balances access to medical innovations with the need for rigorous evidence.

## References


Acemoglu, D. and J. Linn (2004). Market size in innovation: Theory and evidence from the pharmaceutical industry. *Quarterly Journal of Economics* 119(3): 1049–1090.

Adams, C. P. and V. V. Brantner (2006). Estimating the cost of new drug development: Is it really $802 million? *Health Affairs* 25(2): 420–428.

Aryal, G., F. Ciliberto, L. E. Farmer, and E. Khmelnitskaya (2024). Valuing pharmaceutical drug innovations. SSRN Working Paper No. 4300678.

Avorn, J., A. Sarpatwari, and A. S. Kesselheim (2015). Forbidden and permitted statements about medications—Loosening the rules. *New England Journal of Medicine* 373(10): 967–973.

Bebchuk, L. A. and A. Cohen (2003). Firms' decisions where to incorporate. *Journal of Law and Economics* 46(2): 383–425.

Berger, B., A. Chandra, and C. Garthwaite (2021). Regulatory approval and expanded market size. NBER Working Paper No. 28889.

Berndt, E. R., A. H. Gottschalk, T. J. Philipson, and M. W. Strobeck (2005). Industry funding of the FDA: Effects of PDUFA on approval times and withdrawal rates. *Nature Reviews Drug Discovery* 4(7): 545–554.

Berry, H., A. Kaul, and N. Lee (2021). Follow the smoke: The pollution haven effect on global sourcing. *Strategic Management Journal* 42(13): 2420–2450.

Blume-Kohout, M. E. and N. Sood (2013). Market size and innovation: Effects of Medicare Part D on pharmaceutical research and development. *Journal of Public Economics* 97: 327–336.

Bothwell, L. E., J. A. Greene, S. H. Podolsky, and D. S. Jones (2016). Assessing the gold standard—Lessons from the history of RCTs.

Bradford, W. D., J. L. Turner, and J. W. Williams (2018). Off-label use of pharmaceuticals: A detection controlled estimation approach. *Journal of Industrial Economics* 66(4): 866–903.

Budish, E., B. N. Roin, and H. Williams (2015). Do firms underinvest in long-term research? Evidence from cancer clinical trials. *American Economic Review* 105(7): 2044–2085.

Cain, M. D. and S. M. Davidoff (2012). Delaware's competitive reach. *Journal of Empirical Legal Studies* 9(1): 92–128.

Cerami, E., J. Gao, B. E. Gross, S. O. Sumer, B. A. Aksoy, A. Jacobsen, C. J. Byrne, M. L. Heuer, and E. Larsson (2012). The cBio Cancer Genomics Portal: An open platform for exploring multidimensional cancer genomics data. *Cancer Discovery* 2(5): 401–404.

Cha, Y., T. Erez, I. Reynolds, D. Kumar, J. Ross, G. Koytiger, R. Kusko, B. Zeskind, S. Risso, E. Kagan, and others (2018). Drug repurposing from the perspective of pharmaceutical companies. *British Journal of Pharmacology* 175(2): 168–180.

Chakravarty, D., J. Gao, S. Phillips, R. Kundra, H. Zhang, J. Wang, J. E. Rudolph, R. Yaeger, T. Soumerai, M. H. Nissan, and others (2017). OncoKB: A precision oncology knowledge base. *JCO Precision Oncology* 1: 1–16.

Chandra, A., A. Finkelstein, A. Sacarny, and C. Syverson (2016). Health care exceptionalism? Performance and allocation in the U.S. health care sector. *American Economic Review* 106(8): 2110–2144.

Chandra, A. and C. Garthwaite (2017). The economics of indication-based drug pricing. *New England Journal of Medicine* 377(2): 103–106.

Chandra, A., C. Garthwaite, and A. D. Stern (2019). Characterizing the drug development pipeline for precision medicines. In E. R. Berndt, D. P. Goldman, and J. W. Rowe (Eds.), *Economic Dimensions of Personalized and Precision Medicine*, pp. 115–157. Chicago: University of Chicago Press.

Chandra, A., J. Kao, K. L. Miller, and A. D. Stern (2026). Regulatory incentives for innovation: The FDA's breakthrough therapy designation. *Review of Economics and Statistics* 108(2): 1–46.

Cheng, F., W. Lu, C. Liu, J. Fang, Y. Hou, D. E. Handy, R. Wang, Y. Zhao, Y. Yang, J. Huang, D. E. Hill, M. Vidal, C. Eng, and J. Loscalzo (2019). A genome-wide positioning systems network algorithm for in silico drug repurposing. *Nature Communications* 10(1): 3476.

Cohen, L., U. G. Gurun, and S. D. Kominers (2019). Patent trolls: Evidence from targeted firms. *Management Science* 65(12): 5461–5486.

Cohen, L., U. G. Gurun, and D. Li (2021). Internal deadlines, drug approvals, and safety problems. *American Economic Review: Insights* 3(1): 67–82.

Congressional Research Service (2021). Drug pricing and the FDA: How the approval process affects the cost of prescription drugs.

Cook, D., D. Brown, R. Alexander, R. March, P. Morgan, G. Satterthwaite, and M. N. Pangalos (2014). Lessons learned from the fate of AstraZeneca's drug pipeline: A five-dimensional framework. *Nature Reviews Drug Discovery* 13(6): 419–431.

CSDD (2014). Costs to develop and win marketing approval for a new drug is $2.6 billion. `http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study`, Tufts Center for the Study of Drug Development.

Dafny, L. and D. Dranove (2009). Regulatory exploitation and management changes: Upcoding in the hospital industry. *Journal of Law and Economics* 52(2): 223–250.

Dafny, L. S. (2005). How do hospitals respond to price changes? *American Economic Review* 95(5): 1525–1547.

Danzon, P. M. and E. L. Keuffel (2014). Regulation of the pharmaceutical-biotechnology industry. In N. L. Rose (Ed.), *Economic Regulation and Its Reform: What Have We Learned?*, pp. 407–484. Chicago: University of Chicago Press.

DiMasi, J. A. (2001). New drug development in the United States from 1963 to 1999. *Clinical Pharmacology & Therapeutics* 69(5): 286–296.

DiMasi, J. A., R. W. Hansen, and H. G. Grabowski (2003). The price of innovation: New estimates of drug development costs. *Journal of Health Economics* 22(2): 151–185.

Douglas, J. L. (2016). New wine into old bottles: Fintech meets the bank regulatory world. *North Carolina Banking Institute* 20: 17.

Dranove, D., C. Garthwaite, and B. Wu (2022). The returns to medical inventions. *Journal of Law and Economics* 65(S2): S389–S417.

Dubois, P., O. De Mouzon, F. Scott Morton, and P. Seabright (2015). Market size and pharmaceutical innovation. *RAND Journal of Economics* 46(4): 844–871.

Dubois, P., E. Gentry, and T. Tunçel (2025). Strategic submissions: A cross-country analysis of supplemental drug approvals. TSE Working Paper No. 23-1459.

Eguale, T., D. L. Buckeridge, A. Verma, N. E. Winslade, A. Benedetti, J. A. Hanley, and R. Tamblyn (2016). Association of off-label drug use and adverse drug events in an adult population. *JAMA Internal Medicine* 176(1): 55–63.

Eisenberg, R. S. (2005). The problem of new uses. *Yale Journal of Health Policy, Law, and Ethics* 5: 717–740.

Ellias, J. A. (2018). What drives bankruptcy forum shopping? Evidence from market data. *Journal of Legal Studies* 47(1): 119–149.

Ellison, G. and S. F. Ellison (2011). Strategic entry deterrence and the behavior of pharmaceutical incumbents prior to patent expiration. *American Economic Journal: Microeconomics* 3(1): 1–36.

FDA (1998). Guidance for industry: FDA approval of new cancer treatment uses for marketed and biological products.

FDA (2014). Guidance for industry: Distributing scientific and medical publications on unapproved new uses—recommended practices.

FDA (2024). The drug development process—Step 3: Clinical research. `https://www.fda.gov/patients/drug-development-process/step-3-clinical-research`, accessed on 2024-05-04.

Friedman, M. (1996). Testimony on supplemental indications for approved prescription drugs. House Committee on Government Reform and Oversight, Subcommittee on Human Resources and Intergovernmental Relations.

Galasso, A. and H. Luo (2017). Tort reform and innovation. *Journal of Law and Economics* 60(3): 385–412.

Gelijns, A. C., N. Rosenberg, and A. J. Moskowitz (1998). Capturing the unexpected benefits of medical research. *New England Journal of Medicine* 339(10): 693–698.

Grennan, M. and R. J. Town (2020). Regulating innovation with uncertain quality: Information, risk, and access in medical devices. *American Economic Review* 110(1): 120–161.

Holmes, T. J. (1998). The effect of state policies on the location of manufacturing: Evidence from state borders. *Journal of Political Economy* 106(4): 667–705.

IQVIA (2023). Success multiplied: Launch excellence for multi-indication assets. `https://www.iqvia.com/library/white-papers/success-multiplied-launch-excellence-for-multi-indication-assets`, accessed on 2024-05-07.

IQVIA Institute (2018). Global oncology trends 2018. `https://www.iqvia.com/insights/the-iqvia-institute/reports/global-oncology-trends-2018`, accessed on 2021-01-13.

Jayasundara, K., A. Hollis, M. Krahn, M. Mamdani, J. S. Hoch, and P. Grootendorst (2019). Estimating the clinical cost of drug development for orphan versus non-orphan drugs. *Orphanet Journal of Rare Diseases* 14: 1–10.

Joskow, P. L. (2005). Regulation and deregulation after 25 years: Lessons learned for research in industrial organization. *Review of Industrial Organization* 26: 169–193.

Kakani, P., M. Chernew, and A. Chandra (2022). The contribution of price growth to pharmaceutical revenue growth in the United States: Evidence from medicines sold in retail pharmacies. *Journal of Health Politics, Policy and Law* 47(6): 629–648.

Kao, J. (2025). Charted territory: Mapping the cancer genome and R&D decisions in the pharmaceutical industry. Working paper.

Krieger, J., D. Li, and D. Papanikolaou (2022). Missing novelty in drug development. *Review of Financial Studies* 35(2): 636–679.

Larkin, I., D. Ang, J. Avorn, and A. S. Kesselheim (2014). Restrictions on pharmaceutical detailing reduced off-label prescribing of antidepressants and antipsychotics in children. *Health Affairs* 33(6): 1014–1023.

Lee, E., A. R. Teschemaker, R. Johann-Liang, G. Bazemore, M. Yoon, K.-S. Shim, M. Daniel, J. Pittman, and A. K. Wutoh (2012). Off-label prescribing patterns of antidepressants in children and adolescents. *Pharmacoepidemiology and Drug Safety* 21(2): 137–144.

Maini, L. and F. Pammolli (2023). Reference pricing as a deterrent to entry: Evidence from the European pharmaceutical market. *American Economic Journal: Microeconomics* 15(2): 345–383.

Malani, A. and T. Philipson (2012). The regulation of medical products. In *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*, pp. 101–140. Oxford: Oxford University Press.

Martin, L., M. Hutchens, C. Hawkins, and A. Radnov (2017). How much do clinical trials cost? *Nature Reviews Drug Discovery* 16(6): 381–382.

McKibbin, R. (2023). The effect of RCTs on drug demand: Evidence from off-label cancer drugs. *Journal of Health Economics* 90: 102779.

Michaeli, T., H. Jürges, and D. T. Michaeli (2023). FDA approval, clinical trial evidence, efficacy, epidemiology, and price for non-orphan and ultra-rare, rare, and common orphan cancer drug indications: Cross sectional analysis. *BMJ* 381: e073242.

Miller, K. L. and M. Lanthier (2018). Investigating the landscape of U.S. orphan product approvals. *Orphanet Journal of Rare Diseases* 13: 1–8.

Moore, T. J., H. Zhang, G. Anderson, and G. C. Alexander (2018). Estimated costs of pivotal trials for novel therapeutic agents approved by the U.S. Food and Drug Administration, 2015–2016. *JAMA Internal Medicine* 178(11): 1451–1457.

Mulligan, C. B. (2022). Peltzman revisited: Quantifying 21st-century opportunity costs of Food and Drug Administration regulation. *Journal of Law and Economics* 65(S2): S355–S387.

Olson, M. K. (2002). Pharmaceutical policy change and the safety of new drugs. *Journal of Law and Economics* 45(S2): 615–642.

Peltzman, S. (1973). An evaluation of consumer protection legislation: The 1962 drug amendments. *Journal of Political Economy* 81(5): 1049–1091.

Pfister, D. G. (2012). Off-label use of oncology drugs: The need for more data and then some. *Journal of Clinical Oncology* 30(6): 584–586.

Pleasance, E., A. Bohm, L. Williamson, J. Nelson, Y. Shen, M. Bonakdar, E. Titmuss, V. Csizmok, K. Wee, S. Hosseinzadeh, and Others (2022). Whole-genome and transcriptome analysis enhances precision cancer treatment options. *Annals of Oncology* 33(9): 939–949.

Pollman, E. (2019). Tech, regulatory arbitrage, and limits. *European Business Organization Law Review* 20: 567–590.

Posen, H. A. (2015). Ridesharing in the sharing economy: Should regulators impose Über regulations on Uber. *Iowa Law Review* 101: 405.

Radley, D. C., S. N. Finkelstein, and R. S. Stafford (2006). Off-label prescribing among office-based physicians. *Archives of Internal Medicine* 166(9): 1021–1026.

Rao, H., L. Q. Yue, and P. Ingram (2011). Laws of attraction: Regulatory arbitrage in the face of activism in right-to-work states. *American Sociological Review* 76(3): 365–385.

Richardson, E. (2016). Off-label drug promotion. *Health Affairs* Health Policy Brief, DOI: 10.1377/hpb20160630.920075.

Schuhmacher, A., M. Hinder, N. Boger, D. Hartl, and O. Gassmann (2022). The significance of blockbusters in the pharmaceutical industry. *Nature Reviews Drug Discovery*.

Sertkaya, A., H.-H. Wong, A. Jessup, and T. Beleche (2016). Key cost drivers of pharmaceutical clinical trials in the United States. *Clinical Trials* 13(2): 117–126.

Shapiro, B. T. (2018). Informational shocks, off-label prescribing, and the effects of physician detailing. *Management Science* 64(12): 5925–5945.

Sondka, Z., S. Bamford, C. G. Cole, S. A. Ward, I. Dunham, and S. A. Forbes (2018). The COSMIC Cancer Gene Census: Describing genetic dysfunction across all human cancers. *Nature Reviews Cancer* 18(11): 696–705.

Stafford, R. S. (2008). Regulating off-label drug use—Rethinking the role of the FDA. *New England Journal of Medicine* 358(14): 1427–1429.

Stern, A. D. (2017). Innovation under regulatory uncertainty: Evidence from medical technology. *Journal of Public Economics* 145: 181–200.

Suehnholz, S. P., M. H. Nissan, H. Zhang, R. Kundra, S. Nandakumar, C. Lu, S. Carrero, A. Dhaneshwar, N. Fernandez, B. W. Xu, and others (2024). Quantifying the expanding landscape of clinical actionability for patients with cancer. *Cancer Discovery* 14(1): 49–65.

Sytch, M. and Y. H. Kim (2021). Quo vadis? From the schoolyard to the courtroom. *Administrative Science Quarterly* 66(1): 177–219.

Tanoli, Z., M. Vähä-Koskela, and T. Aittokallio (2021). Artificial intelligence, machine learning, and drug repurposing in cancer. *Expert Opinion on Drug Discovery* 16(9): 977–989.

Tate, J. G., S. Bamford, H. C. Jubb, Z. Sandra, D. M. Beard, N. Bindal, H. Boutselakis, C. G. Cole, C. Creatore, E. Dawson, P. Fish, B. Harsha, C. Hathaway, S. C. Jute, C. Y. Kok, K. Noble, L. Ponting, C. C. Ramshaw, C. E. Rye, H. E. Speedy, R. Stefancsik, S. L. Thompson, S. Wang, S. Ward, P. J. Campbell, and S. A. Forbes (2018). COSMIC: The catalogue of somatic mutations. *Nucleic Acids Research* 47(D1): D941–47.

TCGA Research Network (2011). Integrated genomic analyses of ovarian carcinoma. *Nature* 474(7353): 609–615.

Tunçel, T. (2025). Should we prevent off-label drug prescriptions? Empirical evidence from France. *Review of Economic Studies* 92(3): 2027–2070.

Uffelmann, E., Q. Q. Huang, N. S. Munung, J. De Vries, Y. Okada, A. R. Martin, H. C. Martin, T. Lappalainen, and D. Posthuma (2021). Genome-wide association studies. *Nature Reviews Methods Primers* 1(1): 59.

Vives, X. (2019). Digital disruption in banking. *Annual Review of Financial Economics* 11: 243–272.

Weinstein, J. N., E. A. Collisson, G. B. Mills, K. R. Shaw, B. A. Ozenberger, K. Ellrott, I. Shmulevich, C. Sander, and J. M. Stuart (2013). The Cancer Genome Atlas Pan-Cancer analysis project. *Nature Genetics* 45(10): 1113–1120.

Wittich, C. M., C. M. Burkle, and W. L. Lanier (2012). Ten common questions (and their answers) about off-label drug use. *Mayo Clinic Proceedings* 87(10): 982–990.

Wong, H.-H., A. Jessup, A. Sertkaya, A. Birkenbach, A. Berlind, and J. Eyraud (2014). Examination of clinical trial costs and barriers for drug development final. Office of the Assistant Secretary for Planning and Evaluation, U.S. Department of Health & Human Services.

Wouters, O. J., M. McKee, and J. Luyten (2020). Estimated research and development investment needed to bring a new medicine to market, 2009-2018. *JAMA* 323(9): 844–853.

## Tables and Figures

TABLE 1: DESCRIPTIVE STATISTICS

| | Mean | SD | Min | Max |
|---|---|---|---|---|
| **Drug level** | | | | |
| Number of Unique Approval Indications | 4 | 6 | 1 | 35 |
| Number of Unique Trial Indications | 46.7 | 23.6 | 1 | 78 |
| Share with Orphan Disease Designation | 0.56 | 0.50 | 0 | 1 |
| Share with Accelerated Approval | 0.34 | 0.48 | 0 | 1 |
| **Drug-indication level** | | | | |
| Market Size: Approval Indications (Diagnoses) | 985 | 1,749 | 2.4 | 9,104 |
| Market Size: Trial Indications (Diagnoses) | 1,616 | 3,218 | 4.6 | 17,915 |
| Market Size: Potential Off-Label (Diagnoses) | 36,632 | 54,492 | 0 | 202,661 |
| IP Protection: Primary (Months) | 123.5 | 55.3 | 0 | 277 |
| IP Protection: Potential (Months) | 173.9 | 50.6 | 44 | 346 |
| Competition: Approval Indications (Total Approvals) | 3.1 | 3.6 | 0 | 20 |
| Competition: Trial Indications (Total Approvals) | 3.3 | 3.8 | 0 | 21 |

NOTES: This table shows summary statistics for our dataset of cancer drugs first approved from 1978 to 2016. Statistics are at the cancer site level for trial indications and the cancer site-stage level for approval indications and potential off-label market size. Market size is measured by new diagnoses for an indication in the SEER data, while off-label market size is measured by the proportion of new diagnoses for any potential off-label indications, with the proportions given by our disease similarity index.

Table 2: Ordering of Market Entry Decisions, Incorporating Off-Label Opportunities

| | Dependent variable: Indication order | | | |
|---|---|---|---|---|
| | Clinical trials | | Regulatory approvals | |
| | (1) | (2) | (3) | (4) |
| Log(Focal market size) | -1.016*** | | -0.00284 | |
| | (0.120) | | (0.120) | |
| Log(Total market size) | | -1.110*** | | -0.146* |
| | | (0.102) | | (0.0843) |
| Mean of dep. var | 10.454 | 10.454 | 1.764 | 1.764 |
| Observations | 1,523 | 1,523 | 182 | 182 |
| *Controls:* | | | | |
| Initial approval year | yes | yes | yes | yes |
| Indication group | yes | yes | yes | yes |
| Competition | yes | yes | yes | yes |
| Regulatory incentives | yes | yes | yes | yes |
| Intellectual property | yes | yes | yes | yes |

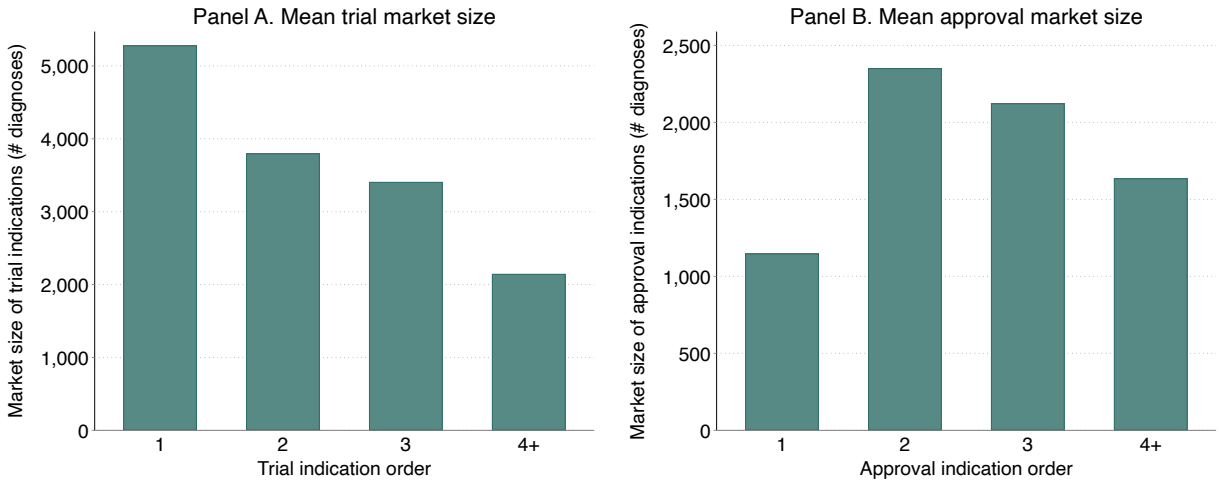
Notes: This table shows the relationship between indication order and market size for cancer drugs first approved from 1978 to 2016. The level of observation is the drug-indication order. Columns 1 and 2 examine clinical trials, and Columns 3 and 4 examine regulatory approvals. The outcome variable in Columns 1 and 2 is trial indication order, while that in Columns 3 and 4 is approval indication order. Focal market size is measured by new diagnoses for an indication in the SEER data. Total market size is measured by new diagnoses for the focal indication plus a proportion of new diagnoses for any potential off-label indications, with the proportions given by our disease similarity index. For both variables, we use the log of the five-year average market size associated with indication order. Robust standard errors are in parentheses. * p<0.1, ** p<0.05, *** p<0.01.

Table 3: Regulatory Approvals and Total Market Size, Using Alternative Similarity Measures

| | Dependent variable: Indication order | | | | | |
|---|---|---|---|---|---|---|
| | **All genes** | | | **Cancer Gene Census** | | |
| | Top 10% (1) | Top 20% (2) | Top 30% (3) | Top 10% (4) | Top 20% (5) | Top 30% (6) |
| Log(Total market size) | -0.146* | -0.158* | -0.162* | -0.145* | -0.164* | -0.160* |
| | (0.0843) | (0.0879) | (0.0867) | (0.0822) | (0.0851) | (0.0840) |
| Mean of dep. var | 1.764 | 1.764 | 1.764 | 1.764 | 1.764 | 1.764 |
| Observations | 182 | 182 | 182 | 182 | 182 | 182 |
| *Controls:* | | | | | | |
| Initial approval year | yes | yes | yes | yes | yes | yes |
| Indication group | yes | yes | yes | yes | yes | yes |
| Competition | yes | yes | yes | yes | yes | yes |
| Regulatory incentives | yes | yes | yes | yes | yes | yes |
| Intellectual property | yes | yes | yes | yes | yes | yes |

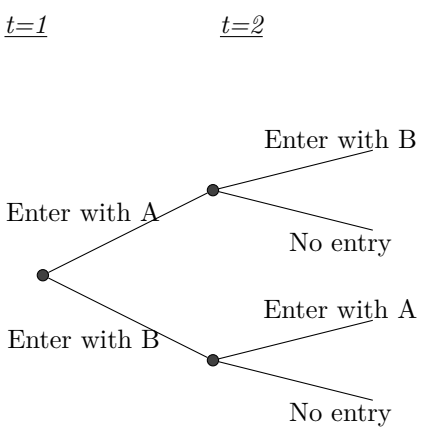
Notes: This table shows the relationship between indication order and total market size for regulatory approvals associated with cancer drugs first approved from 1978 to 2016, using alternative similarity measures. The level of observation is the drug-indication order. Alternative measures are generated by directly using cancer genome sequencing data from 168 large-scale mapping studies. Genetic mutations are restricted to those that occur at a high frequency within each mapping study, where a genetic mutation is "high frequency" within a cancer if it occurs in the top 10 percent (Columns 1 and 4), top 20 percent (Columns 2 and 5), or top 30 percent (Columns 3 and 6) of most frequently occurring mutations. Columns 1 to 3 focus on genetic mutations occurring among all genes. Columns 4 to 6 focus on the set of genetic mutations occurring among genes found in the COSMIC Cancer Gene Census (CGC). Column 1 corresponds to the estimate in Column 4, Table 2. The outcome variable is approval indication order. Total market size is measured by new diagnoses for the focal indication plus a proportion of new diagnoses for any potential off-label indications, with the proportions given by our disease similarity index. We use the log of the five-year average market size associated with indication order. Robust standard errors are in parentheses. * p<0.1, ** p<0.05, *** p<0.01.

FIGURE 1: MARKET SIZE AND INDICATION ORDER



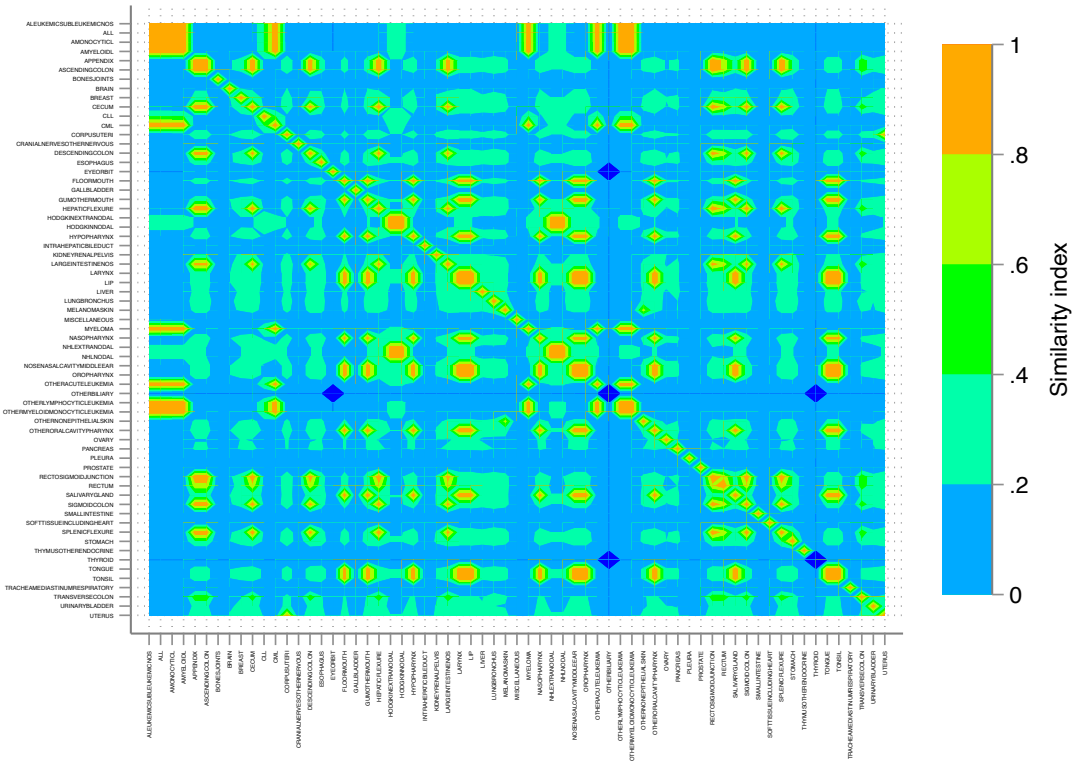

NOTES: This figure shows the mean market size by indication order for both clinical trials (Panel A) and regulatory approvals (Panel B) for cancer drugs first approved from 1978 to 2016. Market size is measured by new diagnoses for an indication in the SEER data. Trial indications are measured at the cancer site level and approval indications are at the cancer site-stage level.

FIGURE 2: TWO-PERIOD FRAMEWORK OF INDICATION CHOICE



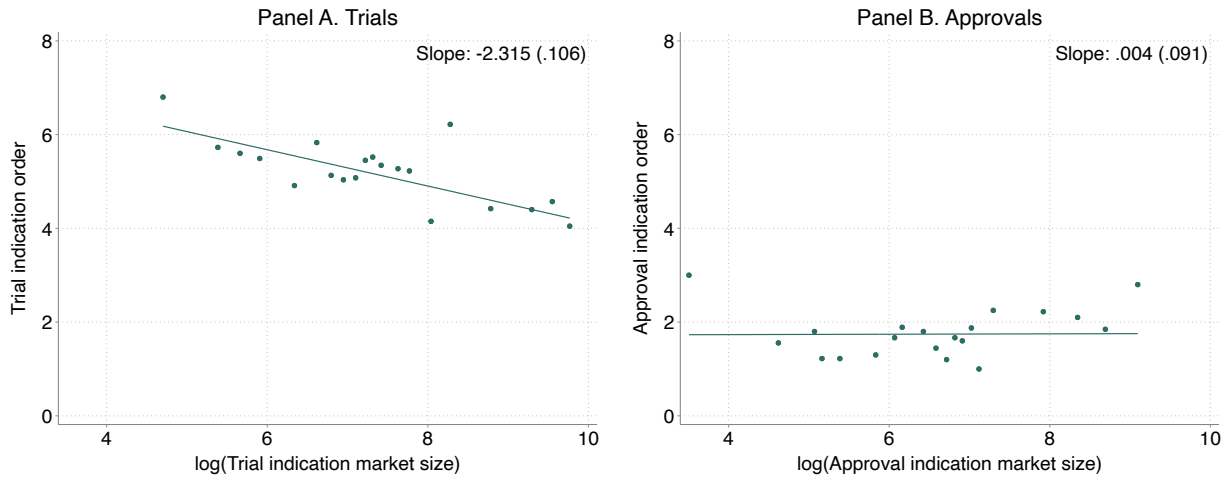

NOTES: This figure shows the firm's decision tree. In the first period, the firm chooses for which indication $i \in I = \{A, B\}$ to seek regulatory approval (enter), where indication $A$ has a large potential market and $B$, a small one. In the second period, the firm chooses whether to seek regulatory approval or not for the remaining indication.

FIGURE 3: SIMILARITY INDEX HEAT MAP



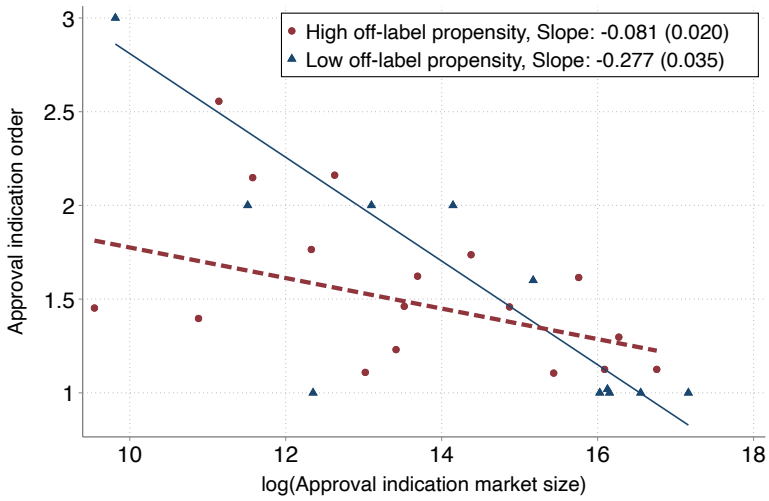

NOTES: This figure shows a heat map of our similarity index across all cancer sites in the cancer genome mapping data used in our analysis. Cancer site pairs associated with lighter colors are more similar.

FIGURE 4: TRENDS IN MARKET ENTRY DECISIONS



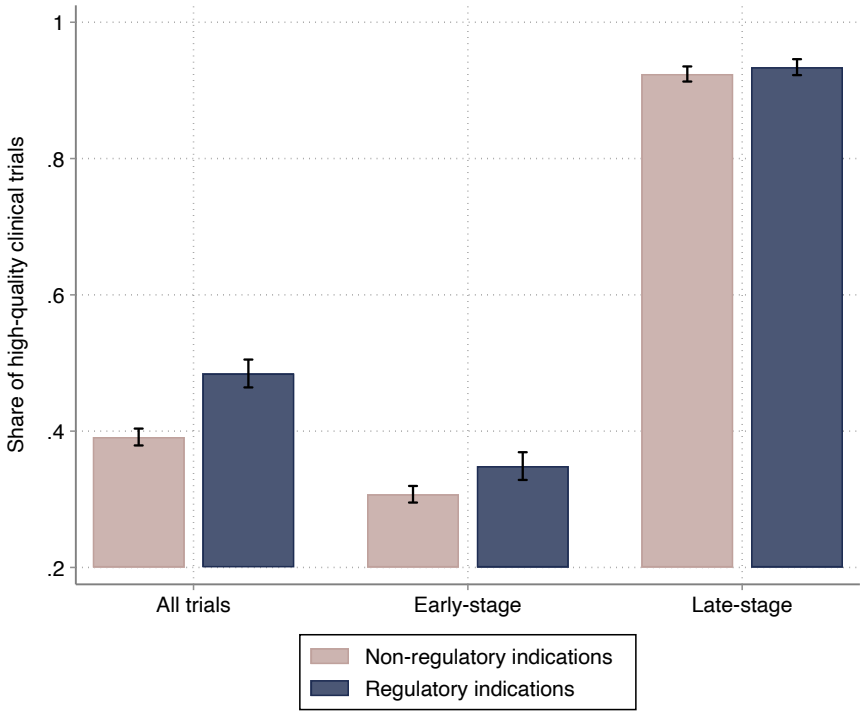

NOTES: This figure shows binned scatter plots examining trends in market entry decisions for cancer drugs first approved from 1978 to 2016. The level of observation is the drug-indication order. Panel A shows the relationship between trial indication order and market size; the number of observations is 1,980. Panel B shows the relationship between approval indication order and market size; the number of observations is 187. Market size is measured by new diagnoses for an indication in the SEER data. We use the log of the five-year average market size relative to either the trial start year (Panel A) or approval year (Panel B).

FIGURE 5: TRENDS IN REGULATORY APPROVALS ACROSS DISEASES, BY PROPENSITY FOR OFF-LABEL DRUG USE



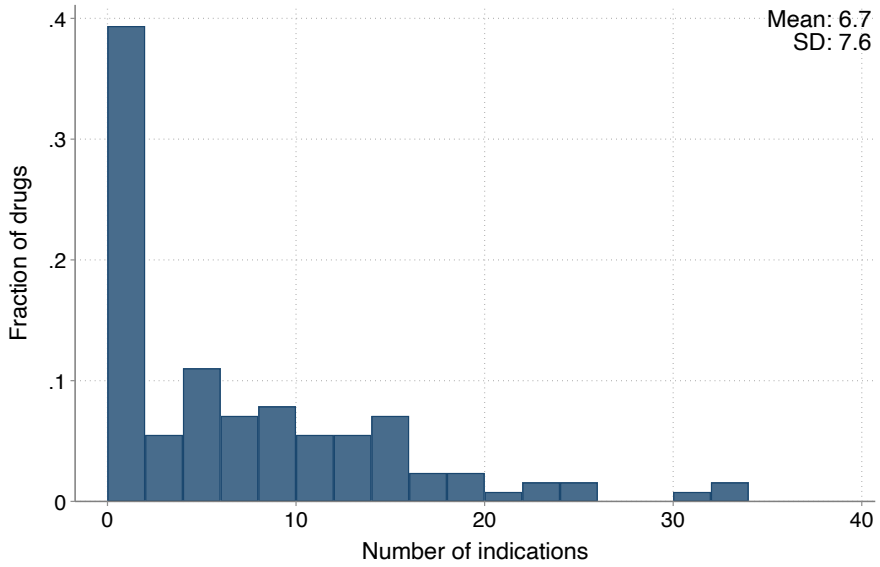

NOTES: This figure shows a binned scatter plot examining the relationship between regulatory approvals and market size for approved drugs across several disease categories from 1998 to 2021, by propensity for off-label drug use. The level of observation is the drug-indication order, where an indication corresponds to an ICD-9 code. Market size is measured by new diagnoses for an indication (ICD-9) in the MEPS data. We use the log of the market size associated with indication order averaged over 1996 and 1997.

FIGURE 6: QUALITY OF CLINICAL TRIALS: NON-REGULATORY VS. REGULATORY INDICATIONS




NOTES: This figure shows differences in the quality of clinical trials for non-regulatory versus regulatory indications for cancer drugs first approved from 1978 to 2016. High-quality clinical trials refer to trials that are randomized and controlled. Bars give shares, while capped ranges provide 95-percent confidence intervals.

FIGURE 7: DISTRIBUTION OF OFF-LABEL INDICATIONS

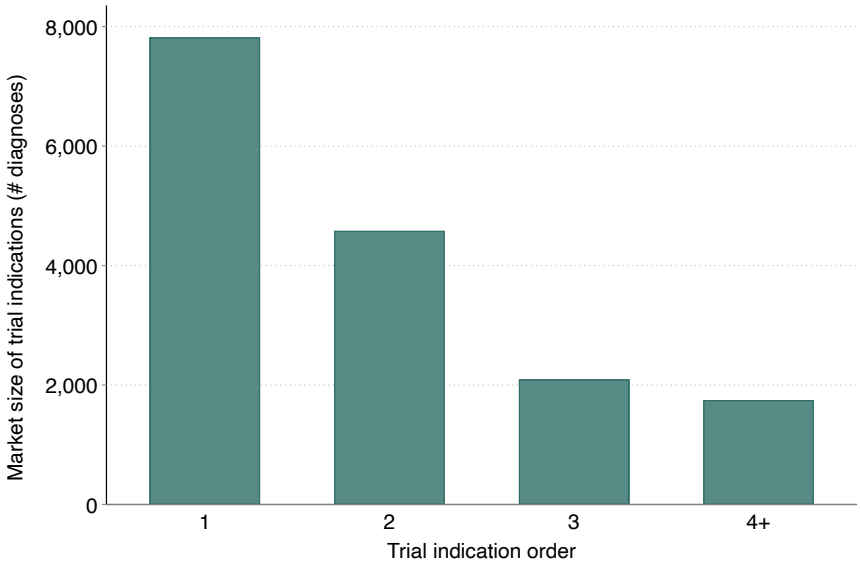



NOTES: This figure plots the distribution of off-label indications for cancer drugs first approved from 1978 to 2016. Number of drugs is 127.

# Appendices

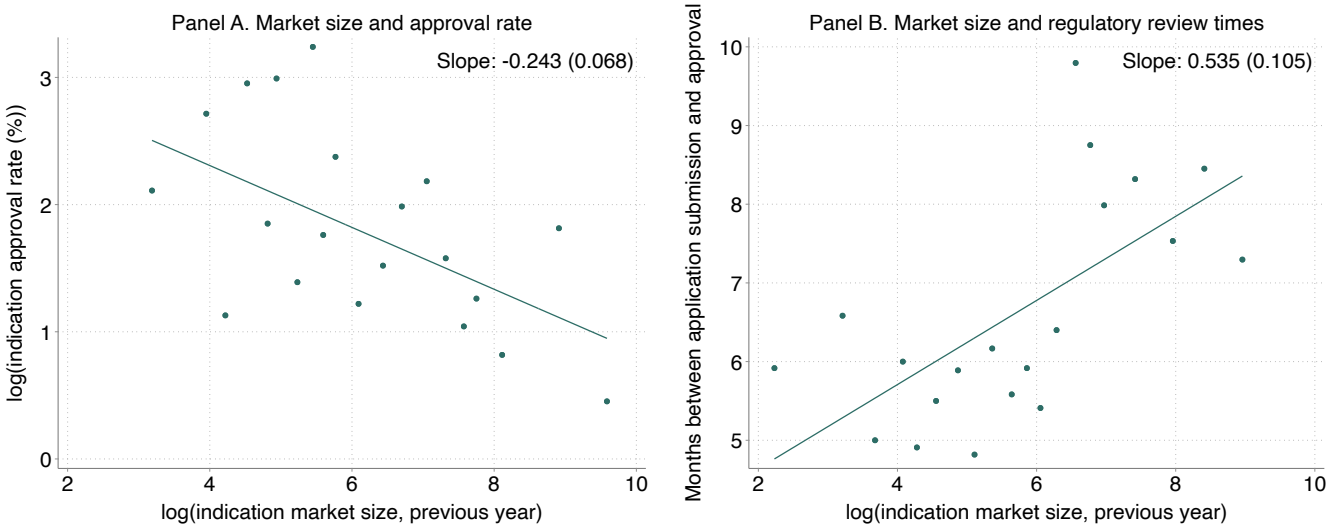
## A Trends in Market Entry Decisions and Regulatory Review Processes

FIGURE A1: PHASE III TRIAL MARKET ENTRY DECISIONS



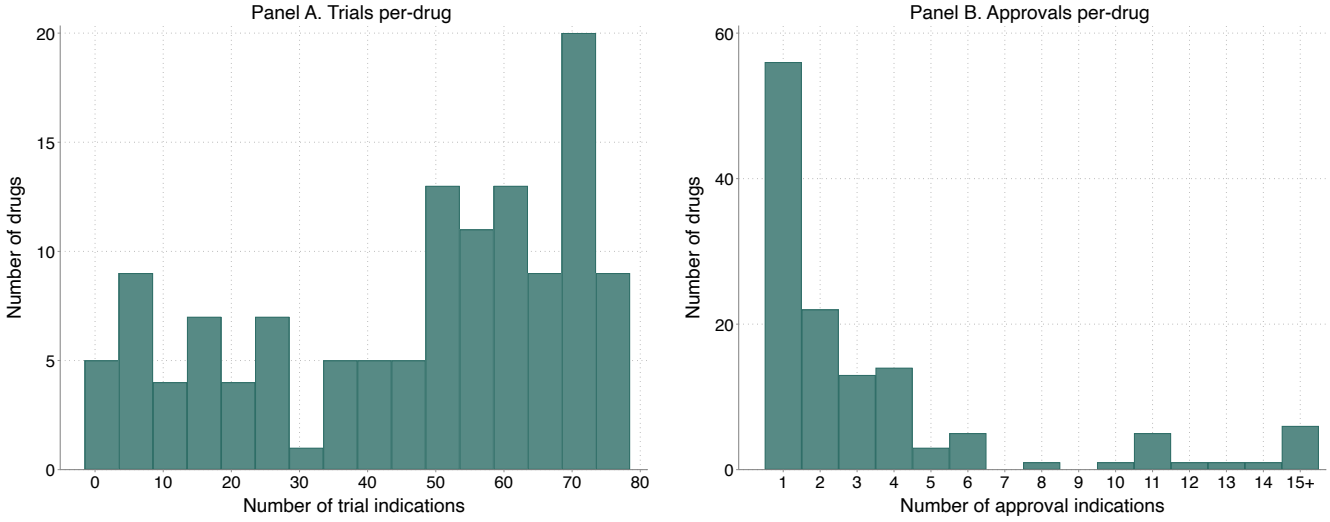

NOTES: This figure shows the mean market size by indication order for phase III clinical trials for cancer drugs first approved from 1978 to 2016. Market size is measured by new diagnoses for an indication in the SEER data. Trial indications are measured at the cancer site level.

FIGURE A2: APPROVAL RATES AND REGULATORY REVIEW TIMES ACROSS INDICATIONS



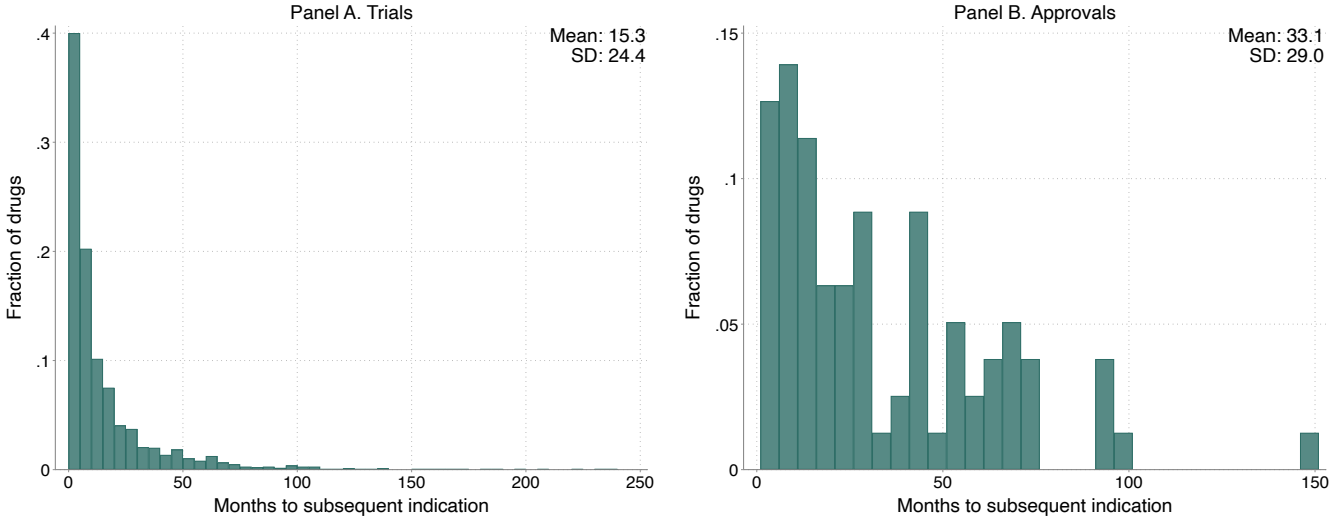

NOTES: This figure shows binned scatter plots examining indication approval rates and regulatory review times across cancer sites, for cancer drugs first approved from 1978 to 2016. The level of observation is the cancer site-year. Indication approval rate is defined as the probability that a drug tested in pre-clinical research in a given year advances to approval. Regulatory review time is the number of months between application submission and approval. Panel A compares the log of the indication approval rate to the log of the market size in the year prior to pre-clinical testing. Panel B compares the regulatory review time to the log of the market size in the year prior to pre-clinical testing.

FIGURE A3: PER-DRUG DISTRIBUTION OF MARKET ENTRY DECISIONS




NOTES: This figure shows the distribution of market entry decisions for cancer drugs first approved from 1978 to 2016. Panel A gives the per-drug distribution of trial indications; number of drugs is 127. Panel B gives the per-drug distribution of approval indications; number of drugs is 129.

FIGURE A4: TIME BETWEEN MARKET ENTRY DECISIONS




NOTES: This figure shows the months between market entry decisions for cancer drugs first approved from 1978 to 2016. Panel A gives the distribution of months between successive trial indications. Panel B gives the distribution of months between successive approval indications.

## B Model Proofs

### B.1 Proof for Proposition 3

$$\begin{aligned} EV_{B,A} = \ & 2p_B[M_B + M_A + M_{B'}] - p_A M_{A'} - K_B - K_A > \\ & 2p_A[M_A + M_B + M_{A'}] - p_B M_{B'} - K_A - K_B \ = EV_{A,B} \end{aligned} \tag{13}$$

Distributing terms gives:

$$\begin{aligned} & 2p_B M_B + 2p_B M_A + 2p_B M_{B'} - p_A M_{A'} - K_B - K_A > \\ & 2p_A M_A + 2p_A M_B + 2p_A M_{A'} - p_B M_{B'} - K_A - K_B \end{aligned} \tag{14}$$

Simplifying gives us:

$$\begin{aligned} & 2p_B M_B + 2p_B M_A + 3p_B M_{B'} > \\ & 2p_A M_A + 2p_A M_B + 3p_A M_{A'} \end{aligned} \tag{15}$$

Combining terms, we have:

$$\begin{aligned} & 2p_B[M_B + M_A] + 3p_B M_{B'} > \\ & 2p_A[M_A + M_B] + 3p_A M_{A'} \end{aligned} \tag{16}$$

### B.2 Proof for Proposition 4

$$\begin{aligned} EV_{B,A} = \ 2p_B T_B \ + \ p_A[(1-d_{A,B})M_A + \sum_{\substack{j\in\mathcal{O}_A \\ j\neq B}} d_{A,j}(1-d_{B,j})M_j] - K_B - K_A \ > \\ 2p_A T_A + p_B[(1-d_{A,B})M_B + \sum_{\substack{k\in\mathcal{O}_B \\ k\neq A}} d_{B,k}(1-d_{A,k})M_k] - K_A - K_B \ = EV_{A,B} \end{aligned} \tag{17}$$

Distributing terms gives:

$$\begin{aligned} 2p_B T_B + p_A M_A - p_A d_{A,B} M_A + p_A \sum_{\substack{j\in\mathcal{O}_A \\ j\neq B}} d_{A,j} M_j - p_A \sum_{\substack{j\in\mathcal{O}_A \\ j\neq B}} d_{A,j} d_{B,j} M_j \ > \\ 2p_A T_A + p_B M_B - p_B d_{A,B} M_B + p_B \sum_{\substack{k\in\mathcal{O}_B \\ k\neq A}} d_{B,k} M_k - p_B \sum_{\substack{k\in\mathcal{O}_B \\ k\neq A}} d_{B,k} d_{A,k} M_k \end{aligned} \tag{18}$$

We note that $\sum\limits_{\substack{j\in\mathcal{O}_A \\ j\neq B}} d_{A,j} M_j = T_A - d_{A,B} M_B$ and substitute:

$$\begin{aligned} 2p_B T_B + p_A M_A - p_A d_{A,B} M_A + p_A (T_A - d_{A,B} M_B) - p_A \sum_{\substack{j\in\mathcal{O}_A \\ j\neq B}} d_{A,j} d_{B,j} M_j \ > \\ 2p_A T_A + p_B M_B - p_B d_{A,B} M_B + p_B (T_B - d_{A,B} M_A) - p_B \sum_{\substack{k\in\mathcal{O}_B \\ k\neq A}} d_{B,k} d_{A,k} M_k \end{aligned} \tag{19}$$

We rearrange terms, rewrite $T_A$ as $M_A + \sum_{j\in\mathcal{O}_A} d_{A,j} M_j$ (and $T_B$ accordingly), and simplify:

$$\begin{aligned} p_B[\sum_{k\in\mathcal{O}_B} d_{B,k} M_k + d_{A,B}(M_A + M_B) + \sum_{\substack{k\in\mathcal{O}_B \\ k\neq A}} d_{B,k} d_{A,k} M_k] \ > \\ p_A[\sum_{j\in\mathcal{O}_A} d_{A,j} M_j + d_{A,B}(M_A + M_B) + \sum_{\substack{j\in\mathcal{O}_A \\ j\neq B}} d_{A,j} d_{B,j} M_j] \end{aligned} \tag{20}$$

## C Ordering of Market Entry Decisions

Table C1: Ordering of Market Entry Decisions

| | Dependent variable: Indication order | | | |
|---|---|---|---|---|
| | Clinical trials | | Regulatory approvals | |
| | (1) | (2) | (3) | (4) |
| Log(Focal market size) | -2.315*** | -1.016*** | 0.00411 | -0.00284 |
| | (0.106) | (0.120) | (0.0910) | (0.120) |
| Mean of Dep. Var. | 10.963 | 10.454 | 1.743 | 1.764 |
| Observations | 1,980 | 1,523 | 187 | 182 |
| *Controls:* | | | | |
| Initial approval year | no | yes | no | yes |
| Indication group | no | yes | no | yes |
| Competition | no | yes | no | yes |
| Regulatory incentives | no | yes | no | yes |
| Intellectual property | no | yes | no | yes |

Notes: This table shows the relationship between indication order and market size for cancer drugs first approved from 1978 to 2016. The level of observation is the drug-indication order. Columns 1 and 2 examine clinical trials, and Columns 3 and 4 examine regulatory approvals. The outcome variable in Columns 1 and 2 is trial indication order, while that in Columns 3 and 4 is approval indication order. Market size is measured by new diagnoses for an indication in the SEER data. We use the log of the five-year average market size associated with indication order. The number of observations differs between Columns 1 and 2 (and between Columns 3 and 4) due to missing data on control variables. Robust standard errors are in parentheses. * p<0.1, ** p<0.05, *** p<0.01.

# D Robustness Checks

## D.1 Incorporating Trials Linked to FDA-Approved and Unapproved Drugs

TABLE D1: ORDERING OF MARKET ENTRY DECISIONS WITH ALL CLINICAL TRIALS

| | Dependent variable: Indication order | |
|---|---|---|
| | (1) | (2) |
| Log(Focal market size) | -104.6*** | |
| | (1.520) | |
| Log(Total market size) | | -235.9*** |
| | | (1.624) |
| Mean of dep. var | 3303.213 | 3303.213 |
| Observations | 1,012,583 | 1,012,583 |
| *Controls:* | | |
| Initial approval year | no | yes |
| Indication group | no | yes |
| Competition | no | yes |
| Regulatory incentives | no | yes |

NOTES: This table shows the relationship between indication order and market size for FDA-approved and unapproved cancer drugs with an initial trial between 1998 and 2021 (corresponding to the most complete coverage of our trials dataset). The level of observation is the drug-indication order. Both columns examine clinical trials, where the sample of clinical trials consists of all trials (not just those that are linked to FDA-approved drugs). The outcome variable is trial indication order. Market size is measured by new diagnoses for an indication in the SEER data. We use the log of the five-year average market size associated with indication order. We omit controls for intellectual property protection since this sample includes drugs developed both within and outside the U.S., where intellectual property protections vary. Robust standard errors are in parentheses. * p<0.1, ** p<0.05, *** p<0.01.

## D.2 Cross-Disease Analysis

### D.2.1 Controlling for Drug and Market Characteristics

TABLE D2: ORDERING OF REGULATORY APPROVALS ACROSS DISEASES, BY PROPENSITY FOR OFF-LABEL DRUG USE

| | Dependent variable: Indication order | | | |
|---|---|---|---|---|
| | Low off-label diseases | | High off-label diseases | |
| | (1) | (2) | (3) | (4) |
| Focal market size | -0.277*** | -0.403*** | -0.0815*** | 0.0271 |
| | (0.0350) | (0.0752) | (0.0200) | (0.0333) |
| Mean of Dep. Var. | 1.138 | 1.121 | 1.503 | 1.503 |
| Observations | 152 | 140 | 650 | 598 |
| *Controls:* | | | | |
| Initial approval year | no | yes | no | yes |
| Indication group | no | yes | no | yes |
| Competition | no | yes | no | yes |
| Regulatory incentives | no | yes | no | yes |

NOTES: This table shows the relationship between indication order for regulatory approvals and market size for approved drugs across several disease categories from 1998 to 2021, by propensity for off-label drug use. The level of observation is the drug-indication order. The outcome variable is approval indication order. Market size is measured by new diagnoses for an indication (ICD-9) in the MEPS data. We use the log of the market size associated with focal indication order averaged over 1996 and 1997. The number of observations differs between Columns 1 and 2 (and between Columns 3 and 4) due to missing data on control variables. Robust standard errors are in parentheses. * p<0.1, ** p<0.05, *** p<0.01.

### D.2.2 Controlling for ATC Classification

TABLE D3: ORDERING OF REGULATORY APPROVALS ACROSS DISEASES, BY PROPENSITY FOR OFF-LABEL DRUG USE, WITH ALTERNATIVE DISEASE CONTROLS

| | Dependent variable: Indication order | |
|---|---|---|
| | Low off-label diseases (1) | High off-label diseases (2) |
| Focal market size | -0.234*** | 0.0293 |
| | (0.0531) | (0.0323) |
| Mean of Dep. Var. | 1.121 | 1.503 |
| Observations | 140 | 598 |
| *Controls:* | | |
| Initial approval year | yes | yes |
| ATC classification | yes | yes |
| Competition | yes | yes |
| Regulatory incentives | yes | yes |

NOTES: This table shows the relationship between indication order for regulatory approvals and market size for approved drugs across several disease categories from 1998 to 2021, controlling for each drug's ATC classification. The level of observation is the drug-indication order. There are 14 mutually exclusive ATC categories: alimentary tract and metabolism, anti-infectives for systemic use, antineoplastic and immunomodulating agents, antiparasitic products, insecticides and repellents, blood and blood forming clots, cardiovascular system, dermatologicals, genitourinary system and sex hormones, musculoskeletal system, nervous system, respiratory system, sensory organs, systemic hormonal preparations, and various. The outcome variable is approval indication order. Market size is measured by new diagnoses for an indication (ICD-9) in the MEPS data. We use the log of the market size associated with focal indication order averaged over 1996 and 1997. Robust standard errors are in parentheses. * p<0.1, ** p<0.05, *** p<0.01.

### D.2.3 Incorporating an Alternative Measure of Actual Off-Label Drug Use

We incorporate into the cross-disease analysis an alternative measure of actual off-label drug use using physician prescribing data from the IMS Health National Disease and Therapeutic Index$^{TM}$ (NDTI$^{TM}$) from 2004 to 2009. The NDTI$^{TM}$ provides data based on surveys of practicing physicians, allowing us to measure both on-label and off-label drug use. For each drug, we calculate the share of prescriptions that are off-label in a given year. To examine how off-label use shapes the indication order-market size relationship, we restrict our analysis to drug approvals over a given period and control for the share of off-label prescriptions in the year prior to the start of the analysis period. For example, Panel A in Table D4 focuses on the set of all drugs approvals starting in 2005. Column 1 shows the correlation between indication order and market size. Column 2 controls for the share of off-label prescriptions in 2004 and shows that the indication order-market size correlation is more negative after accounting for off-label drug use. We observe a similar pattern in subsamples beginning in subsequent years (2006, 2007, 2008, 2009, and 2010).

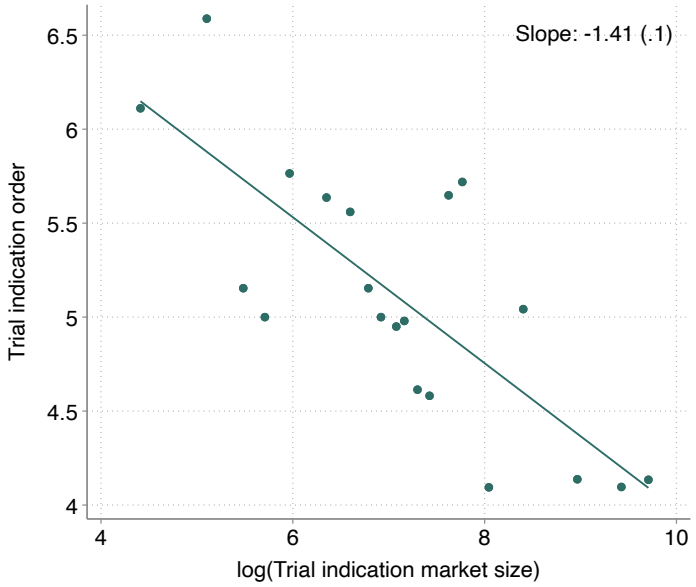
TABLE D4: ORDERING OF REGULATORY APPROVALS ACROSS DISEASES, ACCOUNTING FOR ACTUAL OFF-LABEL DRUG USE

| | Dep. Var.: Indication order | |
|---|---|---|
| | (1) | (2) |
| *Panel A. Drugs approved 2005+* | | |
| Focal market size | -0.0963*** | -0.0994*** |
| | (0.0197) | (0.0195) |
| Mean of Dep. Var. | 1.585 | 1.585 |
| Observations | 716 | 716 |
| *Panel B. Drugs approved 2006+* | | |
| Focal market size | -0.0963*** | -0.102*** |
| | (0.0201) | (0.0196) |
| Mean of Dep. Var. | 1.579 | 1.579 |
| Observations | 680 | 680 |
| *Panel C. Drugs approved 2007+* | | |
| Focal market size | -0.0963*** | -0.102*** |
| | (0.0209) | (0.0203) |
| Mean of Dep. Var. | 1.591 | 1.591 |
| Observations | 650 | 650 |
| *Panel D. Drugs approved 2008+* | | |
| Focal market size | -0.104*** | -0.109*** |
| | (0.0214) | (0.0209) |
| Mean of Dep. Var. | 1.576 | 1.576 |
| Observations | 618 | 618 |
| *Panel E. Drugs approved 2009+* | | |
| Focal market size | -0.112*** | -0.115*** |
| | (0.0224) | (0.0219) |
| Mean of Dep. Var. | 1.592 | 1.592 |
| Observations | 584 | 584 |
| *Panel F. Drugs approved 2010+* | | |
| Focal market size | -0.108*** | -0.114*** |
| | (0.0234) | (0.0229) |
| Mean of Dep. Var. | 1.614 | 1.614 |
| Observations | 547 | 547 |

NOTES: This table shows the relationship between indication order for regulatory approvals and market size for approved drugs across several disease categories. Each coefficient is from a separate regression. Regressions in Column 2 control for the share of off-label prescriptions in the year prior to the start of the analysis period, while those in Column 1 do not. The outcome variable is approval indication order. Market size is measured by new diagnoses for an indication (ICD-9) in the MEPS data. We use the log of the market size associated with focal indication order averaged over 1996 and 1997. Robust standard errors are in parentheses. * $p<0.1$, ** $p<0.05$, *** $p<0.01$.

## D.3 Trial End Dates

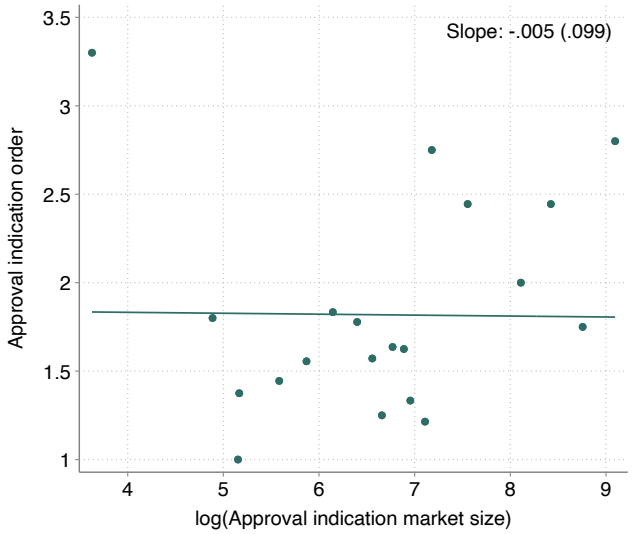
FIGURE D1: TRENDS IN CLINICAL TRIALS, WITH INDICATION ORDER DETERMINED BY TRIAL END DATES




NOTES: This figure shows a binned scatter plot examining trends in clinical trials for cancer drugs first approved from 1978 to 2016, with indication order determined by trial end dates. The level of observation is the drug-indication order. Market size is measured by new diagnoses for an indication in the SEER data. We use the log of the five-year average market size.

## D.4 Submission Dates

FIGURE D2: TRENDS IN REGULATORY APPROVALS, WITH INDICATION ORDER DETERMINED BY SUBMISSION DATES




NOTES: This figure shows trends in regulatory approvals for cancer drugs first approved from 1978 to 2016, with indication order determined by FDA submission dates. The level of observation is the drug-indication order. Market size is measured by new diagnoses for an indication in the SEER data. We use the log of the five-year average market size.