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ABSTRACT

We explore how firms respond to downstream product shocks. We find that affected firms increase R&D and make additional safety-related investments in their existing assets-in-place. These investments vary with firm capabilities and across shock severity. Competitors appear to vicariously learn and also engage in similar upstream investments. We present evidence that these upstream investments have important performance implications. First, these investments are positively related to transition probabilities and approval rates for products that received them. Second, these investments are related to a decrease in the intensity and rate of future downstream product shocks. Surprisingly, however, these investments appear to have limited impact on mitigating the negative demand response caused by these shocks.

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1.0 Introduction

Significant attention and effort has focused on innovation and the underlying firm capabilities, processes, resources, routines, and organizational structures that drive it. Once a new product is created it passes along to a firm's downstream co-specialized assets (*e.g.*, manufacturing, marketing, etc.) and attention returns to the 'next innovation'. An inherent assumption in this transition from upstream to downstream is that a new product is without flaw, error, or defect. Unfortunately, products stumble and sometimes fail - spectacularly at times – creating unanticipated downstream product shocks that can have large adverse consequences for firm revenues and profits. How should firms respond to these kinds of negative shocks?

Recent work by Krieger *et al.* (2022) finds that firms facing these kinds of challenges will frequently increase their research and development (R&D) efforts through acquisitions to 'find-and-replace' a failed technology with another technology. Firms turn to acquisitions because the downstream product shock creates an immediacy need from lost revenues and slack commercialization assets. In this setting, acquiring new technologies may be the fastest way - especially if they have no other products close to market - to address both of these issues and generate value for the firm.

However, if a firm has other R&D projects or assets-in-place, then solely adopting a find-and-replace strategy may risk throwing the proverbial technological 'baby out with the bathwater'. While the acquisition of new, external technology may serve to replace revenues and re-engage slack downstream capabilities, it does not address whether the problem that caused the downstream shock may be lurking elsewhere within a firm's R&D portfolio. This would be an especially acute concern for a firm if they had other pipeline products *within* the same market as the focal product that experienced the downstream shock. Failure to address this concern potentially exposes them to suffering the same shock in the future. What is needed, therefore, is a complementary strategy focused on these assets-in-place.

The purpose of this paper is to explore such a complementary strategy. Specifically, we focus on specific firm investments that utilize existing upstream development capabilities to generate new safety insights and information about their existing assets-in-place. The new information gathered from these investments serve to reduce the uncertainties created by the product shock for their assets-in-place (*e.g.*, Liu *et al.*, 2017; Kalaignanam *et al*., 2013; Oriani and Sobrero, 2008). The ultimate goal of these efforts are to ensure that similar shocks do not occur in the future as existing assets-in-place (*i.e.*, R&D pipeline projects) transition to downstream products. While all products undergo some type of pre-market testing (as they do in our research setting), the difference with these *ex post* investments are that, due to the shock, firms know exactly what problem they are trying to address.[1]

[1] An example, in a difference context than our research setting, are the flight control software issues that led to two crashes and eventual grounding of the Boeing 737 Max aircraft. Once the problem revealed itself, Boeing was able

Our research setting is the pharmaceutical industry and following the literature (Higgins *et al.*, 2021; Krieger *et al.*, 2022) we use data from FDA mandated drug relabeling events as our downstream shocks. We focus on a complementary strategy to the acquisition channel (Krieger *et al*., 2022) that involves upstream investments by firms in their assets-in-place. Specifically, we show that firms make additional investments in early-stage safety testing – what we term '*phase expansion'*. We demonstrate that the assets-in-place that undergo phase expansion experience improved transition probabilities and approval rates. Critically, we find that these assets-in-place have a lower probability of experiencing a future relabeling event (*i.e.*, downstream product shock) and a less intense shock, should one occur.

With these findings we make several important contributions to the literature. First, there is a well-established literature recognizing the relationship between downstream demand and upstream innovation, including debates around Porter's hypothesis (*e.g.*, Griliches and Schmookler, 1963; Schmookler, 1966; Nordhaus, 1969; Chakraborty and Chatterjee, 2017). By utilizing their existing upstream development capabilities (*i.e.*, the 'D' in R&D), we provide a channel through which firms are able to respond to unanticipated downstream negative product shocks on their assets-in-place (Manso *et al*., 2023; Armand and Mendi, 2018; Paunov, 2012). Our results demonstrate the importance for firms to maintain upstream development capabilities that match their downstream markets. This need to maintain upstream capabilities, however, is not without a potential cost as it creates and reinforces a lock-in effect within particular markets (Chan *et al*, 2007).

Second, in the product recall literature firms try to learn from negative events (*e.g.*, Haunschild and Sullivan, 2002; Haunschild and Rhee, 2004), want to improve reliability following failure (*e.g.*, Chao *et al.*, 2009) with the goal of preventing future incidents (Kalaignanam *et al*., 2013). In our setting, we provide a mechanism for how firms are able to precisely do this. In response to a change in safety related information about their product, firms make a specific type of upstream investment (*i.e.*, phase expansion). We show that these investments are related to a decrease in rate and intensity of future downstream product shocks (*i.e.*, relabeling events). Surprisingly, and in contrast to the extant literature (*e.g.*, Souiden and Pons, 2009; Bala *et al.,* 2017), these investments do not appear to mitigate the negative demand response for the focal product from the downstream shock (Higgins *et al.*, 2021).

Extensive interviews with physicians provide insights as to why they do not switch patients back to the focal drug. Explanations are consistent with the positive-negative asymmetry effect (*e.g.*, Peeters and Czapinski, 1990) and models of trust (*e.g.*, Mayer *et al.*, 1995). While our focus is on a firm's pipeline or

to make investments to fix the flight control software and control wiring in aircraft tails. These changes were made to their existing products (*i.e.*, grounded aircraft) as well as their existing assets-in-place (*i.e.*, planes in current production). In the current paper, our focus is on the investments made to a firm's assets-in-place or their existing R&D pipeline projects.

assets-in-place, the inability to mitigate the demand loss of the focal product reinforces the importance of the acquisition channel described by Krieger *et al*. (2022). Combined our two papers present complementary strategies on how firms respond to downstream product shocks. On one hand, the acquisition channel (ala Krieger *et al*) deals with the revenue loss and slack commercialization assets of the focal product. On the other hand, this paper, focuses on investments in a firm's assets-in-place to avoid similar shocks in the future.

Finally, our results have implications for pharmaceutical firms as they face a tension between length and breadth of development efforts and getting new drugs to market. On the one hand, firms want to conduct trials sufficient enough to ensure FDA approval. On the other hand, once patents have been granted, delays in getting a drug approved cut into their market exclusivity and future expected value. Multiple regulatory pathways have been created to expedite development of new drugs.[2] However, drugs that have gone through one of these expedited pathways have an increased risk of experiencing a relabeling event (Mostaghim *et al.*, 2017; Moore and Furberg, 2014; Carpenter *et al.*, 2008; Olson, 2008) and the significant negative demand impacts resulting from them (Higgins *et al.*, 2021). Our findings provide a channel through which firms can attempt to mitigate both the rate and intensity of these events allowing them to continue to utilize these expedited pathways.

The remainder of the paper proceeds as follows. Section 2 provides institutional background on the drug approval process and FDA relabeling. Sections 3 and 4 discuss relevant literature on downstream product shocks and upstream investments, respectively. Our empirical strategy and data are discussed in Section 5 and empirical results are presented in Section 6. We discuss our results and conclude in Section 7.

2.0 Institutional background: Clinical trials and FDA drug relabeling

The drug development process is highly regulated and drug candidates undergo a series of clinical trials before being submitted to the FDA for approval. These clinical trials are broken down into three types of trials: Phase I, Phase II, and Phase III. Phase I trials focus on assessing the safety of the drug. These trials focus on a small number of human participants and average several months to a year to complete. Phase II trials focus on evaluating the efficacy of the drug, are larger in size, and can take several years, on average, to complete. Finally, Phase III trials involve large-scale human trials to test efficacy and to monitor for adverse reactions. These trials are expensive and can take years to complete.

[2] These include including priority reviews, breakthrough therapy, accelerated approval, and fast track status. For more details see https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review.

Evidence and results from these three phases are submitted to the FDA in the application for approval.[3] This submission also includes the safety label for a drug, which needs to be approved by the FDA.

One of the major goals of the clinical trial process is to understand and identify any safety-related issues with a drug. Possible risks or side effects due to the use of a drug are included as part of the FDA approved label and insert that accompanies a new drug. Given the limited nature of the clinical trial process, not all of these risks and side effects are known at the time of approval. After a drug has been approved, the FDA continues to monitor drug safety. This includes the evaluation of patient and physician reports, results of post-approval clinical trials, and the academic literature. If the FDA begins to detect the presence of unanticipated side-effects, they will convene a panel to consider changes to a drug's safety label. Many panels are convened with no further action (Krieger *et al*., 2022). However, if the FDA deems a change is necessary, they will then announce their decision through a public health advisory.

Important for our identification strategy, which we discuss below, will be the fact that safety label changes mandated by the FDA are beyond the control of the drug manufacturer. While firms are able to monitor many of the same channels as the FDA to watch for safety-related concerns, they do not have clarity about outcomes until the reviews are completed. It is also not certain that reviews will translate into action. As Krieger *et al*. (2022) point out "…in 2017 the FDA Office of Surveillance and Epidemiology supported 7,466 safety reviews, of which 2,860 were part of biweekly surveillance…only 11 cases rose to the level of a public health advisory".[4] As such, given that anticipating the precise timing and severity of these label changes possess challenges, these events can be viewed as plausibly exogenous (Higgins *et al.*, 2021; Krieger *et al.*, 2022).

3.0 Negative downstream product shocks

Negative downstream product shocks tend to be widely publicized events. For example, in 2015, Chipotle Mexican Grill was linked to hundreds of illnesses (Noack *et al*., 2019). They can also be catastrophic, such as when a product defect in a rudder control system led to a crash of a U.S. Air Boeing 737 killing 132 people (Bosch *et al*., 1998). More recently, Tesla's autopilot technology has been associated with 17 fatal car incidents and Boeing is confronting door plug failure.[5] Some have argued that growing product complexity is a contributing factor behind these kinds of occurrences (Zhao *et al.*, 2013). In all cases, these kinds of product shocks tend to have negative impacts on firm performance (*e.g.*, Davidson and Worrell, 1992; Bosch *et al*., 1998; Liu *et al.*, 2017) and dictate some kind of firm (*e.g.*,

[3] Please see https://www.fda.gov/patients/drug-development-process/step-3-clinical-research for a more complete description of the clinical trial process.
[4] https://www.fda.gov/drugs/drug-safety-and-availability/advances-fdas-drug-safetyprograms
[5] https://www.washingtonpost.com/technology/2023/06/10/tesla-autopilot-crashes-elon-musk/ and https://www.wsj.com/business/airlines/boeing-manufacturing-737-max-alaska-door-plug-spirit-18f7e233. Accessed 25 June 2024.

Haunschild and Rhee, 2004; Bloom *et al*., 2016; Flammer and Ioannou, 2021) and often competitor response (*e.g.*, Ball *et al*., 2022).

Firms affected by negative product shocks can broadly respond in two ways. First, they can respond through downstream efforts, for example, by initiating marketing or advertising campaigns to improve their image (*e.g.*, Souiden and Pons, 2009; Bala *et al.,* 2017). Alternatively, firms can respond through upstream investments, including remedial efforts (Liu *et al.*, 2017), quality improvements (Haunschild and Rhree, 2004), increased R&D expenditures or acquisitions (Krieger *et al.*, 2022). In general, these kinds of upstream investments reflect a firm's desire to resolve uncertainties surrounding the product shock (Kalaignanam *et al*., 2013; Oriani and Sobrero, 2008), including replacing lost revenues (Krieger *et al.*, 2022).

Within the pharmaceutical industry, negative product shocks arise mainly from unforeseen adverse safety events associated with drug use. Formally, these events can range in severity from adverse reactions to "Black Box" or box warnings (Mostaghim *et al*., 2017), or in rare cases removal of products from the market. For example, Vioxx was a highly effective arthritis drug however it was also found to cause increased risk of cardiovascular events like stroke and heart attacks. As a result, Vioxx was removed from the market in 2004, five years after FDA approval, costing an estimated loss of $2.5 billion (Bala *et al*., 2017). Trends suggest that adverse safety events have been increasing (Moore *et al*., 2007) and have been associated with declines in pre-approval times (Olson, 2003).

Responses to these adverse events can come from both sides of the market. On the demand side of the market, physicians may respond by shifting patients (consumers) away from a drug due to a safety concern (Higgins, *et al.*, 2021). A number of studies, focusing on specific therapeutic markets, support this association (*e.g*., Dranove and Olsen, 1994; Dorsey *et al.*, 2010; Kales *et al.*, 2011; Lu *et al.*, 2014). These concerns appear to also spill over to competitor drugs in the same therapeutic market (Cawley and Rizzo, 2008). More recently, Higgins *et al*. (2021) causally show the negative demand impacts across every impacted therapeutic category, accounting for all plausible substitution patterns. They found the average loss in sales over the remaining lifecycle for affected drugs was $186 million and event study results suggested an average loss between $569 million and $882 million.

On the supply side of the market, Krieger *et al*. (2022) examine how pharmaceutical firms use acquisitions in response to downstream product shocks. Theoretically, Krieger *et al.* (2022) argue that revenues for the affected drugs fall to zero. Due to this loss of revenues and slack commercialization assets, an immediacy need is created that leads firms to acquire external technology within that therapeutic market. This immediacy need created by a shock in the product market is similar to the immediacy need created by a late-stage clinical trial failure (*e.g.*, Higgins and Rodriguez, 2006; Chan *et al.*, 2007; Danzon *et al.*, 2007; Hermosilla, 2021). These papers find that pharmaceutical firms turn to the

external technology markets to acquire or license drugs to fill R&D gaps created by pipeline failures. By acquiring within the same focal therapeutic market as the shock, firms are able to acquire in areas for which they have R&D capabilities (*e.g.*, Higgins and Rodriguez, 2006; Bena and Li, 2014) and downstream co-specialized assets (Chan *et al.*, 2007).

4.0 Safety-related upstream investments: Phase expansion

The above dynamics suggest that when drugs face negative product shocks but are not fully recalled or removed from the market, revenues do decline, but not to zero. Evidence exists that some kinds of commercialization assets are reallocated (*e.g.*, Krieger *et al.*, 2022) but not all (*e.g.*, Higgins *et al.*, 2021; Macher and Wade, 2016). Consistent with prior research (*e.g.*, Higgins and Rodriguez, 2006; Chan *et al.*, 2007; Danzon *et al.*, 2007), Krieger *et al.* (2022) show that firms engage in acquisitions within the same therapeutic market as the downstream product shock to 'find-and-replace' or help fill the gap.

While an acquisition strategy can serve to replace revenues or reengage slack downstream capabilities, the strategy does not assuage physician beliefs about the safety of *other* products by the affected firm (Roehm and Tybout, 2006) or other products by competitors in the affected therapeutic market (Cawley and Rizzo, 2008; Bunninran *et al.*, 2009; Dorsey *et al*., 2010). This is of particular concern for firms that have other products under development within the same therapeutic market as the focal product affected by the product shock. For example, assume that the expected value of a pipeline project at time *t* can be calculated as a function of some probability weighted discounted cash flow. The revelation of a new safety concern can negatively impact the probability that a pipeline product will eventually reach the market, thereby lowering its expected value.

A solution to address these concerns is to make upstream, remediation type investments (Liu *et al.*, 2017) in an effort to reduce the uncertainty surrounding the shock (Kalaignanam *et al*., 2013; Oriani and Sobrero, 2008). Conversations with senior executives at several leading pharmaceutical companies suggest exactly this; firms make upstream investments in order to understand the safety-related implication of these negative shocks not only on the focal product but also on their existing portfolio. This allows them to directly address the negative impact that a downstream shock may have on the expected value of their pipeline projects. Specifically, they are able to take the specific safety-related information identified in the relabeling event and use that to design new clinical trials (*i.e.*, phase expansion).

Specifically, by *ex-ante* knowing the concerns that they are looking for, firms can create targeted multi-arm trials (*i.e.*, single- and double-blind), across different control groups (*e.g.*, historical, placebo, and active), and patient populations. Phase expansion also allows for the consideration of multiple different endpoints (*e.g.*, continuous endpoints, categorical endpoints, and event-time endpoints). The ultimate goal of phase expansion is the revelation of new information related to the negative shock. This

information should allow for improvements to protocol and trial design for those products still under development which should positively impact transition and approval rates. Given these additional trials, pipeline products that undergo phase expansion should also have a lower likelihood of experiencing a future relabeling event. Finally, this new scientific information can also be used in direct marketing efforts to physicians (*i.e.*, detailing) in an effort to stem the demand decline of the focal product (Higgins *et al.*, 2021).

These actions described by industry are entirely consistent with problemistic search theory (*e.g.*, Posen *et al.*, 2018). Aspirations are important to the triggering of problemistic search. One strand of this literature focuses on financial performance as the aspiration (*e.g.*, Miller and Chen, 2004). Thus, when faced with performance below aspiration, a firm begins a process of search to discover a solution. In our setting, firms experience exogenous shocks to existing products, causing financial performance to fall thereby triggering the firm to engage in search (*i.e.*, phase expansion).[6] Importantly, we expect the intensity of these search activities to be directly related to the magnitude of the shock and performance shortfall (Posen *et al.*, 2018).

5.0 Empirical strategy and data

5.1 Empirical strategy

Following Higgins *et al.* (2021) and Krieger *et al.* (2022), we exploit FDA relabeling events to estimate a difference-in-differences (diff-in-diffs) specification. Similar to Krieger *et al.* (2022) we start by exploring the responsiveness of R&D expenditures to these events. If R&D expenditures increase, it suggests firms are allocating additional resources to R&D to respond to these events. In contrast, if R&D expenditures do not change, it is suggestive that firms may be substituting financial resources away from existing projects to fund phase expansion. Unfortunately, these data are not available at the therapeutic market level, so our initial analysis explores the R&D response at the firm level. As such, we estimate the following model:

$$Y_{it} = \alpha + \beta(Relabel_{it}) + \gamma(Controls_{it}) + \mu_i + \delta_t + \epsilon_{it} \qquad (1)$$

where Y_{it} is defined as the natural log of R&D expenditures for firm i in year t. $Relabel_{it}$ is a dummy variable that takes the value of one in year t and the following time periods, zero otherwise. Our baseline specification considers a three-year treatment window after a relabeling event. This time period encompasses the majority of first instances of relabeling events and also ensures the branded drugs are still within their market exclusivity period.[7] We include a number of controls, which we discuss below, as well as firm fixed effects (μ_i) to control for time-invariant heterogeneity between firms and year fixed

[6] Krieger *et al.* (2022) is also entirely consistent with problemistic search theory.
[7] Results are robust to alternative treatment windows. Note, a branded drug within their market exclusivity period has not yet faced generic entry.

effects (δ_t) to control for common shocks impacting all firms across time. Equation (1) is a diff-in-diffs regression with multiple events where treated observations will be those that recently experience a relabeling event. Control observations include similar firms that do not or have not yet experienced a relabeling event. In Equation (1), the treatment effect estimates the marginal impact of a relabeling event on R&D expenditures.

In our second analysis, we consider firm response, through phase expansion, to relabeling events within (and across) therapeutic markets. Therapeutic markets are defined by the anatomical therapeutic chemical (ATC) market that a drug was approved in, or pipeline project was assigned to (discussed below). The ATC classification is controlled by the World Health Organization and was designed to categorize drugs into different groups based on the system that they treat.[8] As such, we estimate the following model:

$$Y_{ijt} = \alpha + \beta(Relabel_{ijt}) + \gamma(Controls_{ijt}) + \mu_i + \theta_{jt} + \delta_t + \epsilon_{ijt} \quad (2)$$

here Y_{ijt} is defined as the number of early-stage trials initiated (*i.e.*, phase expansion) by firm *i*, in therapeutic market *j*, in year *t*. $Relabel_{ijt}$ is a dummy variable that takes the value of one if a drug marketed by firm *i,* in therapeutic market *j*, in year *t* experiences a relabeling event, zero otherwise. We include a number of controls, which we discuss below as well as firm fixed effects (μ_i) to control for time-invariant heterogeneity between firms. We also include therapeutic market fixed effects (θ_{jt}) to control for unobserved time-varying differences across markets and year fixed effects (δ_t) to control for common shocks impacting all firms across time. Our coefficient of interest across these models is β and it represents the impact induced by relabeling events on upstream investments in phase expansion.

Our identification strategy relies on the key assumption that treatment states have similar trends to the control states in the absence of treatment. Given that relabeling events themselves remain exogenous, we would *ex ante* expect the parallel trends assumption to hold. To test this assumption, we estimate an event study that examines the dynamics of our coefficient of interest around relabel events. Coefficient estimates with 95 percent confidence interval bands for R&D expenditures and phase expansion are presented in Figure 1A and 1B, respectively. Each of the figures demonstrates insignificant estimates in the leads which implies that the parallel trends assumption is not violated.

Additionally, we also use a placebo specification to further test the parallel trend assumption (Higgins *et al.,* 2021). We take our pre-trend data and split it in half, defining the midpoint as an arbitrary treatment event. We implement our main specification in Equation (2). If the parallel trend assumption is violated the coefficient β will be statistically significant. The results for this placebo test are reported in

[8] For more information, please see: https://www.who.int/tools/atc-ddd-toolkit/atc-classification

Appendix Table 1. The coefficient of interest is not statistically significant across any model. Combined together both of these tests lend support that the critical assumption of parallel trends is not violated.

5.2 Data

We construct our sample from a number of data sources. We start by collecting project level drug development data from Pharmaprojects for the years 2008 to 2020. With this data we are able to construct pipeline and product portfolios, by therapeutic market, for each firm over this time period.[9] For each approved product we collected drug relabeling data from FDA MedWatch (pre-2016) and the FDA Drug Safety-related Labeling Changes database (post-2016). There are five possible relabeling events including: box warnings (most severe), contraindications, warnings, precautions, and adverse reactions (least severe). While it is possible that an approved drug can experience multiple relabeling events over time, we focus on their first event.[10]

Next, we collect and merge additional clinical trial data from ClinicalTrials.gov. While commercial databases, such as Pharmaprojects, may identify a drug in clinical trial development, they do not capture the disaggregate data relating to the number and types of those trials.[11] Given that we are concerned about safety-related events (*i.e.*, drug relabeling), we focus on matching all Phase I trial data into our sample. The only refinement we make with this data is that we require there be an identifiable experimental intervention arm. Finally, we match firm names from Pharmaprojects with Compustat to collect financial data. We report descriptive statistics in Appendix Table 2.

Dependent variables. Using data from Compustat we define our first dependent variable, $ln(R\&D+1)_{it}$, as the natural logarithm of R&D expenditures plus one for firm i in year t. This dependent variable is utilized in Equation (1) for our initial analysis. Our baseline dependent variable in Equation (2) is *Phase expansion* or the number of additional Phase I clinical trials for an existing pipeline drug, regardless of phase, until the drug fails, is discontinued, or approved. For our intramarket analysis we focus on phase expansion *within* the same therapeutic market j as the downstream shock. We define $Phase\ expansion_{ijt,}$ as the number of additional Phase I clinical trials initiated by firm $i,$ in therapeutic market $j,$ at time $t.$ For our intermarket analysis, we focus on phase expansion in therapeutic markets k that includes all other therapeutic markets besides the therapeutic market j of the downstream shock. Thus, we define

[9] Pharmaprojects reports pipeline data at the ATC-2 level so this is our default therapeutic market categorization. The anatomical therapeutic chemical (ATC) classification system categorizes active substances into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. ATC was developed and maintained by WHO: https://www.who.int/tools/atc-ddd-toolkit/atc-classification.

[10] We utilize the full relabeling experience of an approved drug in Table 7b where we are interested in the overall intensity of relabeling events. In all other specifications, we consider only the first instance of a relabeling event.

[11] For example, within a therapeutic market, Pharmaprojects may identify a drug in Phase I clinical trial but there may be a number of actual trials that were run during that phase. Additionally, if a drug is identified in Phase II or Phase III, Pharmaprojects generally does not identify if (or all) additional Phase I trials that might be run.

Phase expansion$_{ikt,}$ as the number of additional Phase I clinical trials initiated by firm *i,* in therapeutic market *k,* at time *t.*

Independent variables and controls. In order to implement our diff-in-diffs strategy, we define a dummy variable (*Relabel*) that equals one for all observations after an approved drug's first relabeling event, zero otherwise. Approximately, 57 percent of approved drugs experience a first relabeling event. Important to our analysis will be ensuring that we are controlling for pipeline drugs that are actively being developed. Using data from Pharmaprojects we create a pipeline control variable (*Pipeline*) that is a count of drugs in development for each firm. This variable controls for upstream capabilities that firms are able to deploy in response to downstream product shocks. They also control for experience and expertise in drug development as prior research demonstrates that successful trials in the past increase the likelihood of future clinical trial success (Lo *et al.*, 2018).

In addition to controlling for the size of a firm's pipeline portfolio, we also control for the number of approved products for each firm. We define *Portfolio* as the count of approved products by firm *i* starting five years before the start of our sample period. Approvals during this time period will still have market exclusivity at the start of our sample. By building this stock over time we control for downstream cospecialized assets and the commitment (or lock-in) that firms may have to specific therapeutic categories (Chan *et al.*, 2007). Second, this variable also controls for regulatory experience in drafting protocols and navigating the underlying regulatory process of drug submissions. Finally, this variable proxies for firm size; larger firms have more robust portfolios of approved products.

6.0 Empirical findings

6.1 Downstream shocks and R&D expenditures

We start our analysis by considering what happens to R&D expenditures in the face of downstream product shocks. If firms respond by making upstream investments, we should see those investments reflected in R&D expenditures. Using Equation (1), we test this conjecture in Table 1 and find a positive and significant increase in R&D expenditures in both a two-year (Model 1) and three-year (Model 2) treatment window. The marginal effect of our result is around 18 percent, which is remarkably close to the 21.4 percent reported by Krieger *et al.* (2022). We caution that these results are suggestive since R&D expenditures are aggregated at the firm level. Optimally, we would want to explore these impacts on project level R&D data, but such data does not publicly exist. Critically, however, these results suggest that new resources are being allocated to fund these efforts as opposed to being reallocated from some other existing R&D program.

Logically, R&D expenditures should vary with the severity of the downstream product shock. This is not unexpected since the magnitude of the safety-related event and resulting demand response varies with severity (Higgins *et al.*, 2021). In Table 2, we split the sample into less severe (Model 1) and

more severe (Model 2) types of drug relabels. While the coefficient on our variable of interest, $Relabel_{it}$, is significant across both models, the magnitude is almost twice as large for more severe events (Model 2). Overall, these increases are suggestive that R&D investments are being made and they appear to vary in ways that we might *ex ante* predict.

6.2 Upstream investments in phase expansion

Intramarket phase expansion. The demand impacts on a focal drug when it experiences a relabel are well understood (Higgins *et al*., 2021); physicians begin to shift patients away from the affected drug to substitute products. Unfortunately, these effects are not isolated. Physicians also proactively shift patients away from other drugs within the same therapeutic class of an affected drug (Cawley and Rizzo, 2008; Bunninran *et al.*, 2009; Dorsey *et al*., 2010; Higgins *et al.,* 2021). This suggests that a firm needs to determine whether the cause of the downstream shock is present in their other assets-in-place within the affected therapeutic market. We consider this conjecture in Table 3.

The dependent variable, $Phase\ expansion_{ijt}$, across all three models captures the expansion of safety-related trials for existing pipeline products in focal firm *i*'s R&D portfolio within the affected therapeutic market *j* (*i.e.*, intramarket) at time *t*. Model 1 is our baseline model and includes time, therapeutic market, and firm fixed effects. Model 2 includes portfolio and R&D pipeline controls along with time and therapeutic market fixed effects. Finally, Model 3 includes portfolio, R&D pipeline, and financial controls along with time and therapeutic market fixed effects. The coefficient on our variable of interest, $Relabel_{ijt}$, is positive, significant, and relatively stable across all three models. For those firms that experience a drug relabel, the expected phase expansion for their assets-in-place *within* the same market, increases by a factor of 2.04 (Model 1) to 2.60 (Model 3).

These results are consistent with the product recall literature that find firms make investments in remediation (Liu *et al.*, 2017) and quality improvements (Haunschild and Rhree, 2004). The increased spending on phase expansion is also consistent with our finding above related to increased R&D expenditures. These results also compliment Krieger *et al.* (2022) who show an increase in R&D expenditures after similar shocks. Given their focus on acquisitions, they relate the increase in expenditures to the generally accepted accounting principles that in-process R&D assets should be expensed. Our results suggest that firms are also making R&D investments in phase expansion for their existing pipeline products to ensure that future products do not face similar shocks.

Intermarket phase expansion. While firms would prefer that negative downstream product shocks were contained to the focal product itself, our prior discussion demonstrates that concerns ripple back though other products within the affected therapeutic market. Unfortunately, the concerns do not stop here. Evidence exists that concerns from product shocks, spillover to other firm products (Roehm and Tybout, 2006; Freedman *et al.*, 2012). This negative halo effect in our setting would manifest as a

concern for drugs in a firm's pipeline portfolio *outside* the affected therapeutic area. Given the significant market effects from drug relabels, we would expect firms to respond by also making these investments across their portfolio.

We test this conjecture in Table 4. The dependent variable in this specification, *Phase expansion*$_{ikt}$, captures the expansion of clinical trials initiated by firm *i*, in therapeutic market *k*, at time *t*. Importantly, our variable of interest, *Relabel*$_{ijt}$, is focused on therapeutic market *j* which is excluded from therapeutic market *k*. Thus, this specification will capture firm response across other therapeutic markets (*i.e.*, intermarket). All other variables and specifications are the same as our intramarket analysis (Table 3). Across all models, we find a positive and significant coefficient on our variable of interest, *Relabel*$_{ijt}$. The magnitude of this coefficient suggests that firms that experience a drug relabel in therapeutic market *j*, increases phase expansion in market *k* by a factor of 1.93 (Model 3). Not unexpectedly this intermarket response lies below their intramarket response.

While halo effects may be general, the specific underlying safety concern will be more relevant to intermarket drugs (*i.e.*, those in therapeutic market *k*) that are more technologically similar to the affected drug (*i.e.*, in therapeutic market *j*) that experienced the relabel. We consider this possibility in Appendix Table 3. To determine technological similarity, we use the Jaro distance metric comparing the action of mechanism of a relabeled drug in therapeutic market *j* with pipeline drugs in therapeutic market *k.* We calculate the mean of the Jaro distance and define those pipeline drugs above the mean as *High technological similarity* and those below the mean as *Low technological similarity*. As expected, we find a larger impact for *High technological similarity* (Model 2). These results are intuitive given that their mechanism of action is closer to the affected drug. If firms want to ensure that safety issues are not lurking in other pipeline drugs, those closest in technology to the affected drug would be the natural place to search.

Competitor response. Firms appear to be well-informed of the successes and failures of competitor products (*e.g.*, Wu 2013; Thirumalai and Sinha 2011). This is no different with drug relabel activity (*e.g.*, Cawley and Rizzo, 2008; Macher and Wade, 2016; Higgins *et al.*, 2021; Krieger *et al.*, 2022) and we expect to see competitors vicariously learn (*e.g.*, Kim and Miner, 2007) from these product shocks and respond accordingly (Ingram, 2002). Importantly, there is a risk that a negative shock to a focal firm's product will spillover to a competitor's product (Bakhtavoryan *et al*., 2014; Bala *et al.,* 2017). We test this conjecture in Table 5. The dependent variable, *Phase expansion*$_{hjt,}$ across all three models captures the expansion of safety-related trials for existing pipeline products in competitor firm *h*'s R&D portfolio within the affected therapeutic market *j* at time *t*. Model 1 is our baseline model and includes time, therapeutic market, and firm fixed effects. Model 2 includes portfolio and R&D pipeline controls

along with time and therapeutic market fixed effects. Finally, Model 3 includes portfolio, R&D pipeline, and financial controls along with time and therapeutic market fixed effects.

The coefficient on our variable of interest, $Relabel_{ijt}$, is positive, significant, and relatively stable across all three models. Consistent with the literature (*e.g.*, Cawley and Rizzo, 2008; Bakhtavoryan *et al*., 2014), these concerns appear to spillover to competitor drugs in the same therapeutic market. For firms whose competitors experience a drug relabel, their expected phase expansion increases by a factor of 1.92 (Model 3). Krieger *et al.* (2022) found that firms respond to a competitor's product shock by diversifying their pipeline portfolio into other therapeutic markets. Critically, however, they focus on the number of *new projects initiated* by a focal firm whereas we focus on investments in *existing pipeline projects* (*i.e.*, phase expansion); these are not 'newly initiated' pipeline projects.

6.3 Phase expansion and firm performance

Drug development remains a risky endeavor. Recent evidence places the overall success rate of clinical trials at 7.9 percent (Kim *et al.*, 2003). The FDA offers a number of programs to help speed the development and review process. Evidence exists that these programs have been successful (Chambers e*t al.*, 2017). However, evidence also exists that drugs approved through these expedited pathways are also more likely to suffer from more serious relabel events (*e.g*., Mostaghim *et al.*, 2017). When faced with downstream product shocks we have thus far presented evidence that focal and competitor firms make upstream, safety-related investments. We now explore whether (and how) these investments have an impact on firm performance.

Do upstream investments in phase expansion improve clinical trial success? We start by exploring whether investments in phase expansion have an impact on clinical trial success. Additional trials allow a firm to push down their learning curve and improve trial design. This improved trial design, for example, could manifest itself in more stable key parameters, such as patient populations, allowing for improvements in trial outcome. In other words, these shocks provide information on where firms need to look for potential gaps (Madsen and Desai, 2010). We start by considering whether these upstream investments in phase expansion impact the transition probability for those pipeline drugs that received the investment. We explore this possibility in Table 6a. Model 1 focuses on a firm's intramarket portfolio response while Model 2 focuses on a firm's intermarket portfolio response. For this analysis we focus on the transition from Phase I to Phase II.

Across both models we find a positive and significant relationship between *Phase expansion* and transitioning to the next stage of clinical development. While the intramarket response (Table 3) by firms was, on average, more robust than their intermarket response (Table 4), the magnitudes across both of these Models (Table 6a) are similar. Each additional early-stage trial (*i.e.*, phase expansion) increases the mean likelihood of eventual transition by 1.61 percent and 1.14 percent, respectively. Interestingly, this

similarity in performance suggests that early-stage clinical trial capabilities may be a more general-purpose capability as opposed to a market-specific capability (Pisano, 2017). That is, it may be more important to have the capabilities to design, draft, and place early-stage clinical trials as opposed to the capabilities to design, draft, and place early-stage therapeutic specific trials.

Do upstream investments in phase expansion improve approval rates? Given that it appears there is a relationship between phase expansion and clinical trial transition, we next consider whether these upstream investments improve overall approval rates. Are the effects limited to early-stage transition or does the new information allow for improved parameters or trial design over the entire clinical trial process? For the same reasons as above, we should expect to see improvements in overall approval rates. We test this conjecture in Table 6b where we explore the relationship between *Phase expansion* and the probability of eventual drug approval. In this specification we capture all upstream investments in phase expansion for pipeline drugs, in a focal therapeutic market, until those pipeline drugs either fail or reach FDA approval. In Model 1, we find a positive relationship between *Phase expansion* and the probability of eventual approval. More specifically, each additional early-stage trial increases the mean likelihood of eventual approval by 2.02 percent. In Model 2, however, the inclusion of a squared term shows that this effect, as expected, is not linear (Haans *et al*, 2016).

Do investments in phase expansion prevent future relabeling events? Kalaignanam *et al.* (2013) find that a firm's experience with product recalls is associated with improved product reliability of other unaffected products, leading to reduced rates of future product recalls. In our context this would translate into whether accumulated phase experience lowers the probability of a future relabel event. We test this conjecture in Table 7a. The dependent variable is a dummy variable equal to one if an approved drug experiences a relabeling event. The independent variable, *Phase expansion experience*, measures the accumulated number of post-relabel phase expansion trials by focal firm *i*, in therapeutic market *j,* over time period *t* where *t* represents the five-year period prior to drug approval.[12] In Model 1 (intramarket) and Model 2 (intermarket), we find a negative and significant relationship between *Phase expansion experience* and the probability of a future relabeling event. The coefficients in Models 1 and 2 imply that for every additional upstream trial, the mean likelihood of future relabel events decreases by 1.86 percent and 2.58 percent, respectively.

In addition to decreasing the probability of a future relabeling event, it is possible that upstream investments in phase expansion decreases the *intensity* of future relabeling events, should they occur. Heretofore, we have focused on the first instance of a relabeling event. We now relax that restriction as many drugs experience multiple relabeling events, often increasing in severity. If a firm can decrease the

[12] Given that experience may diminish with time, we apply a yearly discount rate of 15 percent (Griliches, 1984).

intensity of the relabeling events, they may be able to lessen the negative impact of these events on the firm. We consider this possibility in Table 7b where we define the dependent variable, *Relabel intensity*, as the cumulative number of relabel events experienced by firm *i*, in therapeutic market *j*, in time *t.* Our independent variable remains the same as the previous specification (Table 7a).

In Model 1 and Model 2, we find a negative and significant relationship between *Phase expansion experience* and the number of future relabel events. The coefficient in Model 1 implies that for every additional upstream trial, the mean expected number of future relabel events decreases by 23.9 percent. In Model 2 we add the square of *Phase expansion experience* to test whether this relationship is non-linear; the coefficient on the squared term is indeed positive and significant. Intuitively, this relationship should be non-linear, otherwise firms could simply drive down the number of relabel events to zero by continually making upstream investments in phase expansion. In sum, however, our evidence is consistent with findings in other industries (*e.g.*, automobiles, airlines, and medical devices); prior experience improved future performance (*e.g.*, Kalaignanam *et al.*, 2013; Thirmalai and Sinha, 2011; Madsen and Desai, 2010; Haunschild and Sullivan, 2002).

Do upstream investments mitigate negative downstream demand responses? The second channel through which accumulated experience from upstream investments in phase expansion can have an impact is on the affected drug that experienced the relabeling event. Prior research demonstrates that there is a significant negative demand response for drugs that experience relabeling events (Higgins *et al.*, 2021). They show that in response to these shocks physicians appear to be proactively shifting consumers to other drugs both within the same therapeutic market and to substitutes in closely related therapeutic markets. Accumulated experience in *ex post* phase expansion, creates a stock of safety-related information that firms can legally use in detailing efforts to assuage physician concerns and possibly mitigate this negative demand response.

In order to consider this possibility, we obtained data from Higgins *et al.* (2021). With a smaller overlapping dataset (due to different study periods), we replicate their main drug-level specification but consider the impacts of accumulated phase expansion experience.[13] We take merged data and split the sample above and below the mean of *Phase expansion experience* defining *High firm capability* and *Low firm capability*, respectively. In Table 8, *High capability firms* (Model 1) have a less negative coefficient on the variable of interest (*Relabel x U.S.*) as opposed to *Low capability firms* (Model 2). These

[13] Higgins *et al.* (2021) exploit relabeling events to estimate a diff-in-diffs specification. Their treated group includes drugs sold in the U.S. while their control group is comprised of the same exact drugs as those in the treated group but sold in the U.K. The coefficient on their main variable of interest, *Relabel x U.S.*, represents the impact induced by drug relabeling events on U.S. drugs relative to U.K. drugs. Their identification strategy relies on the fact that the control group is not exposed to treatment in either period; the FDA does not have regulatory jurisdiction over drugs sold in the U.K.

coefficients translate into marginal effects of 15.6 percent and 16.7 percent, respectively. For comparative purposes, Higgins *et al.* (2021) found average aggregate demand declines of 16.9 percent across their sample. In sum, we find no evidence that accumulated experience from phase expansion mitigates the negative demand response from downstream product shocks.

From conversations with senior executives at several global leading pharmaceutical companies, our *ex ante* expectations were that these investments should have mitigated (or more significantly mitigated) the negative demand response documented by Higgins *et al.* (2021). These marketed products clearly have value and are important to the firm, which is why we see increases in their *ex post* detailing efforts (*Lagged promotion stock*). The lack of causal evidence, therefore, is surprising. In the food industry, for example, the extant literature (*e.g.*, Heiman and Lowengart, 2008) finds that advertising and marketing efforts are successful at mitigating negative demand responses. While prospect theory (Tversky and Kahneman, 1992; Kahneman and Tversky, 1979) provides a behavioral explanation as to why physicians may switch consumers to other drugs (Verma *et al*., 2014; Higgins *et al.*, 2021), it doesn't explain why physicians do not appear to update their priors when confronted with new scientific information.

There are a number of possible explanations for what might be occurring and context in our research setting is important. First, in our setting, consumers do not choose which drugs they get prescribed, this choice is left to the physician. While direct-to-consumer advertising is legal in the US, it tends not to focus on the kind of scientific evidence that would be generated by phase expansion. Rather this evidence is communicated directly from the firm (via detailing) to physicians. Any information obtained by consumers would be filtered through their physician, news stories or possibly their own independent research.

Second, in the context of the well-known positive-negative asymmetry effect (*e.g.*, Peeters and Czapinski, 1990), negative information is processed and perceived more strongly than positive information. In other words, the 'bad' is stronger than the 'good' (Baumeister *et al.*, 2001) and bad events wear off more slowly than good events (Brickman *et al*., 1978). Coupled with prospect theory where physicians may be overestimating the probability of future negative events, the asymmetric effect of newly arrived positive information does not appear to be enough to sway physician behavior. They may simply be continuing to outweigh the 'bad' information.

Finally, physicians who previously switched consumers to a new drug (and had to explain why) may be hesitant to switch patients back for fear of losing patient trust. In their model of trust, Mayer *et al*. (1995) identify benevolence, or the perception of a positive orientation of the trustee toward the trustor, as a key factor. A sudden reversal of a prescription very may well cause a patient to question the underlying motivation of their physician, especially if the decision is based on information provided to them by a

pharmaceutical company. Qualitative evidence based on our conversations with physicians supports both of these conjectures.[14] Unfortunately, both provide challenges for firms trying to mitigate the demand loss from downstream product shocks.

7.0 Robustness

Stacked difference-in-differences. There is a growing methods literature involving diff-in-diffs estimators when treatment is staggered and varies with time (*e.g.*, Freedman *et al*., 2023; Roth *et al.,* 2022). While this problem has not yet currently been solved, we take seriously the call by Freedman *et al.* (2023) for researchers to consider multiple estimation approaches. As such, we consider a stacked difference-in-differences approach (Cengiz *et al.*, 2019; Deshpande and Li, 2019). With this approach sub-experiments are created based on common treatment adoption dates. In our setting, these sub-experiments are based on the year of the relabeling event. The control group in this specification are "clean" observations or drugs that have never been treated. Specifically, we match the treated drug to a control drug from a firm with similar size, a similar portfolio size and similar drug but in a different therapeutic market.[15] For comparative purposes between this specification and our main specification (Table 3), we maintain the three-year pre- and post-treatment window. Results are reported in Appendix Table 4 and remain robust to this alternative specification.

Firm capabilities. Appendix Table 5 considers the role that firm capabilities play in responding to these downstream product shocks. Specifically, the capabilities that matter here are development or the "D" in R&D. These include the abilities to draft and execute clinical trial protocols, staff and/or place trials, effectively process and analyze trial results and manage the underlying regulatory process. These capabilities have been shown to be important in the overall success of trials (Kim *et al.*, 2023). While data on these disaggregate activities do not exist, we can proxy for them by looking at the number of prior approved drugs. We take the mean of prior drug approvals across all firms and define them as having *High development capability* if they have above mean number of prior approvals. Likewise, we define a firm as having *Low development capability* if they have less than the mean number of prior approvals.

Not surprisingly, we find a positive and significant coefficient on our variable of interest, $Relabel_{ijt}$, for those firms with *High development capabilities* (Model 1). For these firms the expected phase expansion increases by a factor of 2.73. Maybe a bit more surprisingly, however, is the result for *Low development capabilities* firms (Model 2). While the coefficient is positive, it is not significant. This result could suggest a number of things. First, it could imply that these firms do not have slack

[14] Empirically differentiating these two conjectures would be very difficult. While physician-level prescription data is available one would need to know the underlying *motivation* for why a physician wrote a prescription for a specific drug. That data, to our knowledge, does not exist.

[15] Picking a different market is important given the spillover effects relabeling events have on other drugs within the same market (Higgins *et al.*, 2021).

development capabilities, the ability to shift existing capabilities or the financial resources to commit to phase expansion. Second, these firms could be more dependent upon external technology markets in which case they are more likely to acquire (or license) technologies at later stages (*i.e*., Phase II and III). Such firms may thus be more proficient at running later-stage, as opposed to earlier-stage, clinical trials. However, the lack of earlier stage capabilities may expose the firm to future product shocks from existing assets-in-place within affected therapeutic markets.

8.0 Discussion and conclusion

This paper extends our understanding of how R&D firms are able to utilize upstream resources and capabilities to respond to downstream product shocks. We build on two recent papers that explore the demand implications of these events (Higgins *et al.,* 2021) and the use of acquisitions in response (Krieger *et al.*, 2022). Our evidence suggests that firms engage in phase expansion for their existing pipeline projects. Firms appear to make investments both *within* the affected therapeutic market and *across* technologically similar therapeutic markets. Firms with greater upstream capabilities seem better positioned to respond to these downstream events. Competitors also appear to observe and respond to these events by also engaging in phase expansion within affected therapeutic markets. The goal of phase expansion is to avoid repeating similar product shocks in the future.

Importantly, we find that these investments have performance implications. First, pipeline drugs that experienced phase expansion had a higher probability of transitioning to the next stage of clinical testing and of eventually being approved by the FDA. The learning from these events allows firms to *ex post* improve protocols and the design of their clinical trials. Importantly, phase expansion experience decreased both the probability of future relabeling events and, if they did occur, the intensity of those events. Interestingly, we find limited evidence that phase expansion experience mitigates the negative demand response documented by Higgins *et al.* (2021). This inability to stem the loss of existing sales supports the channel through which firms turn to acquisition, as suggested by Krieger *et al.* (2022). It does, however, leave the firm with the strategic problem of how to rehabilitate the focal product; we leave this for future work.

Given the general findings of the product recall literature, it is not surprising that firms try to respond in some manner to these product shocks as opposed to throwing the proverbial baby out with the bathwater. These assets in place still have value and firms can learn from these events (*e.g.*, Haunschild and Sullivan, 2002; Haunschild and Rhee, 2004). Unlike with product recalls, however, in our setting products are not repaired or removed from the market, rather new information related to their safety is introduced. Consistent with prior findings in the automobile (Kalaignanam *et al*., 2013) and medical device industries (Thirmalai and Sinha, 2011), we show that cumulative experience from upstream investments in phase expansion both decrease the likelihood and intensity of future downstream shocks.

There is a tension that firms face in our research setting. On the one hand, firms need to conduct sufficient clinical trials such that they are able to reach the scientific bar of FDA approval. Unfortunately, this process is extremely expensive with high rates of failure. Moreover, for those drugs that have patents already granted, the longer they stay in development, the shorter their eventual market exclusivity period (*i.e.*, the less valuable they will be). The FDA has introduced a number of expedited pathways that firms can utilize to bring their products to market more quickly. Evidence exists, however, that drugs that go through these pathways are more likely to suffer a safety-label change (Mostaghim *et al.*, 2017; Moore and Furberg, 2014; Carpenter *et al.*, 2008; Olson, 2008). Ultimately, this becomes one more factor firms need to consider when balancing the speed at which they try to move a drug through clinical trial development.

When information is disclosed by firms appears to have significant consequences for a product. During the clinical trial process firms are collecting safety-related information that is submitted as part of the materials to the FDA for approval. If a drug is eventually approved, the FDA also approves the full prescribing information for a drug. Every drug that is approved contains a range of safety-related information. Importantly, the presence of this information is *ex ante* known to physicians (*i.e.*, consumers). With modern computerized medical records this kind of information is often presented to physicians to consider when they type in a prescription. Interestingly, there is a lack of evidence in the literature linking greater *ex-ante* safety-related information with lower sales. However, when new safety-related information is *ex-post* revealed, we see a fairly significant demand response by physicians (Higgins *et al.*, 2021). This differential response adds another layer of complexity to a firm's decision, discussed above, relating to the speed at which they try to bring a new product to market.

Investments in phase expansion are not without costs. More critically, having to write protocols, staff and place trials utilizes existing upstream capabilities. This implies that firms have to make a choice on how best to allocate their development resources and capabilities. But it leads to a question of whether these upstream investments in phase expansion create a drag on existing innovation. A more concrete example of this was Boeing's recent recall of the 737 Max. In order to fix the underlying issues related to 737 Max, Boeing needed to reallocate resources away from other areas, slowing their overall production and delivery of other aircraft. To the extent that responding to these downstream shocks creates a drag on current innovation is an open question that we are currently considering in other work.

There is also an open question on how competition influences this resource allocation decision. Our sample was constructed in a way that we were capturing these relabeling events during a branded products market exclusivity period (*i.e.*, their patents were still in place). This set aside the added complexity of how changing market structure may interact with firm response. All drugs will eventually face generic entry. In the case of chemical-based drugs (*i.e.*, small molecule drugs), for example, we tend

to see dramatic declines in demand as consumers are switched to generics. Interestingly, the demand declines that biologic-based drugs (*i.e.*, large molecule drugs) experience with biosimilars are much smaller. These differential responses may suggest heterogenous upstream responses by firms. What these responses might be, and the welfare implications of those choices are left for future work.

Finally, in this research setting we see firms turning to external technology markets as a way to deal with pipeline shocks (*e.g.*, Higgins and Rodriguez, 2006; Chan *et al.*, 2007; Danzon *et al.*, 2007; Hermosilla, 2021) and now downstream product shocks (Krieger *et al.,* 2022). This rotation towards the external technology market due to an immediacy need is possible because supply-side targets exist. What happens if firms are working in relatively thin technology markets (Byrski *et al.,* 2002)? This is problematic as recent research has also documented that firms have been outsourcing their basic science research (Arora *et al.,* 2018). It is possible for a firm to experience a downstream shock but be unable to turn to the external technology markets due to a lack of supply-side targets. Therefore, the choice to work in a thinner technology area will have implications for firm resource allocation decisions. If a firm chooses to work in one of these areas, it is plausible they will have to build a more robust research infrastructure or pivot to areas with more robust external technology markets. Such decisions have implications for the nature of innovation.

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Figure 1. Parallel trends. Figure 1A and Figure 1B plot the individual treatment effects for each year surrounding a drug relabeling event. Figure 1A plots coefficients for *ln(R&D+1)*. Figure 1B plots coefficients for *Phase expansion*. The vertical lines represent the 95 percent confidence interval while *t* represents the year that an affected firm experienced a relabeling event. We exclude the relative time indicator for *t-1* so that the coefficients for the relative time indicators can be viewed as mean differences from the average value of the outcome in the period before treatment (Baker *et al.*, 2021).

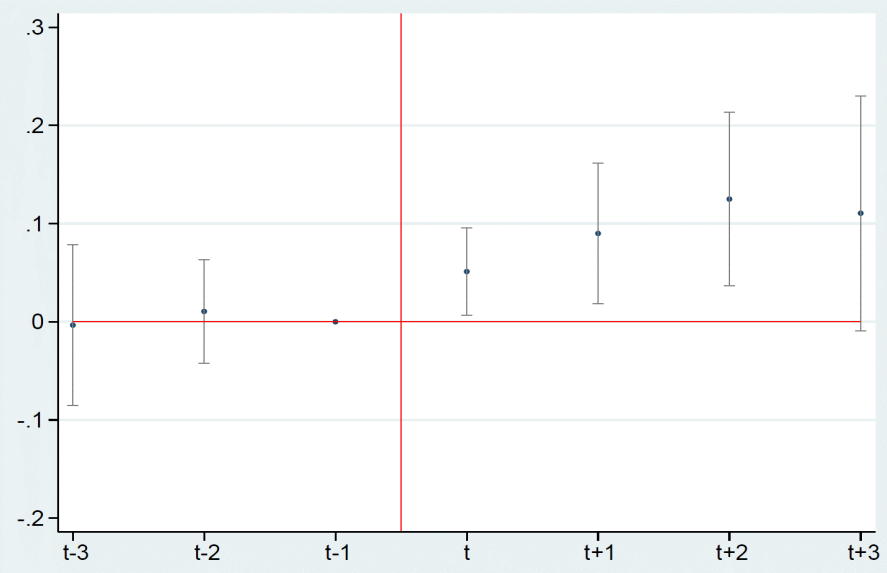

Figure 1A.

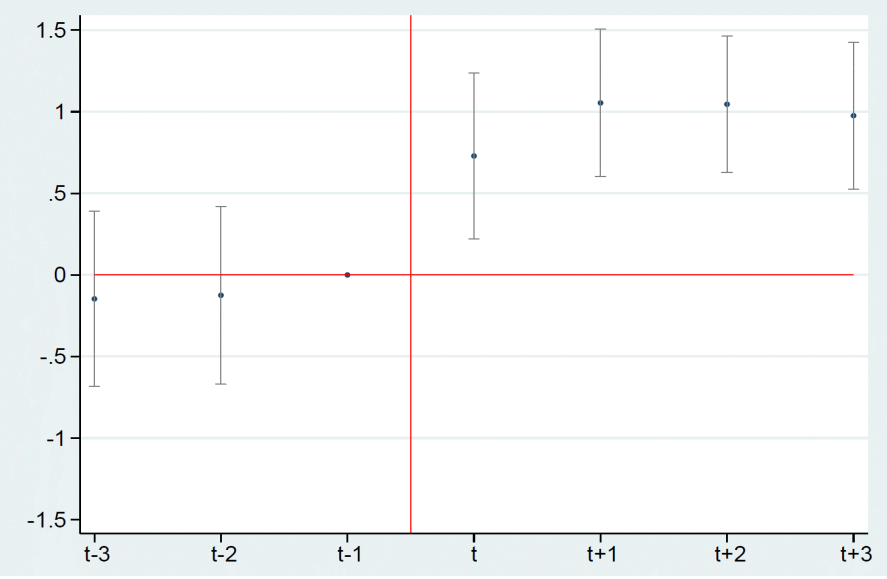

Figure 1B.

Table 1. Effects of relabeling on R&D expenditures. This table provides results for the effects of relabeling on R&D expenditures. The dependent variable is the natural logarithm of R&D expenditures plus one for focal firm *i* in year *t*. *Relabel* takes a value of one if an approved drug from firm *i*, in therapeutic market *j*, and in year *t* receives its first relabel event. Model 1 is based on a treatment window of two years while Model 2 is based on a treatment window of three years. Three years will serve as our baseline treatment window. Portfolio controls include the total number of approved products while pipeline controls include the total number of active clinical trials in each stage of clinical development. Models include combinations of time and firm fixed effects. The estimates are based on ordinary least squares. Constants are included in all models but omitted from the table. Standard errors are in parentheses and are clustered at the firm level. *, **, and *** indicate significance at the 10%, 5%, and 1% level, respectively.

DV: ln(R&D+1)	Model 1 2 years	Model 2 3 years
Relabel	0.161*** (0.038)	0.169*** (0.055)
Portfolio controls	Y	Y
Pipeline controls	Y	Y
Time fixed effects	Y	Y
Firm fixed effects	Y	Y
Adjusted R^2	0.959	0.958
Observations	1,228	1,650

Table 2. Heterogenous effects of relabeling on R&D expenditures. This table provides results for the heterogenous effects of relabeling severity on R&D expenditures. The dependent variable is the natural logarithm of R&D expenditures plus one for focal firm *i* in year *t*. *Relabel* takes a value of one if an approved drug from firm *i*, in therapeutic market *j*, and in year *t* receives its first relabel event. The sample is split into less and more severe types of drug relabeling. We define *Less severe* (Model 1) to include adverse reactions and precautions and *More severe* (Model 2) to include contraindications and box warnings. Portfolio controls include the total number of approved products while pipeline controls include the total number of active clinical trials in each stage of clinical development. Models include combinations of time and firm fixed effects. The estimates are based on ordinary least squares. Constants are included in all models but omitted from the table. Standard errors are in parentheses and are clustered at the firm level. *, **, and *** indicate significance at the 10%, 5%, and 1% level, respectively.

DV: ln(R&D+1)	Model 1 Less Severe	Model 2 More Severe
Relabel	0.164* (0.090)	0.275*** (0.089)
Portfolio controls	Y	Y
Pipeline controls	Y	Y
Time fixed effects	Y	Y
Firm fixed effects	Y	Y
Adjusted R^2	0.959	0.958
Observations	923	340

Table 3. Upstream response: Intramarket. This table provides results for the impact of relabeling on upstream clinical trials within the same therapeutic market as the affected drug. We refer to this as a firm's 'intramarket' pipeline response. The dependent variable, *Phase expansion*, is defined as the number of new Phase I clinical trials launched by focal firm *i* for existing pipeline drugs in therapeutic market *j* in year *t*. *Relabel* takes a value of one if an approved drug from firm *i*, in therapeutic market *j*, and in year *t* receives its first relabel event. Portfolio controls include the total number of approved products while pipeline controls include the total number of active clinical trials in each stage of clinical development. Financial controls include the natural log of total assets and R&D expenditures scaled by total assets. Models include combinations of time, market, and firm fixed effects. The estimates are based on a negative binomial regression. Constants are included in all models but omitted from the table. Standard errors are in parentheses and are clustered at the drug level. *, **, and *** indicate significance at the 10%, 5%, and 1% level, respectively.

DV: Phase expansion	Model 1	Model 2	Model 3
Relabel	0.791***	0.976***	0.959***
	(0.235)	(0.230)	(0.265)
Portfolio controls	N	Y	Y
Pipeline controls	N	Y	Y
Financial controls	N	N	Y
Time fixed effects	Y	Y	Y
Market fixed effects	Y	Y	Y
Firm fixed effects	Y	N	N
Log pseudolikelihood	-1,466.61	-1,542.57	-1,225.89
Observations	2,226	2,226	1,792

Table 4. Upstream response: Intermarket. This table provides results for the impact of relabeling on upstream clinical trials in therapeutic markets other than the therapeutic market of the affected drug. We refer to this as a firm's 'intermarket' pipeline response. The dependent variable, *Phase expansion*, is defined as the number of new Phase I clinical trials launched by focal firm *i* for existing pipeline drugs in therapeutic market *k* (where *k* is not equal to therapeutic market *j*) in year *t*. *Relabel* takes a value of one if an approved drug from firm *i*, in therapeutic market *j*, and in year *t* receives its first relabel event. Portfolio controls include the total number of approved products while pipeline controls include the total number of active clinical trials in each stage of clinical development. Models include combinations of time, market, and firm fixed effects. The estimates are based on a negative binomial regression. Constants are included in all models but omitted from the table. Standard errors are in parentheses and are clustered at the drug level. *, **, and *** indicate significance at the 10%, 5%, and 1% level, respectively.

DV: Phase expansion	Model 1	Model 2	Model 3
Relabel	0.642***	0.696***	0.657***
	(0.179)	(0.181)	(0.209)
Portfolio controls	N	Y	Y
Pipeline controls	N	Y	Y
Financial controls	N	N	Y
Time fixed effects	Y	Y	Y
Market fixed effects	Y	Y	Y
Firm fixed effects	Y	N	N
Log pseudolikelihood	-2,455.51	-2,587.11	-2,048.38
Observations	3,710	3,710	3,024

Table 5. Upstream response: Competitors. This table provides results for the impact of relabeling on competitor firm upstream clinical trials within the same therapeutic market (*i.e.*, intramarket) as the affected drug. The dependent variable, *Phase expansion*, is defined as the number of new Phase I clinical trials launched by competitor firm *h* (where competitor firm *h* is not equal to focal firm *i*) for an existing pipeline drug in therapeutic market *j* in year *t*. *Relabel* takes a value of one if an approved drug from focal firm *i*, in therapeutic market *j*, and in year *t* receives its first relabel event. Portfolio controls include the total number of approved products while pipeline controls include the total number of active clinical trials in each stage of clinical development. Financial controls include the natural log of total assets and R&D expenditures scaled by total assets. Models include combinations of time, market, and firm fixed effects. The estimates are based on a negative binomial regression. Constants are included in all models but omitted from the table. Standard errors are in parentheses and are clustered at the drug level. *, **, and *** indicate significance at the 10%, 5%, and 1% level, respectively.

DV: Phase expansion	Model 1	Model 2	Model 3
Relabel	1.067***	0.769***	0.651***
	(0.130)	(0.179)	(0.219)
Portfolio controls	N	Y	Y
Pipeline controls	N	Y	Y
Financial controls	N	N	Y
Time fixed effects	Y	Y	Y
Market fixed effects	Y	Y	Y
Firm fixed effects	Y	N	N
Log pseudolikelihood	-4,474.31	-5,032.63	-3,258.28
Observations	10,332	10,332	5,815

Table 6a. Probability of clinical trial transition. This table presents the probability that post-relabel focal firm clinical trial expansion has on the transition to the next stage of clinical trial testing. The dependent variable is a dummy variable that equals one if a drug transitions from Phase I to Phase II (*Transition*). Model 1 focuses on intramarket dynamics. *Phase expansion* is defined as the number of new Phase I clinical trials launched by focal firm *i* for existing pipeline drugs in therapeutic market *j* in year *t*. The relabel event is in therapeutic market *j*. Model 2 focuses on intermarket dynamics. *Phase expansion* is defined as the number of new Phase I clinical trials launched by focal firm *i* for existing pipeline drugs in therapeutic market *k* (where *k* is not equal to therapeutic market *j*) in year *t*. The sample is limited to those pipeline drugs that have yet to transition from Phase I. Portfolio controls include the total number of approved products while pipeline controls include the total number of active clinical trials in each stage of clinical development. Models include time and market fixed effects. Estimations are based on a probit regression model. Robust standard errors are reported in parentheses.*, **, and *** indicate significance at the 10%, 5%, and 1% level, respectively.

DV: Transition	Model 1 Intramarket	Model 2 Intermarket
Phase expansion size	0.046***	0.032**
	(0.016)	(0.012)
Portfolio controls	Y	Y
Pipeline controls	Y	Y
Time fixed effects	Y	Y
Market fixed effects	Y	Y
Pseudo R^2	0.038	0.033
Observations	1,409	2,383

Table 6b. Phase expansion and FDA drug approval. This table presents the relationship between the expansion of Phase I clinical trials for pipeline drugs and the probability of final FDA approval. The dependent variable is a dummy variable equal to one if a drug receives FDA approval (*Approval*). The independent variable, *Phase expansion size*, is the number of Phase I clinical trials for a pipeline drug by focal firm *i*, in therapeutic market *j*, at time *t*. Model 2 incorporates a square term to account for a potential non-linear relationship. Portfolio controls include the total number of approved products while pipeline controls include the total number of active clinical trials in each stage of clinical development. Models include time and market fixed effects. Estimations are based on a probit regression model. Standard errors are in parentheses and are clustered at the drug level. *, **, and *** indicate significance at the 10%, 5%, and 1% level, respectively.

DV: Approval	Model 1	Model 2
Phase expansion size	0.076***	0.164**
	(0.022)	(0.037)
(Phase expansion size)^2		-0.008***
		(0.003)
Portfolio controls	Y	Y
Pipeline controls	Y	Y
Time fixed effects	Y	Y
Market fixed effects	Y	Y
Pseudo R^2	0.075	0.078
Observations	7,548	7,548

Table 7a. Phase expansion experience and relabel occurrence. This table considers the relationship between accumulated post-relabel phase expansion experience and the probability of a future drug relabel. The dependent variable is a dummy variable equal to one if a drug experienced a relabeling event (*Relabel*). The independent variable, *Phase expansion experience*, measures the accumulated number of post-relabel Phase I expansion trials launched by focal firm *i*, by therapeutic market *j* until time *t.* Time *t* is the approval date of the focal drug. The variable is calculated over a five-year period and a yearly discount rate of 15 percent (Griliches, 1984) is applied. Model 1 focuses on intramarket dynamics while Model 2 considers intermarket dynamics. The sample is limited to approved drugs as they are the only ones that have a hazard of experiencing a relabeling event. Portfolio controls include the total number of approved products while pipeline controls include the total number of active clinical trials in each stage of clinical development. Models include market and firm fixed effects. The estimates are based on a probit regression model. Constants are included in all models but omitted from the table. Standard errors are in parentheses and are clustered at the drug level. *, **, and *** indicate significance at the 10%, 5%, and 1% level, respectively.

DV: Relabel	Model 1 Intramarket	Model 2 Intermarket
Phase expansion experience	-0.076*** (0.024)	-0.011* (0.006)
Portfolio controls	Y	Y
Pipeline controls	Y	Y
Market fixed effects	Y	Y
Firm fixed effects	Y	Y
Pseudo R^2	0.225	0.256
Observations	259	298

Table 7b. Phase expansion experience and relabel intensity. This table considers the relationship between accumulated post-relabel phase expansion experience and the intensity of drug relabeling activity. The dependent variable is the total number of relabeling events (*Relabel intensity*) for drug by firm *i*, in therapeutic market *j.* The independent variable, *Phase expansion experience*, measures the accumulated number of post-relabel Phase I expansion trials launched by firm *i*, by therapeutic market *j* until time *t.* Time *t* is the approval date of the focal drug. The variable is calculated over a five-year period and a yearly 15 percent discount rate (Griliches, 1984) is applied. Models 1 and 2 focus on intramarket dynamics. The sample is limited to approved drugs as they are the only ones that have a hazard of experiencing a relabeling event. Portfolio controls include the total number of approved products while pipeline controls include the total number of active clinical trials in each stage of clinical development. Models include market and firm fixed effects. The estimates are based on a negative binomial regression. Constants are included in all models but omitted from the table. Standard errors are in parentheses and are clustered at the drug level. *, **, and *** indicate significance at the 10%, 5%, and 1% level, respectively.

DV: Relabel intensity	Model 1	Model 2
Phase expansion experience	-0.274*** (0.092)	-0.347*** (0.099)
(Phase expansion experience)^2		0.007*** (0.003)
Portfolio controls	Y	Y
Pipeline controls	Y	Y
Market fixed effects	Y	Y
Firm fixed effects	Y	Y
Log pseudolikelihood	-464.87	-464.01
Observations	274	274

Table 8. Demand response (Higgins *et al.*, 2021). This table uses the data from Table 3, Model 1 in Higgins *et al.* (2021) and estimates the causal impact of relabeling on demand. The dependent variable is the natural log of sales, ln(*Sales*). The unit of analysis is the drug level. *Price* is instrumented in all models with relevant tests reported in the table. Controls include *Vintage, Number of brands*, and *Number of generics*. We split the sample based on the mean value of *Phase expansion experience* and define *High firm capability* (Model 1) as those firms with above mean expansion experience. Likewise, we define *Low firm capability* (Model 2) as those firms with below mean expansion experience. See Higgins *et al.* (2021) for further details on their identification strategy and data. Standard errors are clustered at the 2-digit ATC market level. Constants are included in all specifications but omitted from the table. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

DV: ln(Sales)	Model 1 High firm capability	Model 2 Low firm capability
Relabel	0.1011**	0.1062***
	(0.0955)	(0.317)
US	1.2005***	0.7084***
	(0.2192)	(0.0338)
Relabel * US	-0.1700**	-0.1827***
	(0.0860)	(0.0255)
ln(Price)	-2.1784***	-0.6093***
	(0.4807)	(0.0536)
ln(Lagged promotion stock)	0.8161***	0.7415***
	(0.0425)	(0.0152)
Controls	Y	Y
Drug Fixed Effects	Y	Y
Market Fixed Effects	Y	Y
Time Fixed Effects	Y	Y
Adjusted R^2	0.870	0.974
First-stage F	1,669.75	2,368.96
Observations	1,003	1,477

Appendix Table 1. Placebo test. This table presents a placebo test for the impact of relabeling on upstream clinical trials. To conduct this test, we take the pre-treatment period and cut the sample in half. We define the arbitrary midpoint of this split sample as our treatment period, *t=0.* The dependent variable, *Phase expansion*, is defined as the number of new Phase I clinical trials launched by focal firm *i* for existing pipeline drugs in therapeutic market *j* in year *t*. *Relabel* takes a value of one if an approved drug from firm *i*, in therapeutic market *j*, and in year *t* receives its first relabel event. Portfolio controls include the total number of approved products while pipeline controls include the total number of active clinical trials in each stage of clinical development. Financial controls include the natural log of total assets and R&D expenditures scaled by total assets. Models include combinations time, market, and firm fixed effects. The estimates are based on a negative binomial regression. Constants are included in all models but omitted from the table. Standard errors are in parentheses and are clustered at the drug level. *, **, and *** indicate significance at the 10%, 5%, and 1% level, respectively.

DV: Phase expansion	Model 1	Model 2	Model 3
Relabel	0.280	0.241	0.416
	(0.258)	(0.261)	(0.284)
Portfolio controls	N	Y	Y
Pipeline controls	N	Y	Y
Financial controls	N	N	Y
Time fixed effects	Y	Y	Y
Market fixed effects	Y	Y	Y
Firm fixed effects	Y	N	N
Log pseudolikelihood	-439.31	-455.58	-356.80
Observations	954	954	779

Appendix Table 2. Descriptive statistics. This table contains descriptive statistics for four different analyses. Panel A presents descriptives relating to focal firm R&D expenditures. Panel B presents descriptives relating to focal firm intramarket upstream response while Panel C presents descriptives for the intermarket response. Panel D presents descriptives relating to intramarket competitor response. Intramarket is defined as *within* the same therapeutic category and intermarket is defined as *across* therapeutic categories.

Panel A: R&D Response					
Variables	**N**	**Mean**	**σ**	**Min**	**Max**
ln(R&D+1)	1,650	7.465	3.118	0	13.173
Relabel	1,650	0.501	0.5	0	1
Phase I projects	1,650	7.303	8.123	0	33
Phase II projects	1,650	10.428	11.999	0	44
Phase III projects	1,650	3.513	3.892	0	16
Approved products	1,650	12.744	11.89	0	41
Panel B: Intramarket Response					
Phase expansion	2,226	0.419	1.731	0	27
Relabel	2,226	0.571	0.495	0	1
Ln(Total assets)	2,226	10.878	1.115	6.994	15.335
R&D/total assets	2,226	0.066	0.048	0.003	0.449
Phase I projects	2,226	17.245	9.460	0	33
Phase II projects	2,226	19.62	9.456	0	44
Phase III projects	2,226	8.814	5.252	0	16
Approved products	2,226	25.343	11.124	1	41
Panel C: Intermarket Response					
Phase expansion	3,710	0.411	1.643	0	27
Relabel	3,710	0.571	0.495	0	1
Ln(Total assets)	3,710	10.458	2.173	1.449	15.334
R&D/total assets	3,710	0.104	0.178	0.001	5.438
Phase I projects	3,710	13.728	10.36	0	27
Phase II projects	3,710	15.462	10.800	0	44
Phase III projeects	3,710	6.794	5.497	0	16
Approved products	3,710	19.964	13.150	0	41
Panel D: Competitor Response					
Phase expansion	10,332	0.236	1.124	0	27
Relabel	10,332	0.571	0.495	0	1
Ln(Total assets)	5,815	9.039	3.334	0.267	15.335
R&D/total assets	5,815	0.398	4.511	0	242
Phase I projects	10,332	7.469	9.899	0	33
Phase II projects	10,332	8.386	10.286	0	44
Phase III projects	10,332	3.433	4.844	0	16
Approved products	10,332	10.287	12.699	0	41

Appendix Table 3. Upstream response: Intermarket technological similarity. This table provides results for the impact of relabeling on upstream clinical trials in therapeutic markets other than the therapeutic market of the affected drug (*i.e.*, intermarket) across different levels of technological similarity. The dependent variable, *Phase expansion*, is defined as the number of new Phase I clinical trials launched by focal firm *i* for existing pipeline drugs in therapeutic market *k* (where *k* is not equal to therapeutic market *j*) in year *t*. *Relabel* takes a value of one if an approved drug from firm *i*, in therapeutic market *j*, and in year *t* receives its first relabel event. To determine technological similarity, we use the Jaro distance metric comparing the action mechanism of a relabeled drug in therapeutic market *j* with pipeline drugs in therapeutic market *k.* We calculate the mean of the Jaro distance and define those pipeline drugs below the mean as *Low technological similarity* (Model 1) and above the mean as *High technological similarity* (Model 2). Portfolio controls include the total number of approved products while pipeline controls include the total number of active clinical trials in each stage of clinical development. Models include time and market fixed effects. The estimates are based on a negative binomial regression. Constants are included in all models but omitted from the table. Standard errors are in parentheses and are clustered at the drug level. *, **, and *** indicate significance at the 10%, 5%, and 1% level, respectively.

DV: Phase expansion	Model 1 Low technological similarity	Model 2 High technological similarity
Relabel	0.594**	0.803***
	(0.240)	(0.297)
Portfolio controls	Y	Y
Pipeline controls	Y	Y
Time fixed effects	Y	Y
Market fixed effects	Y	Y
Log pseudolikelihood	-1,289.16	-1,252.14
Observations	1,694	2,016

Appendix Table 4. Stacked diffrence-in-differences: Intramarket response. This table provides results from a stacked difference-in-differences regression for the impact of relabeling on phase expansion within the same therapeutic market as the affected drug. For comparative purposes see Table 4. The dependent variable, *Phase expansion*, is defined as the number of new Phase I clinical trials launched by focal firm *i* for existing pipeline drugs in therapeutic market *j* in year *t*. *Relabel* takes a value of one if an approved drug from firm *i*, in therapeutic market *j*, and in year *t* receives its first relabel event. *Group* is indicator that equals one if a drug is a treated unit within a sub-experiment. Each sub-experiment is defined as having the same year of treatment. Our variable of interest is the interaction, *Relabel x Group*. The control group includes only never treated drugs. Portfolio controls include the total number of approved products while pipeline controls include the total number of active clinical trials in each stage of clinical development. Model 1 includes time and market fixed effects. The estimates are based on a negative binomial regression. Constants are included in all models but omitted from the table. Standard errors are in parentheses and are clustered at the drug level. *, **, and *** indicate significance at the 10%, 5%, and 1% level, respectively.

DV: Phase expansion	Model 1
Relabel	0.685***
	(0.209)
Group	-0.0716
	(0.546)
Relabel x Group	0.307**
	(0.131)
Portfolio controls	Y
Pipeline controls	Y
Time fixed effects	Y
Market fixed effects	Y
Log pseudolikelihood	-3,251.75
Observations	4,347

Appendix Table 5. Upstream response: Heterogenous firm capability. This table provides results for the effects of relabeling on upstream clinical trials for firms with different levels of development capability. The specification is still within the same therapeutic market as the affected drug. The dependent variable, *Phase expansion*, is defined as the number of new Phase I clinical trials launched by focal firm *i* for existing pipeline drugs in therapeutic market *j* in year *t*. *Relabel* takes a value of one if an approved drug from firm *i*, in therapeutic market *j*, and in year *t* receives its first relabel event. The sample is split into two based on the number of approved drugs a firm has relative to the mean across all sample firms. We define *High development capability* as those firms with above mean number of approved drugs (Model 1) and *Low development capability* as those firms with below mean number of approved drugs (Model 2). Portfolio controls include the total number of approved products while pipeline controls include the total number of active clinical trials in each stage of clinical development. Models include time and market fixed effects. The estimates are based on a negative binomial regression. Constants are included in all models but omitted from the table. Standard errors are in parentheses and are clustered at the drug level. *, **, and *** indicate significance at the 10%, 5%, and 1% level, respectively.

DV: Phase Expansion	Model 1 High Development Capability	Model 2 Low Development Capability
Relabel	1.005***	0.603
	(0.238)	(0.613)
Portfolio controls	Y	Y
Pipeline controls	Y	Y
Time fixed effects	Y	Y
Market fixed effects	Y	Y
Log pseudolikelihood	-1,303.05	-211.97
Observations	1,792	434