Title
Investing in Innovation: Evidence from the Pharmaceutical Industry

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Publication Date
2020

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Investing in Innovation: Evidence from the Pharmaceutical Industry

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Management

by

Kira Ellen Stearns

2020

ABSTRACT OF THE DISSERTATION

Investing in Innovation: Evidence from the Pharmaceutical Industry

by

Kira Ellen Stearns

Doctor of Philosophy in Management

University of California, Los Angeles, 2020

Professor Melvin Keith Chen, Co-Chair

Professor Marvin B. Lieberman, Co-Chair

This dissertation explores the role that organizations play in bringing scientific innovations to society. Chapter 1 situates this work in the current landscape of innovation research and motivates the need for further research on this topic. Chapter 2 explores the role that failure, both technological and regulatory, plays in understanding how organizations make future investments in innovative projects. I find that following FDA rejection, biopharmaceutical firms become significantly less likely to further invest in unrelated products already under development. However, they experience a higher proportion of future successes, as they redirect investment into less risky innovations. In contrast, I find no evidence of these effects in response to technological failures at the end of clinical trials, suggesting that this effect is not driven by the loss of firm value nor does it support a traditional Bayesian updating framework. Rather, these findings are consistent with the idea that there is a difference between failure at the technological level versus failure at the decision making level.

Chapter 3 illustrates how the boundaries of an organization influence the type of innovations in which organizations do and not choose to invest following a sudden reshuffling

of consumer demand. I demonstrate that a sudden increase in market size (and therefore expected revenue) increases an established firm's propensity to make larger investments in products in their pipeline that are less likely to receive approval. However, I find that this result only holds for those organizations that diversify into fewer therapeutic spaces and are additionally more centralized. I theorize that, in line with findings from organizational economics and internal capital allocation inefficiency, this is due to management having greater control over resource allocation decisions in more centralized firms.

Finally, Chapter 4 studies how the type of innovation pursued may affect market outcomes and competitive interactions between organizations. Using drug repurposing as a research context, I explore how the repurposing of a pharmaceutical drug for a new disease impacts its sales, and the sales of its competitors, for other approved uses. By leveraging variation in the combination of diseases that one drug treats and the timing of those disease approvals, I find a positive spillover effect of repurposing on sales of the drug for other diseases and this effect also spills over into the drug's close competitors. Furthermore, I find that this growth in sales comes at the expense of competitors further away in therapeutic type. These findings have important implications for a pharmaceutical firm's R&D strategy and the strategic responses to be made by competitors.

The dissertation of Kira Ellen Stearns is approved.

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To Michael

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ACKNOWLEDGEMENTS

First and foremost, I am deeply grateful to my family and friends who have been tirelessly supportive during these past five years. Thank you all for your patience and sacrifices. I am indebted to my co-chairs Keith Chen and Marvin Lieberman. Thank you for the guidance, provocative questions, and insightful observations. I also thank Mariko Sakakibara and Ashvin Ghandi for their time and support on my committee. I have benefitted from the guidance of many other UCLA faculty members including and especially Ian Larkin. Thank you for all of the advice along the way. And to my colleagues Marco Testoni, Pedro Makhoul, Tingyu Du, Taylor Corcoran, Bobby Nyotta, and Camelia Cheng – thank you for your detailed feedback on some of the work included here.

This endeavor has benefitted greatly from colleagues and friends outside of UCLA. I want to especially thank Chirantan Chatterjee and Matthew Higgins for their indispensable input and guidance on the final chapter. I also thank J.P Eggers, Joshua Kreiger, Caroline Fry, Lisa Tang, and Keith Pennington for the thoughtful input on earlier drafts of one or more of these chapters. Additional feedback from faculty members at the Wharton School at the University of Pennsylvania, the Haas School of Business, the Scheller College of Business, the Olin School of Business, the Eccles School of Business and the Leeds School of Business is gratefully acknowledged.

Finally, this dissertation was greatly enhanced by funding from the Strategic Management Society and the Price Center for Entrepreneurship. These grants were integral to my data collection efforts.

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Chapter 1 Innovation and the Organization

The links between innovation and economic growth are largely undisputed. From Schumpeter's discussions of creative destruction to Solow's conception of technological progress, scholars have stressed the importance of continual product and process innovations on a dynamic economy. However, innovations do not magically appear within society. New innovations, both in products or in process, are the result of people or organizations making deliberate choices about what they will explore and how they will explore it.

The literature on innovation spans many social science disciplines and encompasses many research traditions. This research includes studies of lone inventors, studies of patents and property rights, and studies of knowledge dispersion among communities. A subtopic receiving increased attention is the role of organizations, both for profit and not-for-profit, in innovation. While charismatic visionaries receive the majority of media attention, a large amount of invention and innovation takes place within the confines of an organization. In these cases, the resources and capabilities of the organization play an important role in bringing innovations from conception to market. Furthermore, these organizations have myriad choices for how they will develop and market their next technology. They could develop it in house or license the intellectual property from elsewhere. They can have their scientists and engineers work together in centralized campuses or as smaller decentralized units. They can

choose to build on a previous technology or develop something entirely new. These choices have impacts not only for the fate of the organization, but for the well-being of a society.

This dissertation contains three studies that examine how organizations make decisions regarding the types of innovation in which they will invest and the competitive outcomes of such decisions. These studies are linked in the following three ways. First, all studies concern the development of profit-enhancing medical innovations within a profit maximizing firm. Secondly, all chapters acknowledge that choosing where to allocate innovative resources represents a series of tradeoffs for firms. In choosing to pursue one line of research and development, an organization is sacrificing gains that could be made in another line. And lastly, all three chapters focus on the product development aspect of innovation. While many studies in the innovation literature look at intermediate measures like patents or trademarks, this study looks specifically at new consumer products right before or right after they reach market.

Finally, the industry explored in all three chapters is the biopharmaceutical industry, where the chief source of a firm's competitive advantage is in its ability to bring innovative new therapies to consumers. Therefore, efficient and effective decision making by managers within these companies is an important capability. Though this industry follows a highly regulated procedure for bringing products to market, I believe lessons learned in exploring the decisions made can be applied broadly across innovative organizations. Issues explored in the following three chapters, including responses to failure, the effects of demand reshuffling, and the repurposing of technologies are topics any high-tech firm may find itself grappling with.

Chapter 2 Organizational Responses to Failure and Rejection

2.1 Introduction

Failure is widespread in many important industries and interactions, and it can take many forms. It can be highly detailed and personalized, as in a promotion rejection, or lack thorough explanation, as in a prototype failure. It can signal to budding entrepreneurs how they measure up against their peers when they win a business plan competition, or signal to them how they measure up against a subjective threshold when they fail to receive funding from venture capitalists.

One common type of failure that has received limited consideration despite its prevalence for innovative firms and entrepreneurs is rejection from an external party. For example, firms will compete for consulting contracts that they either win or lose, inventors will submit patents that are either accepted or rejected, and employees will apply for promotions that are either granted or deferred. A unique aspect of rejection when compared to traditional definitions of failure is that firms or individuals must explicitly solicit this feedback, often through applications or proposals. Therefore, these individuals likely possess an *a priori*

belief about the quality of their product, invention, or application and therefore their chance of success. For managers receiving negative feedback, or "failing", they learn not just about an external party's assessment of the focal product or application, but about her own ability to make accurate judgments about its likelihood of success. These ramifications are particularly interesting, and still unexplored despite evidence suggesting that people respond differently to failure depending on the source.

This chapter will explore the role of regulatory rejection on a firm's future investment behavior in unrelated technologies that are currently under development within the firm. I find evidence suggesting that rejection of an innovation changes a manager's propensity to make further investments in their next several projects. Additionally, I show that this shift in decision making changes the type of projects a firm will invest in next. To my knowledge, this is the first study exploring how rejection from regulators affects both future investment behavior and future product development successes.

I explore these issues empirically in the context of the pharmaceutical and biotechnology industries where firms must receive Food and Drug Administration ("FDA") approval to market their product in the United States.[1] Because of the R&D-intensive nature of firms in these industries, the pharmaceutical and biotechnology industries have been a popular setting for studies on firm behavior in innovation (DeCarolis and Deeds, 1999; Henderson and Cockburn, 1994; Krieger, 2018).[2] Before applying for FDA approval, firms make a series

[1]Regulatory approval to market and sell products is common in many facets of the healthcare sector, including medical devices.

[2]Additionally, the hesitancy of pharmaceutical firms to terminate lower-quality R&D efforts (leading to inefficient resource allocation) has gained attention within the industry. A vice president of Novartis has lamented that they "always cling to products a year longer than [they] should" ((Lam, 2004): 1). Ken Kaitin, the director of the Tufts Center for the Study of Drug Development, suspects this failure to let go of projects is built on what he calls "selfish-team syndrome," defined as the situation in which "a group that is developing a particular drug makes biased decisions - for example, trying to save the project when it should be

of investments in the development of their product. Furthermore, in these industries, the majority of firms are developing many products at the same time and therefore are managing a pipeline of potential products at various stages of development. This will be crucial for this research in that it allows me to observe the trajectories of research projects already in progress at the time of one product's rejection. I begin by proposing a theoretical framework that describes how firms make these series of investment decisions in their products that are midway through development; that is, after the firm has already developed a belief about the quality of the project following years of collecting information about its performance. I then explore how unanticipated rejections by the FDA affect the firm's beliefs about its other pharmaceutical products under development and how the firm chooses to invest in new rounds of product development.

To estimate the effects of rejection, I compile a large dataset on firm investment decisions in drug development spanning nearly 20 years. These data include information on the firm developing the drug and many characteristics of the molecule under development, including the disease it is intended to treat. With these data, I am able to leverage within-firm variation to explore firm behavior both before and after the negative event. In addition, I collect data to control for demand conditions, product novelty, and other factors that may influence a firm's investment decisions. I also research and compile data describing regulatory decisions by the FDA on every project submitted for review. While the vast majority of applications eventually receive approval (95% of applications submitted in my sample), in some cases the FDA identifies weaknesses that cannot be overcome and the project must be terminated. It

killed - because the team's reputation is tied to the drug's success or because the team members have become emotionally attached to the project" ((Bonabeau, 2002): 115). Another biotechnology executive proclaims that "questionable clinical data tends to get overlooked because there is such a push to do something" (Lam, 2004): 2).

is these "terminal rejections" that I will use to explore the effects of negative feedback on future investment decisions.

One challenge in estimating the effects of rejection on a recipient is in causal identification. That is, the act of choosing to solicit feedback from an external party may be correlated with future behavior patterns, causing the problem of non-random assignment to treatment. Therefore, to causally identify the effects of the negative feedback, I modify an identification approach first proposed by Blankshain et al. (2013). They argue that "surprising" negative regulatory feedback can be treated as an external shock. For this study, I will identify surprise negative regulatory feedback by collecting data on industry experts' predictions of drug quality at the time of the FDA application. I then employ within-firm variation and a difference-in-differences approach to estimate the effect of plausibly exogenous rejections on future investment decisions. If I find no change in a firm's propensity to continue investing in other unrelated projects (while employing fixed effects and controls for relevant product characteristics), one could conclude that this negative feedback does not fundamentally change a firm's investment strategies. A discrete change in the investment decisions of a firm would imply that this type of negative feedback does have spillover impacts on innovation.

In the empirical analyses, I find that immediately following surprising regulatory rejections, managers become over 20% less likely to continue funding other, unrelated products under development and that this effect persists for the next several projects that reach the critical decision stage. In addition, I find a "raising the bar" effect. Because firms discontinue the development of more risky (lower probability of approval) products, they experience better overall performance of those future projects in which they do choose to invest. In traditional studies in learning from failure, observing an increase in the probability of ap-

proval for projects may lead one to believe the firm is "learning" from failure. Here, I can demonstrate that what appears to be improved firm performance is actually the result of more selective investing.

Finally, I show that the effect of negative regulatory feedback makes firms less likely to invest in projects for more novel drugs, that is, those treating rare disease or demonstrating significant improvements over drugs already on the market. This finding demonstrates that programs put into place to encourage more innovative investment do not mitigate the retreat from investment seen following receipt of an FDA rejection. In additional analyses, I demonstrate evidence for why these results are unlikely to stem only from financial constraints experienced by a firm that has lost expected future revenue. I therefore conclude that this type of feedback leads to a change in a firm's appetite for making late stage investments in other innovations.

This study provides two important insights. First, I demonstrate that rejection from entry regulators leads firms to become more conservative in future investments in unrelated technologies. However, those in which they do invest are technologies that are much more likely to eventually receive regulatory approval. I show that this change in behavior persists for several projects in the future but does eventually revert back to normal patterns of investment when controlling for firm effects. This supports the hypothesis that entry regulation may depress innovation, and especially more novel innovation, from the private sector. Secondly, while the firm does achieve a higher proportion of future products receiving approval following full investment, these products are likely to be more incremental rather than novel innovations. This is further illustrated in an analysis exploring post-rejection investment on projects that have already received intermediate-stage *positive* regulatory feedback. Prod-

ucts receiving early feedback from the FDA are more likely to be novel innovations (and therefore qualify for early monitoring and often subsidized development). Following rejection, these novel products become over 60% less likely to receive important investments in development, as compared to novel products in which the firm invested before rejection.

These findings have implications for both strategy and policy scholars. If the role of policy makers is to incentivize innovation in the private sector, these findings suggest the importance of developing mechanisms that mitigate the number of unanticipated rejections. Additionally, these findings make important contributions to the strategy literature in learning from failure. Current empirical research has suggested that firms may respond to negative feedback in several ways, and this may have heterogenous impacts on firm performance. In this setting, I am able to demonstrate how negative feedback leads managers to update their prior beliefs about the success of other unrelated projects and that this may lead to higher perceived performance on certain dimensions. However, I am able to demonstrate that what may appear to be learning in certain contexts is actually a function of increased selectivity in the risks a firm is willing to take. In the next section, I will discuss these literatures in more depth.

2.2 Related Literature

This paper makes several contributions to a research agenda that is of interest to both management and public policy researchers. In this section, I present a cursory overview of related work.

2.2.1 Related literature on failure in innovation

This paper adds additional insight to studies on firm adaptation in response to failures in innovation. The conditions under which firms can learn from failure constitute a research stream that is growing in prominence (see, e.g., Guler, 2018; Khanna et al., 2016; Klingebiel, 2018; Maslach, 2016). However, conclusions regarding a firm's ability to respond to failure have been mixed. One of the difficulties in estimating responses, which may therefore lead to these differences, is the inability to examine the responses to different types of failures both within and across firms. The literature on firm responses to rare, publicly visible failures often relies heavily on case studies (Christianson et al., 2009; Harding et al., 2002; Lampel et al., 2009; Madsen, 2009). Additionally, although exploring firm responses to frequent but small failures allows more data and for comparisons across firms, the definition of failure in this case is narrow. Furthermore, in the case of frequent, small failures, it is often the case that the manager itself had recognized the failure and not that it was decreed by an external party. One may hypothesize that firms capable of understanding when they failed likely have capabilities that make them different from firms that do not know when to admit failure.

It is largely believed that organizations can learn more from failure than from success (Haunschild et al., 2015; Madsen and Desai, 2010). Given the preponderance of failures generated by experimentation and innovation, several scholars have explored whether and how failures in innovation can lead to better future outcomes for the firm. Two papers closely related to this one have explored how the nature of the failed product (whether it was in a new or risky domain) leads to differences in the firm's response. Using data from

the mutual fund industry, Eggers and Suh (2019) find that failures of products launched in new domains leads the firm to retreat, while failures of products launched in experienced domains leads the firm to search both locally and distantly for solutions. Maslach (2016) also explores how the type of failed products affects the firm's adaptations. Using data from the medical device industry, he finds that firms are more likely to persist with failed products when they were incremental innovations. Both studies suggest that firm adaptation depends on the firms ability to learn from failure, with the finding that firms are more likely able to learn when the failure is in a domain with which they have had past experience.

Because of the prevalence of failure in innovative industries, there is a rich literature in organizational learning that explores its effect on future search. However, for an outside researcher to observe an innovation failure within an R&D department, it must be the case that the manager has *judged* the product to be a failure. That is, personnel (often scientists or engineers) must be able to recognize that the product will not be successful on the market and then manage the termination of that product. There is no paucity of evidence that this can be a difficult and often non-incentivized task for managers (Biyalogorsky et al., 2006; March and Shapira, 1987; Simester and Zhang, 2010). Therefore, much of the literature on nfailure in innovation explores the case where the firm recognizes that its product is low quality *and* takes actions to terminate it.

One limitation of this literature has been the difficulty in compiling data on a firm's innovation failures. In previous literature, two main approaches have been used. One approach has been to measure failures in innovation at the patent level by looking at metrics such as patent discontinuations (Khanna et al., 2016; Serrano, 2010). While patents are a good measure of early-stage innovation, they have limitations as a proxy for innovative product

development. The other approach has been to look at failures of innovative products once they reach the market and face the ultimate judgment by consumers or other external critics. Literature in this realm explores firm responses to events such as the addition of a drug safety label (Higgins et al., 2018), the count of adverse events (Maslach, 2016), or a product recall (Freedman et al., 2012). While these events provide useful information on how firms react to negative external criticism following market entry, the effect is likely tangled with effects generated from changing consumer sentiment and changes in immediate revenue. Therefore, it is difficult to disentangle exclusively the effect of the information inherent in the feedback.

2.2.2 Related literature on individual responses to feedback from gatekeepers

Additionally, this study adds to the literature on responses to feedback from a "gatekeeper." Situations in which individuals receive performance feedback, and in which performance must reach a certain threshold for continuation, are pervasive. Consultants pitch projects to potential clients and government agencies. Engineers build prototypes and test them in the lab. And actors audition for roles in front of small groups of producers. Owing to the prevalence of negative feedback in these situations, a growing body of research is beginning to address how this particular type of feedback may impact the future trajectories of its recipient. In studying interim feedback in a tournament model, Ederer (2010) demonstrates that negative feedback may be demotivating for individuals who therefore become aware of asymmetries between themselves and their competitors.

Despite several theoretical contributions to the feedback literature, there is a paucity of

empirical evidence of these predictions. In one of the few empirical studies, Gross (2017) uses data from a commercial logo design tournament and finds empirical support for Ederer's theory. He finds negative feedback reduces future participation in the design contest but improves the quality of future designs. Wooten and Ulrich (2017) come to similar conclusions after implementing a field experiment designed to give artists different types of intermediate feedback on their designs. In general, they find that directed feedback improves the average quality of submitted entries, and the variance of quality declines.

Feedback also plays a role in entrepreneurship and the development of new ventures. In new venture competitions, founders present their business plans to a panel of judges who score and rank the competitors. In studying these data, Howell (2018) finds that negative feedback regarding one's intermediate rank in the competition leads to increased rates of product abandonment among those ranked more poorly. In contrast, Wagner (2017) uses a similar setting but finds that when some founders receive unsolicited qualitative feedback on their ventures, they raise more money in the future and are more likely to survive. These sets of studies are important in that they demonstrate how the nature of feedback an entrepreneur receives prior to entering the market may lead to heterogeneous future outcomes.

2.2.3 Related literature on regulation and innovation

Finally, this study contributes to literature exploring the effects of regulation on innovation. Since the early 1970s, economists and policy scholars have debated whether or not regulation encourages or discourages firms to innovate. Many of the early scholars, including Peltzman (1975) and Wardell and Lasagna (1975), argued that regulation inhibited innovation and

therefore decreased consumer welfare. These conclusions were also suggested by comparisons of the growth of countries with many regulations to those with few regulations (Crafts, 2006). In his analysis of new drug introductions following the Kefauver-Harris Amendment (which created the United States Food and Drug Administration as we know it today), Wiggins (1981) explored the change in marketed new drugs and determined that these regulations decreased new product introductions by 52%.

However, by the 1990s, scholars (including Michael Porter and Claas van der Linde in 1995) were suggesting that regulation may actually stimulate innovation. For example, regulations including patent protections likely created incentives to invest in R&D because firms knew they could appropriate value from their innovations. In addition, antitrust regulation may also stimulate innovation if firms believe they must innovate to maintain a competitive advantage. Furthermore, there is empirical evidence that regulation restricting entry may also have a positive effect on firm innovation. In exploring the effects of environmental regulation on innovation, Jaffe and Palmer (1997) find that environmental compliance expenditures have a significant and positive effect on future R&D expenditures, though not on patent counts. Pickman (1998) and Newell et al. (1999) also find a positive effect of environmental regulation on innovation. The current literature finds many differing effects of environmental regulations on innovation depending on the regulation studied.

Additional studies of regulation on innovation have explored issues such as the possibility of first-mover advantages or disadvantages in industries marked by regulated entry. If regulatory requirements of product entry become stricter as more products populate a therapeutic class, firms may be discouraged from further innovating within a crowded class. Carpenter et al. (2010) find that pharmaceuticals entering a certain therapeutic category first tend to

have decreased time in regulatory review, suggesting the presence of a first-mover advantage. However, Stern (2017) finds the opposite in the medical device industry.

2.3 Setting: The Biopharmaceutical Industry

The setting of this study is the pharmaceutical and biotechnology industries.[3] I study this industry for a few reasons. First, the chief source of a competitive advantage for a pharmaceutical firm is its ability to innovate, that is, introduce new products that have been approved by a government's regulating body.[4] Therefore, efficient and effective decision making by managers within these companies is an important capability. Second, pharmaceutical firms undergo a standardized routine of product development. This makes for ease of comparison both among and within firms at various stages of product development. And finally, the industry is important not only to the global economy but to the health and productivity of its citizens. In the United States, the pharmaceutical industry alone made up 1.9% of GDP in 2016 (United States Department of Commerce, 2016). Additionally, there is evidence that the introduction of new pharmaceuticals can benefit the labor market (Garthwaite, 2012), and decrease the burden on hospitals to provide care (Lichtenberg, 2001, 2007).

The ability to terminate low-quality projects quickly is an important capability for managers overseeing drug development projects (Guler, 2018; Lendrem et al., 2015). The costs of drug development have been increasing over time, and costs for developing a drug increase exponentially as firms continue through each phase of research and development. Estimates

[3]While pharmaceutical and biotechnology companies differ in a few ways, for ease of exposition I will consider all firms within these two industries to be pharmaceutical firms.

[4]In this paper, I will only consider approvals by the United State's Food and Drug Administration, as is common in the literature.

for the total R&D costs of one approved drug now top over $1 billion in 2013 dollars (DiMasi et al., 2016). The research and development of new molecules (which can eventually become marketed drugs) consists of two distinct parts: discovery research and product development. In the discovery research phase, scientists synthesize drugs and conduct preclinical testing. Discovery research often takes between 3 to 6 years. The second part, product development, is the longest and most expensive part of the drug creation process, and will be the focus of this paper. It has been estimated to take an average of 6.5 years (Mestre-Ferrandiz et al., 2016) and can cost upwards of $80 million (Sertkaya et al., 2016).

Drug development is broken out into three phases of clinical trials: Phase I, Phase II, and Phase III. Phase I is the shortest and consists of a firm testing its molecule on 20-100 healthy volunteers to confirm the safety of the molecule. If that is found to be satisfactory, the firm can move to Phase II. Phase II is the first real study of the drug's effectiveness on sick volunteers.[5] Phase III trials are often longer and more expensive versions of Phase II trials, involving up to 3,000 patients, and costing over three times as much (Lam, 2004). A study by the Manhattan Institute suggests that Phase III trials can make up over 90% of the drug's total development costs and represents the largest contributor to the growing costs of drug development (Roy, 2012). After having completed Phase III trials, the firm will submit a New Drug Application ("NDA") or a Biologics Licensing Application ("BLA") to the United States' Food and Drug Administration for review. This application summarizes all of the data generated during preclinical and clinical trials. The FDA is expected to respond to most standard NDAs within 10 months of filing.[6] Only after a drug has been

[5]By Phase II, issues around safety are generally resolved. However proving effectiveness can be more difficult, with more ambiguous requirements (Pak et al., 2015).

[6]This follows the passage of the Prescription Drug User Fee Act of 1992 (Ciociola et al., 2014).

approved by the FDA can it be sold and marketed in the United States.[7]

For this paper, I specifically consider a firm's decision to invest in Phase III clinical trials, that is, to move a product from Phase II to Phase III. Here, I am defining a product to be a molecule-indication dyad. A molecule is the specific drug given to patients and the indication is the specific disease the molecule is targeting (e.g. type II diabetes, non-small cell lung cancer).[8] Many molecules can treat one indication and one molecule can potentially treat many indications. However, a firm must do a separate Phase III trial for every indication it is trying to get approved for a certain molecule. Without an indication specific approval, a firm cannot market that drug for a specific condition. Therefore, a firm may have a different innovation strategy for a molecule it is trying to market for multiple indications than for a molecule hypothesized to treat only one indication.

I choose to explore Phase III investment because it represents the largest resource allocation decision a firm will make in the drug development process. Firms that can terminate a low-quality project before Phase III will still have refrained from making the most costly investment in the product's development. Therefore, one could consider a firm that terminates a product's development before Phase III to be one that demonstrates more risk aversion than a firm that chooses to continue with that same product. In addition, despite being the final step in the drug development program, Phase III trials are still very risky. Recent evidence finds the average probability of a molecule going from Phase III to FDA approval is between 57-71% and can be as low as 34% for certain therapeutic categories (Wong et al.,

[7]While a firm cannot market a drug for a disease for which it has not been approved, a doctor can still prescribe it to a patient for whichever disease she deems fitting. This is called "off-label" prescribing and while it likely has some implications for firm strategy, they are outside the scope of this paper.

[8]An indication can sometimes be a smaller subset within what is commonly thought of as a disease. For example, with the rise of gene-targeted therapies, an indication could be "Ovarian cancer on the BRCA-1 mutation."

2018). For biologics, the probability is even lower. However, these probabilities are more optimistic than the overall success rate of a product beginning at preclinical trials, which can be as low as 3%. This is certainly intuitive. As a drug development program transitions through all of the phases of clinical trials, the researchers get clearer information signals and will therefore only invest in Phase III trials for those molecules with the highest chances of success.

While the majority of NDAs are eventually approved by the FDA, occasionally a firm will be denied approval by the FDA. When the FDA rejects a New Drug Application, it sends the firm a Complete Response Letter (CRL).[9] Receipt of a CRL constitutes a large setback for the firm. Companies are required by law to disclose to their investors if they have received a CRL, however the exact contents of the CRL are rarely made public.[10] Upon receipt of a CRL, the firm has a few options. If possible, a CRL will detail the deficiencies of an application and offer a path forward. In this case, the firm has the option to redo some clinical trials and collect new data that will satisfy the concerns of the FDA. If the firm or the FDA determines the deficiencies are insurmountable, the firm will withdraw the NDA and terminate the project.[11] While the first case may be interesting in some contexts, in this study I am only interested in CRLs that result in termination of the project.

There are many reasons one may believe that firms receiving rejections from the FDA

[9]The FDA did not begin using CRLs for small molecules until 2008, to replace what had previously been either "Approvable" letters or "Non-approvable" letters. They had been standard for biologics since 1998. For consistency throughout this paper, I will refer to a Non-approval letter received before 2008 to be analogous to a CRL.

[10]This is illustrated in the rejection of ImClone's cancer drug Erbitux, which received a "Refuse to File" letter from the FDA given the badly flawed application. While the CEO tried to downplay the FDA's concerns to investors, when excerts from the letter were leaked to the press, detailing the many deficiencies of the clinical trial design, the company found itself in turmoil (Prudhome, 2013).

[11]The firm also has a third option to schedule a hearing with the FDA. Within 60 days of the hearing, the FDA will either approve or reject the application.

had submitted an NDA or BLA while expecting approval. The process of filing an NDA or BLA is time consuming and can even involve the hiring of consultants. Therefore, it is not a decision that the firm makes haphazardly. Additionally, because the receipt of a CRL can impact firm value, it is unlikely a firm would consume resources or undergo this risk if they did not believe their drug at least had a very good chance of being approved. Interviews with industry insiders and company press releases suggest this is largely true. For example, when the company PTC Therapeutics received a CRL for a drug used to treat Duchenne muscular dystrophy, the CEO stated that he was "extremely disappointed for the Duchenne community" and "strongly disagree[d] with the agency's conclusions" (Press release, 11/28/2018). However, to be conservative, in Section 2.5.4, I will explain the method used to segment out FDA rejections that are plausibly truly surprising to the firm and industry.

Industry experts have expressed in interviews that rejection from the FDA can be humbling for both the scientists and the senior management within the firm. Even large and experienced firms can make fundamental errors resulting in the non-approval of their product.[12] For example Astrazeneca received a CRL for their product Numax to treat respiratory syncytial virus due to issues in trial design that resulted in uncertainty regarding the efficacy results (Press Release, 2010). In fact, I will demonstrate evidence that the majority of these rejections are to large firms with vast amounts of experience developing drugs. According to a former Vice President at Bristol-Myers-Squibb, the receipt of a CRL can "beget soul searching" within the firm. Therefore, there is reason to believe, and as suggested by

[12]As one decision maker in a pharmaceutical company explained, "Project teams can be very possessive and defensive of their project that can make it a very challenging situation when tough decisions need to be made on the continued viability of the project" (Donelan et al. (2015): 325).

Haunschild and Rhee (2004), that firm adaptations made in response to a CRL may be different from adaptations made in response to different types of innovation failures, such as late-stage project terminations handled internally.

2.4 Data

2.4.1 Data on Product Development Decisions

To empirically explore the effect negative feedback has on future firm risk taking, I first create a dataset that includes pipeline-level information from Informa's BioMedTracker. The BioMedTracker database provides a timeline of a drug's development from Phase II trials to either approval or termination. This is where I collect data on relevant event dates (here, date the Phase II clinical trials ended, date the project was fully terminated, and/or date of FDA approval). Because I assume FDA approval to be the firm's end goal in this analysis, I treat clinical trials that were terminated in the United States but moved toward development for another country's market as terminated. I am also able to collect a rich amount of data on product characteristics, such as intended indication and inclusion in government sponsored programs from this database. The BioMedTracker database contains data on Phase II and Phase III clinical trials for a wide range of firms, both public and private, from around the world.[13]

Given the vast amount of mergers and acquisitions among pharmaceutical and biotechnology companies, it is important to determine which company owned and was making decisions

[13]While there is some information on Phase I trials and preclinical research, the data on the exact dates of initiation or termination is less complete. This is because not all Phase I clinical trials are required to be registered.

about the molecule at the end of Phase II clinical trials. To correctly match the owner of a drug to the decision maker at Phase II, I create a dataset of mergers and acquisitions (including product acquisitions) as gleaned from EvaluatePharma, another competitive intelligence database. Additional information regarding how I cleaned the data and accounted for missing information can be found in Appendix A.1.

Average and total R&D expenses for publicly traded firms in the sample, as reported by Compustat, are displayed in Figure 2.1. From Figure 2.1(a), it is evident total R&D spending increases over the time period but average spending appears to fall around 2010. Figure 2.1(b) displays the average R&D expenditures for the top ten largest firms (by spending) in the sample. For these firms, average R&D spending appears to be increasing over time. However, the fact that average spending stays relatively constant between 2010 and 2015 may suggest the dip in average spending among the full sample may also be a function of macroeconomic factors like the global recession.

Despite a non-decreasing level of R&D expenditures by pharmaceutical firms, the average number of FDA approvals for firms in the sample has not monotonically increased over time. Figure 2.2 illustrates these trends for both the full sample, and the averages for just the top ten biggest spenders.

Given the importance conditional transition probabilities will play in the regression specifications, I first explore what these data suggest regarding the probability of investment in Phase III clinical trials and the probability of approval, given the firm has completed Phase II clinical trials. Figure 2.3 illustrates these average probabilities for the year in which the Phase II clinical trial concluded. Interestingly, the probability of investment in Phase III and the probability of FDA approval appear to move together over time. While one may initially

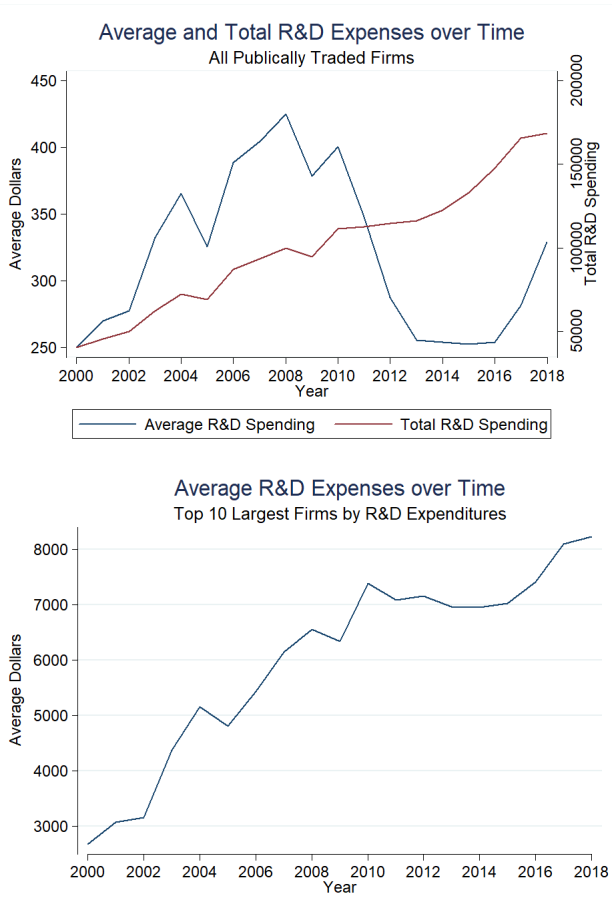

Figure 2.1: This figure plots (a) Average and total R&D expenses for the publicly traded firms in the sample (b) Average R&D expenditures for the top ten largest firms (by spending) in the sample. Data from Compustat.

hypothesize that the probability of investing in Phase III clinical trials has decreased over time due to improved technologies leading to better decision making, the fact that average approval rates have not increased suggest that this may not be the case.

One weakness of a simple graphical approach is that it does not take into account how characteristics of the drugs pursued over time change. As described above, transition probabilities are historically different depending on the therapeutic class and are often heterogeneous within class, given the indication pursued and the drug's mechanism of action.[14] In

[14]The mechanism of action (MOA) is how the drug "works." Oftentimes, this is consequence of the drug-receptor interaction.

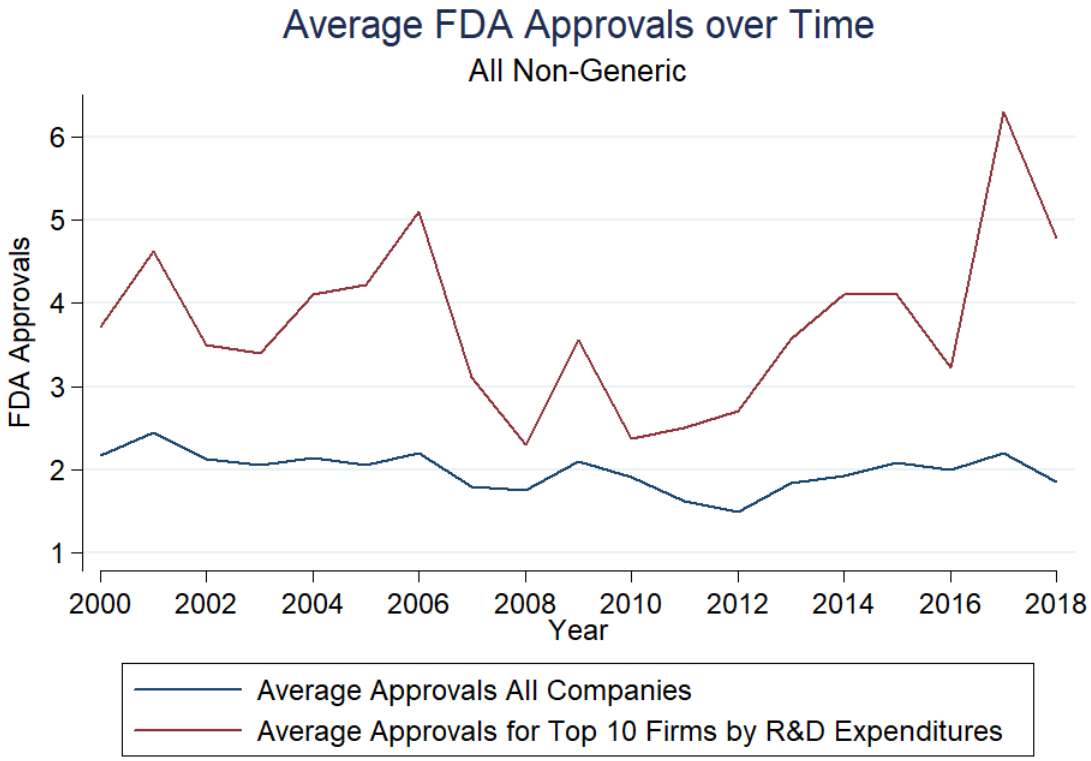

Figure 2.2: This figure plots the average number of FDA approval by firm and year for (1) All Companies in the Sample and (2) Only the Top 10 Firms by R&D Expenditures. Approvals include NMEs, BLAs, NDAs, and sNDAs. On the x-axis is the year of FDA approval. Data on R&D expenditures from Compustat. Data on FDA approvals from BioMedTracker and FDA.gov.

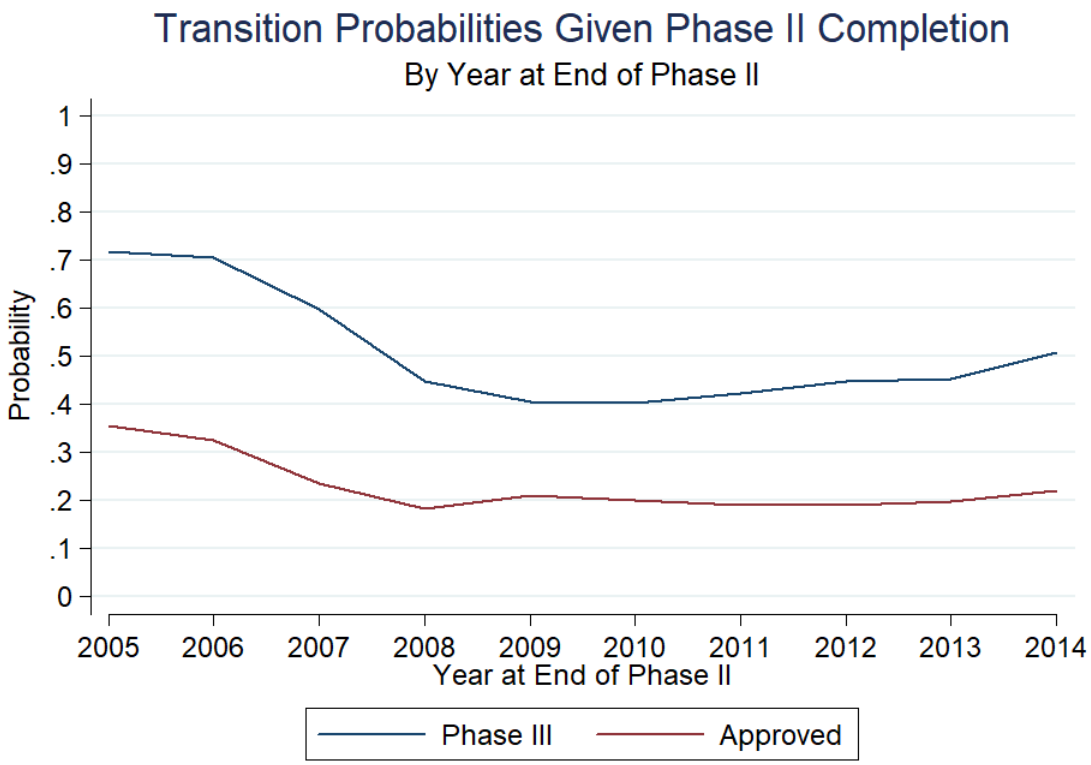

Figure 2.3: This figure plots the probability over time of (1) investing in Phase III clinical trials and (2) receiving FDA approval for each molecule having completed Phase II trials for a specific indication. Data from BioMedTracker and FDA.gov.

addition, the types of products being developed by an organization, or the number of organizations which specialize in certain therapeutic classes, may change over time. To explore this further, I consider four of the largest therapeutic classes in the dataset: Cardiovascular, Neurology, Oncology, and Endocrine Systems. Figure 2.4 illustrates how the number of Phase III clinical trials (and the percentage of those resulting in approved products) changes over time. These graphs illustrate that while oncology was the largest class in 2004, it grew by nearly 50%, and a larger percentage of those achieved FDA approval. In contrast, the number of Phase III clinical trials in neurology decreased over time, and the percentage of those approved became smaller as well.

I also consider the change in transition probability from Phase II to III for those four classes over time in Figure 2.5. Despite a growth in the number of oncology products reaching Phase III, the percentage moving from Phase II to Phase III actually decreases over time, and this is true with nearly all classes. This is likely because as knowledge about the disease increases over time, firms are able to make better decisions about Phase III investments.

2.4.2 Data on FDA Rejections

As an important addition to these data, I collect information on receipt of Complete Response Letters (or "Non-Approvables" if it is before 2008) and other forms of rejection by the FDA that result in termination of the project. Following the collection of historic data on company interactions with the FDA (and confirmed by interviews with a consultant to this industry), it becomes clear there a few reasons a company may terminate a project following an NDA or BLA filing. First, a company may receive a CRL requesting more data to be

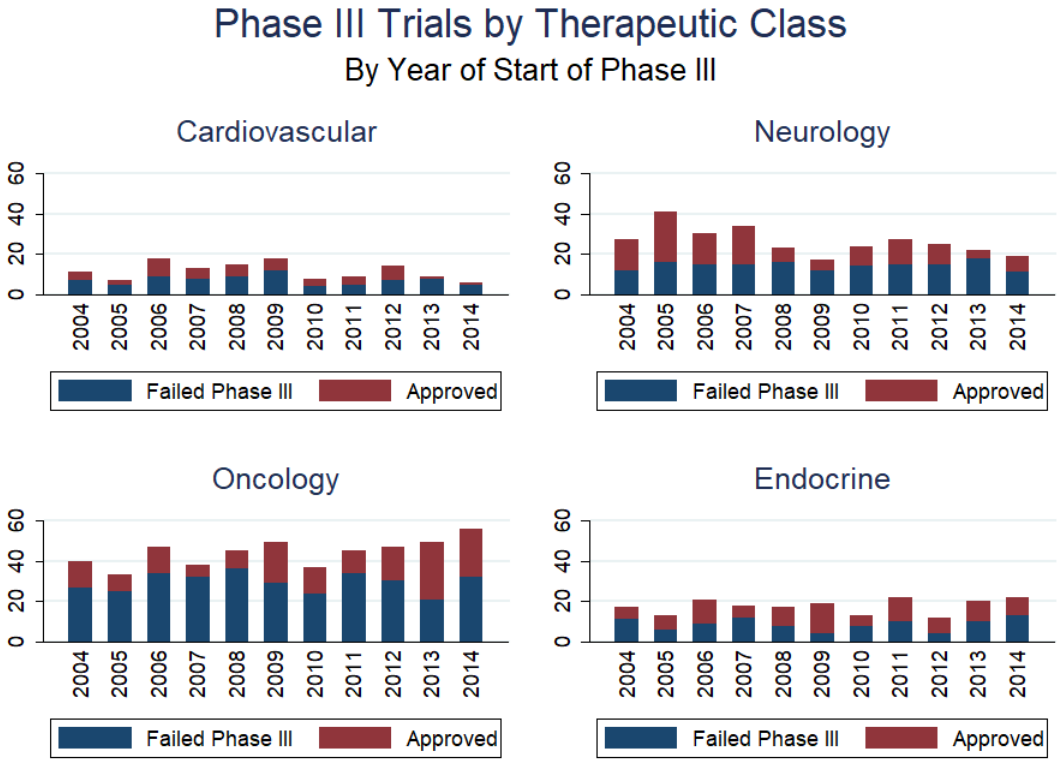

Figure 2.4: This figure illustrates the heterogeneity in the number of Phase III clinical trials and FDA approvals over time and by therapeutic classes. Those for the four largest classes are displayed here. Therapeutic class is defined by BioMedTracker. On the x-axis is the year at the start of Phase III clinical trials. Data from BioMedTracker and FDA.gov.

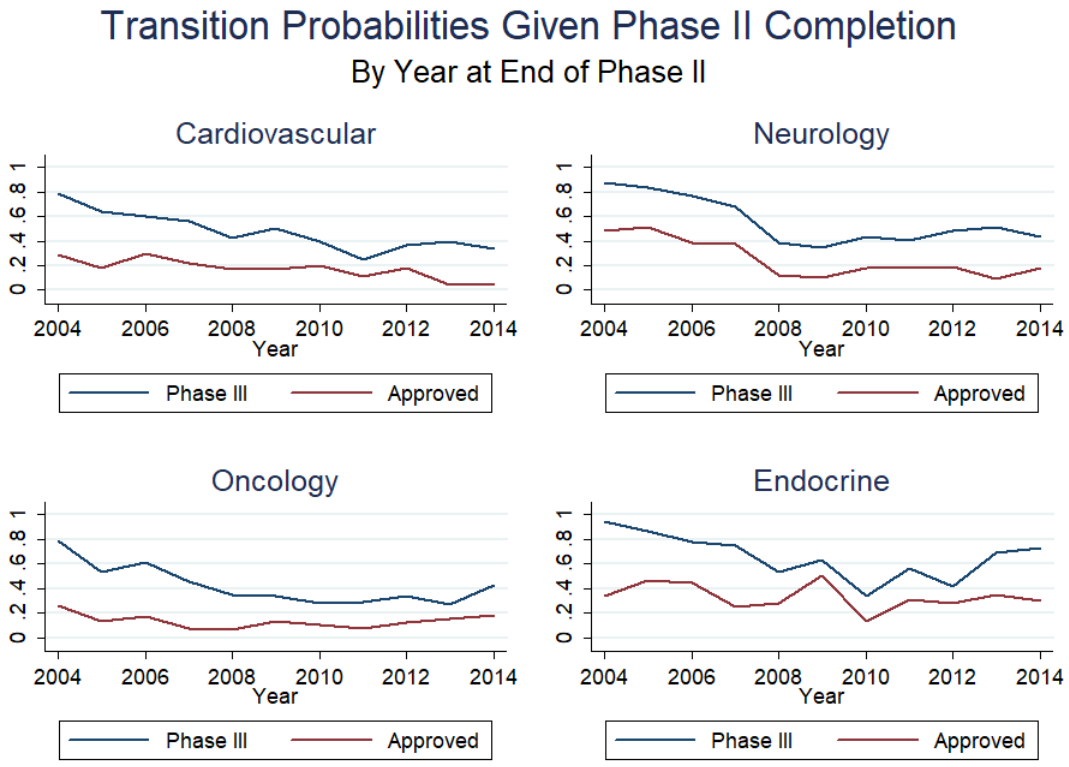

Figure 2.5: This figure illustrates the heterogeneity in the proportion of (1) Phase II clinical trials that continue to Phase III clinical trials and (2) FDA approvals over time and by therapeutic classes. Those for the four largest classes are displayed here. Therapeutic class is defined by BioMedTracker. On the x-axis is the year at the end of Phase II clinical trials. Data from BioMedTracker and FDA.gov.

collected before the possibility of approval. A firm that is unable to then demonstrate that the product is approvable (or determines it is too costly) will terminate development of that drug.[15] Secondly, the firm may terminate the project (and withdraw the NDA) if they receive negative feedback from the FDA advisory committee. The advisory committee is comprised of external experts who offer advice to the FDA, but do not make finals decisions regarding product approval. However, a "no" vote from the advisory committee sends a negative signal about its probability of approval. And finally, the FDA may issue a "Refuse to File" notice following an NDA or BLA application. The FDA will usually file an application within 60 days of receipt if the application is complete. A Refuse to File notice is issued if the application is incomplete. Some application deficiencies are easily correctable, others are more complex. In the case of insurmountable deficiencies, the company may choose to terminate the project.

Despite playing an important role in the innovation process in this industry, there have been few studies done on the role of CRLs, and this is likely because they are not available to the public. The FDA currently treats them as confidential. Any public knowledge of CRLs often comes from a firm's own press release, which many are compelled to make due to US securities laws requiring companies to disclose any information that may impact an investor's decision. However, even press releases are unlikely to give complete information as to why the FDA rejected a marketing application.[16] A study conducted by FDA researchers (who have access to historical CRLs) find that press releases documenting the failure of an application

[15] In some instances, firms will re-do trials many times and still not receive an approval from the FDA. While interesting, these cases are outside the scope of this paper.

[16] Following Abbvie and Abbot's receipt of a CRL for Certriad, the investing advice website The Motley Fool noted that "in typical pharma fashion, the companies didn't give any indication what problem the FDA had with Certriad."

often omit or give incomplete information regarding the reasoning for that rejection (Lurie et al., 2015). For example, they find while 48% of issued CRLs note deficiencies in both safety and efficacy of the product, only 13% of matching press releases divulge this information. These issues highlight the difficulty in determining the exact characteristics of the product that caused it to fail.

For this study, I treat all terminations by the firm due to regulatory feedback as effectively the same. Because the receipt of a CRL is the most common reason for the termination of a project following an NDA or BLA application, for ease of exposition I will refer to all of these cases as "terminal CRLs" or "rejections." I will identify these as cases in the data where one can see the filing of an NDA followed by the termination of the project without approval.[17] Because the data on these types of terminations is not as complete in the 1990s, I subset the data to only those products for which their Phase II trials were completed between 2000-2018. However, I find in robustness checks (not presented here) that these results are robust to various expansions and contractions in the considered time period. Figure 2.6 illustrates the number of FDA rejections and approvals over time.[18] As illustrated, full rejections by the FDA are very rare in comparison to approvals and appear to be heterogeneous across time. Wong et al. (2018) similarly find they account for roughly 3% of all NDA applications.

Of the 1,929 companies on which I have collected pipeline data, only 78 have ever received a terminal CRL (or other negative feedback from the FDA) on a project for which they were

[17]The FDA may initially reject an application only to have the firm redo the trials and eventually receive approval. While a potentially interesting phenomenon, I do not include those as failures for the purposes of this paper.

[18]The number of approvals is higher than normally discussed in the popular press because these tables include counts of NMEs (new molecular entities), sNDAs (which include new indications or reformulations approved for an already approved NME) and biologics. In discussions regarding the number of FDA approved drugs by year, often just NMEs are reported.

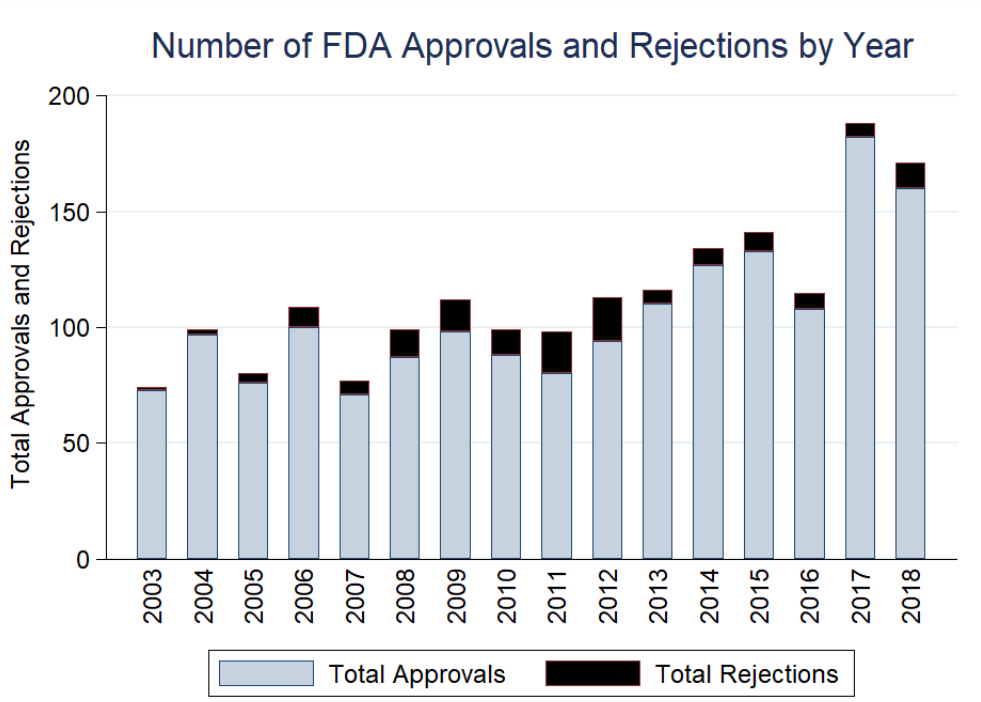

Figure 2.6: This figure displays the aggregate number of FDA approvals and rejections over time. Approvals include NMEs, BLAs, NDAs, and sNDAs. On the x-axis is the year of either FDA approval or rejection. Data from BioMedTracker and FDA.gov.

the lead developer. When looking at failures for the companies involved in development at any capacity, 142 ever received a terminal CRL. Though initially counter-intuitive, companies included in this group consist of nearly all of the largest "big pharma" companies that have had extensive experience compiling NDAs and BLAs. One-hundred percent of the top 10 companies by FDA approved products have received a terminal CRL and over half of the top 50 firms have received one. This provides some evidence that terminal CRLs are not necessarily driven by inexperienced firms being unable to meet the FDA requirements for approval. This is a boon for the researcher though, because these large and experienced companies provide enough data on investment decisions to make using within-firm variation feasible for the empirical analyses.

Table 2.1 displays the number of CRLs and approvals by therapeutic class. In comparing the two, they appear positively correlated. For example, the highest number of CRLs were issued for oncology products, and this therapeutic class also saw the largest number of approvals. Additionally, 4.2% of all CRLs were on drugs with "Breakthrough" status, which is nearly equivalent to the number of Phase II products with Breakthrough status (4.4%). A slightly higher percentage of products being terminated following rejection were orphan drugs (24.4%) than the percentage of orphan drugs at Phase II (12.6%). However, given the benefits that accrue with approval of an orphan drug (namely, extra years of exclusivity) it is not surprising that firms would be more likely to take bigger risks with those products. In the regressions, I will control for all of these characteristics of the product.

Table 2.1: Number of CRLs and Approvals by Therapeutic Class
2000 - 2018

Therapeutic Class	Number of CRLs	Number of Approvals
Allergy	1	44
Autoimmune/immunology	11	254
Cardiovascular	14	213
Dermatology	14	60
ENT/Dental	0	2
Endocrine	14	265
Gastroenterology	3	66
Hematology	7	111
Infectious disease	13	442
Metabolic	6	55
Neurology	25	320
Obstetrics/Gynecology	0	20
Oncology	28	374
Ophthalmology	8	92
Orthopedics	0	3
Psychiatry	6	142
Renal	0	15
Respiratory	2	86
Rheumatology	1	8
Urology	1	33

This table compares the number of FDA Rejections (CRLs) to the number of FDA Approvals by Therapeutic Class across the time period of this study. Therapeutic Class is defined by BioMedTracker.

2.5 Methods

2.5.1 Main Empirical Model

If firms become more risk-averse following rejection by the FDA, one should see a decrease in the probability of investing in Phase III for the next several products that reach the end of Phase II clinical trials, the stage at which the firm must decide if it wants to make a large investment in continuing development. If firms become less risk averse, one should see an increase in the probability of continuation, ceteris paribus.

To test this finding rigorously, I collect data on investment and termination decisions for all firms in the data, regardless of whether or not they receive a CRL during the time period. (However, once I include firm fixed effects in the specifications, the "control" firms should not impact the coefficient estimate.) I then construct a difference-in-differences econometric model to estimate the probability of continuation to Phase III clinical trials. I consider this decision to be a function of properties of the drug, the experience level of the firm, and the current competitive landscape. The empirical model is described in detail below.

$$\Pr(\text{Phase III}|\text{Phase II})_{ijrt} = \alpha_0 + \beta \text{Post-rejection}_{ijrt} + \Theta X_{ijt} + \delta_r + \mu_t + \epsilon_{ijrt} \tag{2.1}$$

where X is a vector of Project-time controls. δ_r and μ_t represent fixed effects for firm-therapeutic department and year respectively. Detailed information on variable definition and construction is in Appendix A.2.

To construct a dataset for this estimation, I collect the date for when each Phase II trial for a molecule-indication ended. This is the date that a firm must make a continuation or termination decision. I consider the continuation decision for the next product within that therapeutic research group, so long as it is not the same molecule being applied to a different indication or affecting the same target. Because many large pharmaceutical firms have a different key decision maker within each therapeutic class (and are occasionally even located in separate cities), it is more plausible that failures only impact decisions made within a therapeutic class. Research by Gaba and Joseph (2013), in a study on M-form organizations, also finds that negative feedback at the business unit level leads to improved future performance within that business unit. This assumption will likely not make a difference for smaller, centralized firms that are likely to specialize in only one therapeutic class.

If a firm is pursuing several indications for the same molecule, a substantial failure for one indication may impact the nature of trials for other indications due to information spillovers about the particular technology. To be as conservative as possible, I throw out cases of additional work on the same molecule and other drugs that have the same intended biological target as the rejected drug. Most results are robust to additionally considering only those next projects in different therapeutic subclasses as well.[19]

[19]In these data, a therapeutic class contains on average, five therapeutic subclasses. For example, the therapeutic class "ophthalmology" contains eight subclasses, including "retinopathy," "uveitis," "glaucoma," and "corneal conditions."

2.5.2 Endogeneity and Identification

One of the challenges in the organizational learning and feedback literatures is the difficulty in identifying a true causal relationship between the feedback and subsequent firm decisions (Certo et al., 2016; Hamilton and Nickerson, 2003). This is difficult for many reasons. First, is the issue of non-random assignment to "treatment" or sample selection bias. At the end of Phase III clinical trials, a firm forms the final assessment of its product based on its expectations about the FDA regulators. A firm that does not believe their product will be approved does not submit an application to the FDA. However, for those who do submit an application to the FDA and receive a rejection, it is unclear what their beliefs were when they chose to solicit FDA feedback. This makes the demand of feedback endogenous. Filing an application is very cheap when compared to the costs of development[20] and firms may have different quality threshold requirements before filing.[21] One example of a situation that would lead to endogeneity in the model is if there was reverse causality or simulteneity. Imagine a firm with one product in Phase III and a second in Phase II. The firm must decide whether or not to submit an NDA for the first project but the firm believes rejection is likely. Imagine also that the firm believes the second project is of low quality. It is straightforward to conjure up a scenario in which the firm is more likely to submit an NDA for their first project if it believes the second project is also a dud. This would result in a firm appearing to become more risk averse following rejection, though it would not be caused by rejection.

[20] One may wonder why *all* firms do not submit an application even if they believe their chance of approval is low. Based on my interviews with managers at several pharmaceutical firms, this can be attributed to the fact that these interactions with the FDA are not one-shot games. Nor are they anonymous. Managers therefore are not inclined to "clog up" the FDA with applications for drugs that they believe will have slim chance of approval.

[21] For a game theoretic model demonstrating this these trade-offs, see Carpenter and Ting (2007).

To adequately identify firm responses to FDA rejection, I modify a strategy undertaken by Blankshain et al. (2013). They propose that the trick to eliminating the endogeneity between regulatory decisions and firm decisions is to "focus on firm reactions to unanticipated changes in regulation, or to 'surprise' regulatory decisions" (pg. 3).[22] Their strategy is to look at changes in asset prices following negative regulatory decisions, under the assumption that larger relative drops signaled more surprising decisions. Under the assumption that market prices reflect full information, one would assume no abnormal return following a rejection if it was not truly surprising. This is because the knowledge that the product would not be approved would be already baked into the price prior to the announcement.

Despite a substantial history of looking at cumulative abnormal returns in the strategy and economics literature, this method has many limitations in the context of this setting. First, a number of firms in my data are private companies, or were when they received an FDA rejection. And secondly, the probability of seeing a statistically significant asset price dropped will be correlated with the value of the product that was under development. A rejection of a potential blockbuster product would then likely result in a larger price drop compared to an application for an indication extension even if the latter rejection was more "surprising" to managers than the former. For example, consider the case of the CRL issued for Amgen's Xgeva in treatement for castration-resistant prostate cancer. According to Amgen, the FDA suggested the reason for non-approval was that the provided data didn't show that the drug's benefits were great enough to outweigh the risks in the intended population. However, following this announcement on April 27, 2012, there is no

[22]The role of surprise to facilitate causal inference between inputs and outputs is a common strategy in other groups as well. See e.g., Atanasov and Black (2016) and Azoulay et al. (2010).

statistically significant decrease in returns. This may be because Xgeva was already approved for a related indication, which the firm was clear to stress in their announcement.

Finally, the way in which FDA rejections are timed and responded to makes it difficult to even find cumulative abnormal returns following FDA rejection.[23] At the receipt of the first CRL, firms issue a press release, often while maintaining conviction that the drug will be approved after meeting with the FDA. As described above, these statements often obfuscate the true nature of the CRL. In many cases the firm will go back and conduct more trials or collect more data, occassionally collecting several CRLs as they work to ameliorate the concerns of the FDA. This process could take months to years before the firm finally terminates the project. Any beliefs about the project's probability of success has likely been decreasing over time in these cases. It is therefore unlikely that a research would see a strong negative stock response at the time of termination.

To combat the limitations mentioned, I propose the following strategy for identifying plausible unanticipated regulatory decisions. The pharmaceutical industry relies on many private Pharma Intelligence companies who gather data on projects under development and regulatory decisions. Many of these companies also provide the service of industry analysts, who make predictions given all available information about the drug's probability of success. These include predictions regarding the probability of approval once a firm submits an NDA. I collect data on these predictions from the industry analysts at BioMedTracker. Following conversations with these analysts, I learn that these predictions are composed of two pieces: a disease group "baseline" score given historical success rates of other drugs in that disease

[23] In exploring this on the subset of public firms in this study, I find only a handful of statistically significant instances of abnormal returns following receipt of the first CRL. In exploring the cases where the drop in return is statistically significant, I find that these constitute nearly all cases where the receipt of the CRL resulted in immediate termination (that is, the date of the CRL and the date of termination were the same).

group and an "Analyst Opinion Subjective Score" that is updated following every piece of new information (including all trial data) as it is released. A score above the average baseline indicates that analysts believe the drug is likely to be approved. In evaluating their prediction performance, BioMedTracker determined that 99% of their predictions were correct in recent years.

As my identification strategy, I consider only those rejections for which analysts believed were highly likely (probability above average for the therapeutic class) to be accepted. The assumption underlying this strategy is that firms will always submit a New Drug Application for review if there is reason to believe that their product had a very high (usually at least over 90%) probability of approval. This allows me to treat the subsequent rejections as exogenous, or unanticipated, shocks.

Table 2.2 provides descriptive statistics of characteristics of the products that meet this criteria. Over a quarter are "secondary indications", which suggest that the product has already been approved for, or extensively studied for, another indication.[24] And those rejected products that were nonetheless approved in another country make up 28% of FDA rejections. Counterintuitively, a large majority of these products were neither biologics (for which approval has historically been more difficult to achieve) or the novel set of products that achieve preliminary advantages ("Receiving Gov Subsidies").

A list of all drugs treated as "surprise" rejections is presented in Table 2.3.

[24]The exploration of already approved drugs is often called "drug repurposing" and is an important innovation strategy in the biopharmaceutical industry. To repurpose a drug often results in cheaper Phase I and II clinical trials as the product has already been shown to be safe (Pushpakom et al., 2019).

Table 2.2: Descriptive Statistics of Rejected Projects
2000-2018

Characteristic	Proportion of of Rejected	Proportion of Approved
Biologic	19.1%	17.4%
Receiving Gov Subsidies	31.1%	21.5%
Secondary Indications	25.7%	34.6%
Approved Outside USA	27.7%	48.4%
Public Company	90.0%	88.2%
Headquartered USA	46.6%	42.1%

This table presents descriptive statistics of the 43 FDA rejected products that are treated as exogenous shocks in this research.

Table 2.3: Full List of Treated Rejections
2000-2018

Drug Name	Company	Therapeutic Class
Acapodene	GTx Inc.	Oncology
Arcalyst	Regeneron Pharmaceuticals Inc.	Immunology
Arixtra	Mylan Inc.	Cardiovascular
Arxxant	Eli Lilly & Company	Ophthalmology
Asunaprevir	Bristol-Myers Squibb Company	Infectious disease
Avodart	GlaxoSmithKline Plc.	Oncology
Buprenorphine Spray	INSYS Therapeutics Inc.	Neurology
Certriad	AbbVie Inc.	Cardiovascular
Ciltyri	Sanofi	Neurology
Erbitux	Eli Lilly & Company	Oncology
Exanta	AstraZeneca PLC	Hematology
Fentora	Teva Pharmaceutical Industries Ltd.	Neurology
Genasense	Genta Inc.	Oncology
Ilaris	Novartis AG	Immunology
Indiplon IR	Neurocrine Biosciences Inc.	Neurology
Indiplon XR	Neurocrine Biosciences Inc.	Neurology
Kengreal	Chiesi Farmaceutici S.p.A.	Cardiovascular
Lyrica CR	Pfizer Inc.	Neurology

Continued on next page

Table 2.3 – continued from previous page

Drug Name	Company	Therapeutic Class
MoxDuo IR	QRxPharma Limited	Neurology
Naproxcinod	Fera Pharmaceuticals	Rheumatology
Natpara	Shire Pharmaceuticals Group PLC	Endocrine
Numax	AstraZeneca PLC	Infectious disease
Provigil	Teva Pharmaceutical Industries Ltd.	Psychiatry
Reasanz	Novartis AG	Cardiovascular
Rekinla	Jazz Pharmaceuticals plc	Neurology
Remoxy	Pain Therapeutics Inc.	Neurology
Restanza	Advanced Life Sciences Holdings Inc.	Infectious disease
Rocilentinib	Clovis Oncology Inc.	Oncology
Samsca	Otsuka Holdings Co.	Cardiovascular
Satraplatin	Agennix AG	Oncology
Sirukumab	Johnson & Johnson	Immunology
Solithera	Melinta Therapeutics Inc.	Infectious disease
Taltorvic	Takeda Pharmaceutical Company Ltd	Oncology
Thelin	Pfizer Inc.	Cardiovascular
Tipifarnib	Kura Oncology Inc.	Oncology
Velcade	Takeda Pharmaceutical Company Ltd	Oncology
Visamerin	Sanofi	Hematology
Xarelto	Johnson & Johnson	Cardiovascular
Xeljanz	Pfizer Inc.	Immunology
Yondelis	Johnson & Johnson	Oncology
Zalbin	GlaxoSmithKline plc	Infectious disease
Zemdri	Achaogen Inc.	Infectious disease
Zimulti	Sanofi	Metabolic

2.6 Results

2.6.1 Effect of Rejection on Future Investment

To explore the effects of negative feedback on future investment, I first consider how negative feedback affects likelihood of investment in the project immediately following termination (provided it is not the same molecule or pursuing the same biological target). To do this, I estimate Equation 2.1 using a linear probability model with fixed effects. All specifications use robust standard errors clustered at the Firm-Therapeutic Class level. In robustness checks, I find that all specifications in this paper are robust to logit specifications.[25] However, for ease of interpretation, I will only formally report results from the linear probability models. The results, presented in Table 2.4, suggest that firms become much less likely to invest in the very next project following rejection. Because the dependent variable is binary, we can interpret the coefficients as the change in the probability of investment, controlling for drug and indication characteristics. The coefficient on the relevant variable, *Post-rejection* is negative and significant at at least the $\leq 5\%$ significance level under cluster-robust standard errors in all three specifications. The preferred specification, number 3, suggests that immediately following a failure, the firm will be 30 percentage points less likely to take their next project to Phase III, when controlling for project characteristics.

In addition to the hypothesized effects on the coefficient of interest, the coefficients on the control variables are all as expected. The coefficients on ODA, Fast-track, and Breakthrough status (all government programs that reward novel innovations) are all strongly positive

[25] I also drop the project that was rejected from the data before running the regression. Including the rejected project would bias the estimate toward seeing an effect post-rejection.

and statistically significant. The measure for the possibility of spillovers (*Lead Ind * Num Inds*) suggests products with a higher possibility of knowledge spillovers are also much more likely to continue to Phase III clinical trials. The coefficient on number of competitors is negative and significant when not using indication fixed effects and drugs within therapeutic classes with higher approval probabilities are much more likely to continue as well. The variable measuring the amount of experience a company has in conducting clinical trials, *Past Experience*, is not statistically significant. Additionally, I do not find that firm capabilities (as defined in several different ways) significantly affect a firm's response to failure. See Appendix A.4 for this analysis.

To initially estimate Equation 2.1, I had only considered the probability of continuation for the first project immediately following rejection. As an additional possibility, I consider the psychology literature on failure, which indicates that the negative emotions from project failure, while felt strongly initially, will dissipate over time (Shepherd et al., 2011). This phenomenon can also be explained by the availability heuristic (Tversky and Kahneman, 1973). For example, in the model of investment decisions proposed by Jehiel (2018), he finds using data from the mutual fund industry that firm behavior only changes when failure is salient, but returns to being more risk-seeking as that rejection gets further away in the manager's memory. Similarly, Haunschild et al. (2015) find that pharmaceutical firms adapt most from errors in drug safety right after they happen, but are likely to return to past processes as time passes. Therefore, I want to explore if the failure effect displays persistence over time. To analyze this further, I consider the effect of rejection on the next two through eight projects that reach an end-of-Phase II decision node. Results for the linear

Table 2.4: Probability of Investing in Phase III Trials Following FDA Rejection
2000-2018

	Dependent Variable: Investment in Phase III		
	(1)	**(2)**	**(3)**
	Next Project Following Rejection		
Post-Rejection	-0.188**	-0.241***	-0.292***
	(0.08)	(0.08)	(0.10)
ODA	0.234***	0.248***	0.238***
	(0.02)	(0.02)	(0.04)
Breakthrough	0.384***	0.425***	0.402***
	(0.02)	(0.03)	(0.04)
Fasttrack	0.235***	0.242***	0.250***
	(0.02)	(0.02)	(0.03)
Lead Ind*Num Inds	0.0208***	0.0233***	0.0178***
	(0.00)	(0.00)	(0.00)
Num Competitors	-0.000413**	-0.000789	-0.000806
	(0.00)	(0.00)	(0.00)
Past Experience	0.000173	0.000168	0.000192
	(0.00)	(0.00)	(0.00)
Constant	0.592***	0.580***	1.098***
	(0.12)	(0.19)	(0.26)
Indication FE	N	Y	Y
Year FE	Y	Y	Y
Molecule Type FE	Y	Y	Y
Drug Classification FE	Y	Y	Y
Company*Therapeutic Class FE	N	N	Y
Observations	5938	5938	5938
R^2	0.272	0.397	0.662

The dependent variable is equal to 1 if a product began Phase III clinical trials. Post-rejection is an indicator equal to 1 if it was the next product to finish Phase II following the receipt of a CRL and is not the same molecule as the failed product. Robust standard errors in parentheses and clustered at Company*Therapeutic Class level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

probability model are presented in Table 2.5. The coefficients are slightly attenuated from those in Table 2.4, suggesting a decline in the effects of failure over the next few projects. However, they remain negative and statistically significant at the $\leq 10\%$ significance level under cluster-robust standard errors.

Table 2.5: Probability of Investing in Phase III Trials Over Time Following FDA Rejection
2000-2018

	Dependent Variable: Investment in Phase III			
	(1)	**(2)**	**(3)**	**(4)**
	Next 2 Projects	Next 4 Projects	Next 6 Projects	Next 8 Projects
Post-Rejection	-0.220**	-0.172*	-0.165*	-0.146*
	(0.09)	(0.09)	(0.09)	(0.08)
Project-time Controls	Y	Y	Y	Y
Year FE	Y	Y	Y	Y
Molecule Type FE	Y	Y	Y	Y
Drug Classification FE	Y	Y	Y	Y
Company*Therapeutic Class FE	Y	Y	Y	Y
Observations	5938	5938	5938	5938
R^2	0.661	0.661	0.661	0.661

The dependent variable is equal to 1 if a product began Phase III clinical trials. Post-rejection is an indicator equal to 1 if it was the next 2, 4, 6, or 8 products to finish Phase II following the receipt of a CRL and is not the same molecule as the failed product. Robust standard errors in parentheses and clustered at Company*Therapeutic Class level.

* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

One potential concern is that I am picking up a change in the timing of terminations, rather than a decrease in the propensity to invest. For an in-depth analysis suggesting that this is not the case, see Appendix A.5.

2.6.2 Quality of Investments Immediately Following Rejection

So far, I have demonstrated that when firms experience a large, externally-driven failure, they become more conservative in their assessments of the quality of subsequent projects and this persists for the next several projects considered. These results imply that the projects a firm takes to Phase III trials following rejection should be of higher quality (e.g. more likely to be approved) than the product it took to Phase III just before the rejected product.[26] If this was not the case, it would imply that the investment effect could be driven by something other than an effect on the firm's decision on the marginal product. To test this hypothesis, I subset the sample to only those drugs that continued to Phase III trials.

Equation 2.2 gives the regression specification. Using a fixed effects regression with controls for product characteristics and time, I test the hypothesis that projects proceeding to Phase III after the firm experienced a failure are more likely to receive FDA approval than those projects in Phase III trials before the CRL. Here, *Post-rejection* is an indicator equal to 1 if the product is within the next set of projects to continue to Phase III following rejection. As in the previous regressions, I do not include the project if it uses the same molecule as the failed product to exclude any obvious molecule-specific information spillovers.

[26]There is anecdotal evidence about a "raising the bar" effect as well. A year after the rejection of Glaxosmithkline's Avodart, the firm hired a new president of R&D and focused on implementing a "discovery investment board" that would make funding decisions for research projects. The blogger notes that "the company is spending less on R&D and has raised the bar for moving a drug candidate into late-stage development." (Jarvis, 2012)

The dependent variable *Approved* is an indicator equal to 1 if the molecule i received FDA approval for treating indication j.

$$\Pr(\text{Approved}|\text{Phase III})_{ijrt} = \alpha_0 + \beta \text{Post-rejection}_{ijrt} + \Theta X_{ijt} + \delta_r + \mu_t + \epsilon_{ijrt} \qquad (2.2)$$

Results are presented in Table 2.6. Columns 1 and 2 provide strong support for the hypothesis that firms are taking higher quality products to Phase III following the CRL. The estimates suggest that, controlling for product and firm characteristics, the next two projects continuing to Phase III following rejection are 22% more likely to be approved. However, as was suggested in Table 2.5, the effects of rejection appear to attenuate over time. When observing the set of the next four products to receive investment following rejection, the coefficients are smaller and lose statistical significance.

Table 2.6: Probability of Approval Following Phase III Trials
2000 - 2018

	Dependent Variable: FDA Approval			
	(1)	**(2)**	**(3)**	**(4)**
	Next Project	Next 2 Projects	Next 3 Projects	Next 4 Projects
Post-rejection	0.223**	0.194*	0.159	0.151
	(0.11)	(0.10)	(0.11)	(0.10)
Project-time Controls	Y	Y	Y	
Year FE	Y	Y	Y	Y
Molecule Type FE	Y	Y	Y	Y
DrugClass FE	Y	Y	Y	Y
Company*Therapeutic Class FE	Y	Y	Y	Y
Observations	1979	1979	1979	1979
R^2	0.770	0.770	0.770	0.770

The dependent variable is equal to 1 if a product was approved by the FDA and 0 if it was terminated during or after Phase III clinical trials. Post-rejection is an indicator equal to 1 if it was one of the following products to enter Phase III (within the specified timeframe) following the receipt of a CRL for a different molecule. Robust standard errors in parentheses and clustered at Company*Therapeutic Class level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Because it takes many years for a product to transition from Phase III clinical trials to FDA approval this subset of data may suffer from a censoring problem. Consider an FDA rejection for Product A in June of 2015. Then consider a product B, that the same firm begins Phase III trials for in July 2015. In order for this product to be included in the regression, it would have to have either achieved FDA approval or been terminated by 2018 (when the data was collected). I argue that if anything, this censoring problem leads to a more conservative estimate of the effect presented in Table 2.6. Because it takes longer to achieve FDA approval after beginning Phase III than to terminate following Phase III, the data is likely picking up more Phase III terminations in the later portion of the sample period, therefore biasing the estimates downward.

To confirm this intuition, I subset the data to span only those products entering Phase III before 2013 and rerun the regression in Equation 2.2. Table 2.7 present the results. As intuited, the results in Table 2.6 were significantly more conservative due to censoring. The results in Table 2.7 suggest that following FDA rejection, the next two products to receive Phase III investments were nearly 50% more likely than the firm's baseline to receive FDA approval.

2.6.3 The Role of Rejection on Investment in Novel Innovation

In this section, I explore the types of products that are terminated early following FDA rejection. In particular, I consider how rejection affects investment into products that have already received regulatory attention. As described in the variable descriptions above, products that are targeting an unmet therapeutic need are eligible for receiving special designations from

Table 2.7: Probability of Approval Following Phase III Trials
2000 - 2012

	Dependent Variable: FDA Approval		
	(1)	**(2)**	**(3)**
	Next Project	Next 2 Projects	Next 3 Projects
Post-rejection	0.515***	0.428***	0.257*
	(0.15)	(0.16)	(0.15)
Project-time Controls	Y	Y	Y
Year FE	Y	Y	Y
Molecule Type FE	Y	Y	Y
DrugClass FE	Y	Y	Y
Company*Therapeutic Class FE	Y	Y	Y
Observations	1433	1433	1433
R^2	0.802	0.802	0.802

The dependent variable is equal to 1 if a product was approved by the FDA and 0 if it was terminated during or after Phase III clinical trials. Post-rejection is an indicator equal to 1 if it was one of the following products to enter Phase III (within the specified timeframe) following the receipt of a CRL for a different molecule. Robust standard errors in parentheses and clustered at Company*Therapeutic Class level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

the FDA. In these data, I identify those that have received Orphan Drug, Breakthrough, or Fasttrack designations. These statuses allow the firm certain privileges, such as faster review times, smaller Phase III clinical trials, and even additional market exclusivity if approved. To receive these benefits from the FDA, a firm must submit additional documentation either with the Investigational New Drug application or at some point during development. The FDA then considers the preliminary evidence that the drug is likely to be safe and efficacious in the specified disease, and grants the firm one of these coveted designations.

As seen in Tables 2.5 - 2.7, firms are more likely to take products that have received these designations to Phase III and, at least for products designated as either breakthrough or orphan drugs, are more likely to be approved. Unsurprisingly then, the receipt of one of these special statuses also serves as a signal of product quality. Studies have shown that investors are more likely to fund projects with either Fasttrack, Breakthrough or Orphan drug designations (Kim et al., 2018; Meekings et al., 2012). Given the above, one may hypothesize that even if firms are less likely to continue investing in certain products following FDA rejection, these government subsidized products would not be in that subset. To test this formally, I reproduce the regression from Tables 2.4 and 2.5 but with an additional interaction between the indicator for Post-rejection and a dummy variable equal to 1 if the follow product was obtained either Fasttrack, Orphan Drug, or Breakthrough designations. Results are presented in Table 2.8.

Table 2.8: Probability of Investing in Phase III Trials Following FDA Rejection
2000-2018

	Dependent Variable: Investment in Phase III			
	(1)	**(2)**	**(3)**	**(4)**
	Next Project	Next 3 Projects	Next 6 Projects	Next 9 Projects
Post-Rejection * Subsidized	-0.389**	-0.181	-0.258*	-0.279**
	(0.20)	(0.20)	(0.14)	(0.13)
Post-Rejection	-0.268**	-0.146	-0.128	-0.107
	(0.12)	(0.10)	(0.10)	(0.08)
Project-time Controls	Y	Y	Y	Y
Year FE	Y	Y	Y	Y
Molecule Type FE	Y	Y	Y	Y
DrugClass FE	Y	Y	Y	Y
Company*Therapeutic Class FE	Y	Y	Y	Y
Observations	5938	5938	5938	5938
R^2	0.662	0.661	0.661	0.661

The dependent variable is equal to 1 if a product began Phase III clinical trials. Post-rejection is an indicator equal to 1 if it was the next 1, 3, 6, or 9 products to finish Phase II following the receipt of a CRL and is not the same molecule as the failed product. Robust standard errors in parentheses and clustered at Company*Therapeutic Class level.

* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Surprisingly, these results suggest the opposite of my initial conjecture is more likely to be true. Not only are those government subsidized products less likely to receive Phase III investments following FDA rejection, but they appear to encompass a substantial part of the negative effect. This result provides a more nuanced view of what exactly the firm's managers are "learning" following surprising FDA rejections. Despite the favorable incentives given to firms to develop novel drugs for unmet needs, there is likely more uncertainty surrounding their development and probability of getting approved. In fact, surprising FDA rejections of this class of products account for 25% of the surprising rejections, which is greater than the proportion of these products in phase II clinical trials (20%). Table 2.8 suggests that not only are firms more likely to adapt their future investment strategy to discontinue marginally lower quality drugs, but are also less likely to continue investing in more novel drugs for which approval is less certain.

An additional possibility that is supported by these findings is that the managers of these firms lose confidence in the regulators. One of the main incentives of programs like Breakthrough designations or Fasttrack status is that the firm has more opportunities to work with the FDA during clinical development to construct a plan on how to achieve regulatory approval. Following surprising rejections, this incentive may be less appealing to a manager, who already likely feels that they were treated unfairly by the FDA. For example, consider the response by Doug Ingram, CEO of Sarepta in response to a CRL for their drug golodirsen: "We are very surprised to have received the complete response letter this afternoon. Over the entire course of its review, the Agency did not raise any issues suggesting the non-approvability of golodirsen, including the issues that formed the basis of the complete response letter" (Sarepta press release, August 19, 2019).

2.7 Mechanism Exploration

2.7.1 Comparing Rejection to Phase III Failures

This paper demonstrates that when firms experience a large externally-driven failure after investing in an innovation project they become more conservative in their investment decisions immediately following FDA rejection and this often leads to investing in better quality products following this event. This can be visualized as a firm increasing the quality threshold that they require to continue investing in the development of a product. While I attribute this to being due to the firm's leadership re-calibrating its decision-making criteria, one could still argue that this may be due to an information effect. Particularly for firms working on one class of drug or one therapeutic area, experiencing a negative feedback may cause them to re-evaluate other drugs in the same therapeutic class, or with the same target or mechanism of action. While I control for this by including a variable measuring the probability of spillovers and excluding cases where it is the same molecule being developed for a different indication, one could argue that this may be insufficient. Krieger (2018) shows that firms do terminate clinical trials based on negative information (as gleaned from a competitor's termination decisions) about similar drugs. If firms have multiple similar products in their pipeline, then any information gleaned about one product could spill over to others.

If the information hypothesis was correct (or explained the majority of the effect) then one should see changing investment decisions following not just rejections by the FDA, but failures that occur late into Phase III clinical trials as well. A firm terminating a project at the end of Phase III (and therefore deciding to not pursue an NDA or BLA) invests nearly the

same amount of resources as a firm that received an FDA rejection. Recent studies show that these Phase III abandonments can also be distressing for the firm financially (Hermosilla, 2020). However, the main difference between these two types of failure is the source of the information. A firm terminating its Phase III trial has learned of its product's deficiencies internally, while a firm that receives an FDA rejection is informed of their errors from an external judge. As explored by Haunschild and Rhee (2004) and Mody (1993), knowledge gleaned from external arbiters can lead to different types of knowledge generated within the firm and therefore may lead to a difference in future risk preferences. A firm that views its Phase III data and determines that they will not have a successful NDA application will have a different internal narrative of the failure, despite consuming nearly as many resources (and receiving the same information about their product) as those receiving a CRL.

To explore how internally determined product failures can affect an organization's future decision making, I construct a dataset of Phase III trials for which the duration is in the top 75% of Phase III trials for that therapeutic class, but that were voluntarily terminated by the firm. I assume that Phase III trials in the upper end of this distribution use approximately the same amount of resources as a project failing at the NDA stage.[27] However, these situations differ in one key way: here the firm was able to ascertain that its product was not of high enough quality following its review of the data and therefore terminated the project on its own accord. In essence, these failures differ in that they did not experience negative feedback from an outside critic. I then estimate Equation 2.3, which is analogous to Equation 2.1, but with the relevant coefficient being the one on post-Phase III termination. As in Equation 2.1, X is a vector of Project-time controls, and δ_r and μ_t represent fixed

[27]In robustness checks, I find these results are robust to a variety of cutoffs.

effects for firm-therapeutic department and year respectively.

$$\Pr(\text{Phase III}|\text{Phase II})_{ijrt} = \alpha_0 + \beta \text{Post-termination}_{ijrt} + \Theta X_{ijt} + \delta_r + \mu_t + \epsilon_{ijrt} \quad (2.3)$$

Estimates for the coefficients in Equation 2.3 are provided in Table 2.9. The very small and insignificant coefficients on the relevant variable, *Post-termination* suggest that the effects shown in the previous regressions are likely not the result of only learning new information about a technology. These results suggest that following a voluntary late-stage Phase III termination, firms do not appear to become more risk averse, and therefore the following projects they bring are no more likely to be approved than they would without the large failure. Note that these results cannot be interpreted causally but rather signify an association. In addition, these results also lend more evidence contrary to the potential hypothesis that the effect is driven by financial constraints. Phase III trials can cost upwards of $80 million and easily make up the largest costs involved in drug development. If financial constraints were the ultimate driver of the observed behavior change, then one would expect see a similar effect on *Post-termination* in Table 2.9 to the one on *Post-Rejection* in Table 2.4. On the contrary, all coefficients on the relevant variables in Table 2.9 are close to zero and statistically insignificant.

In addition, these results provide interesting insight into the role that the messaging of the feedback plays on a firm's future actions. While literature on feedback has often considered all types of negative feedback to be similar for organizational adaptation, (e.g. whether it is generated from an experiment failure in R&D or customer feedback) this analysis suggests

Table 2.9: The Probability of a Product in Phase II Trials Continuing to Phase III
Following Voluntary Phase III Termination

	Dependent Variable: Investment in Phase III		
	(1)	**(2)**	**(3)**
	Next Project Following Rejection		
Post-termination	0.0229	0.0153	-0.0130
	(0.06)	(0.06)	(0.07)
ODA	0.249***	0.256***	0.235***
	(0.02)	(0.02)	(0.02)
Breakthrough	0.379***	0.425***	0.424***
	(0.02)	(0.03)	(0.03)
Fasttrack	0.234***	0.247***	0.268***
	(0.02)	(0.02)	(0.02)
Lead Ind*Num Inds	0.0218***	0.0239***	0.0224***
	(0.00)	(0.00)	(0.00)
Num Competitors	-0.000517***	-0.000603	-0.000436
	(0.00)	(0.00)	(0.00)
Past Experience	0.000107**	0.000138***	0.000135
	(0.00)	(0.00)	(0.00)
Constant	0.475***	0.655***	1.049***
	(0.14)	(0.18)	(0.26)
Indication FE	N	Y	Y
Year FE	Y	Y	Y
Molecule Type FE	Y	Y	Y
Drug Classification FE	Y	Y	Y
Company*Therapeutic Class FE	N	N	Y
Observations	6353	6353	6353
R^2	0.281	0.402	0.560

The dependent variable is equal to 1 if a product began Phase III clinical trials. Post-termination is an indicator equal to 1 if it was the next product to complete Phase II clinical trials following the voluntary late termination of a Phase III trial. I define a late termination as one that lasted longer than the average for its therapeutic class. Robust standard errors in parentheses and clustered at the Company*Therapeutic Class level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

that is not the case. The main difference between the feedback a firm experienced in this section and in the prior sections is that in the latter, the decision to terminate was internally decided. In the previous investigations, the termination decision was made by an external regulating body. One interpretation of these most recent findings is that firms are more sensitive to negative feedback when they become external, or public affairs. Because receiving a CRL implies the firm did not interpret its own data correctly, this could be a bigger catlayst for the firm to change its subsequent decision-making criteria.

Additionally, I find that these results hold when looking at only those Phase III terminations that lead to a significantly negative cumulative abnormal return following announcment of the trial's termination. This is one way to subset the trials into only those Phase III failures that were truly surprising (as suggested by Blankshain et al., 2013). While this method doesn't come with all of the limitations as it would in the case of CRLs, namely the issue of ascertaining the true timing of the failure, it does require me to restrict the data to only those companies that were public at the time of termination. However, this method demonstrates that these "non-results" hold under a few different methodological approaches. See Appendix A.6 for more information.

2.8 Conclusion

In this paper, I have demonstrated empirically that firms react to unanticipated negative outcomes in their decisions regarding mid-stage innovation projects. Using the setting of the pharmaceutical industry, I examine a decision node in which a firm's managers will have substantial but incomplete information about the product under development. To

empirically test the effect that FDA rejections play on managerial beliefs, I run several models estimating the effect these failures have on investments in future R&D projects, while controlling for many characteristics of the subsequent projects. I find that following these rejections, firms become more conservative investors in future projects under development, that this effect persists for at least several subsequent projects, and that this leads to better outcomes (where "better" here refers to the proportion of successful Phase III investments) for the firm when they do choose to invest further. The evidence suggests these firms are discontinuing their marginally riskier products following failure.

These conclusions will be of interest to both policy makers and those who have personal and financial interests in the commercialization of new drugs. From a policy standpoint, the main conclusion suggested in this paper is that negative regulatory feedback can influence firms to invest fewer dollars in projects that are less likely to succeed. However, this may come at a cost to society if firms are eschewing the more novel products that could substantially raise welfare and promote further innovation. Understanding the aggregate effects of this trade-off is an important topic for future research.

In addition, managers at pharmaceutical firms can benefit from internalizing these results. Understanding how one's competitors are likely to behave is a crucial component of competitive strategy. And there is both anecdotal and statistically consistent evidence that pharmaceutical firms closely watch and anticipate their competitors' innovation developments in making decisions about their own strategies. Given this, these findings have the ability to aid managers in further developing their competitive strategic responses.

And finally, these findings are important for furthering the strategy literature on organizational learning and resource allocation. If we are to think of a firm as a collection of

resources and capabilities that are dependent on past investments in their development, this paper speaks to ways in which that path dependency may be suddenly altered (Nelson and Winter, 1982). This in turn, could have implications on the types of resources and capabilities developed and have implications for firm performance that stretch beyond the short term.

2.8.1 Limitations and Further Research

While the analyses provided here suggest that firms adapt their decision criteria following certain types of negative feedback, there are several limitations to be addressed. One limitation concerns the selection effect into the treatment. While I limit the treatment to be those cases where a firm submitted an NDA or BLA and outside experts strongly believed it would be approved, one could still argue that the type of projects that are rejected are fundamentally different from those that are approved. In robustness tests not displayed formally here, I find the stated results attenuate when including those rejections that were deemed potentially non-surprising by industry analysts. This does provide further evidence that it is the element of surprise, or learning that the firm's beliefs did not coincide with the FDAs, that leads to this change in firm behavior. However, additional research in other industries could further bolster these findings. While I demonstrate that firms may adapt their risk-taking preferences following the information received from FDA rejections, more research on the precise mechanism is needed. Additionally, due to data constraints in this industry, I am only able to observe the effect of rejection on changing investment strategies for *later stage* clinical trials. Exploring the effect of negative feedback on early stage R&D

would provide additional nuance to this story.

This paper has focused on the biopharmaceutical industry. Empirical research in other industries would be a useful addition to the exploration of this effect. While CRLs are unique to the pharmaceutical and biotechnology industries, there are many other industries that require regulatory approval to market a product and for which it is important for firms to terminate bad investments early. This valuable capability requires making sound intra-firm judgments about an innovation project. Understanding if this could be "learned" from rejection could continue to enhance theories of organizational learning.

Chapter 3 Demand Shocks, Decentralization, and Resource Allocation in Innovation

3.1 Introduction

How do firms adapt to demand-side shocks and why do we observe differences in these adaptations? External shocks that shift demand, be it from policy changes, natural disasters, or sudden changes in purchasing priorities, present complex challenges to firms, as they must successfully adapt to maintain a competitive advantage. This is a question important to strategy scholars as it pertains to the strength of dynamic capabilities within a firm (Helfat et al., 2009).

There is a rich literature exploring how firms respond to both technological shocks and negative external shocks like recessions. For example, in studying growth reconfiguration among firms, Chakrabarti (2015) finds that growing firms are more likely to fail during a negative economic shock than firms that responded to the shock by down-scaling. However, despite the prevalence and importance of positive demand-side shocks, there has been limited exploration of the different choices firms make in their responses. One noted exception is Wang et al. (2020) who explore how firms adapt to increased demand for defense technologies

following the attacks of September 11, 2001. They examine the effects of firm capabilities on the direction of adaptation following a sudden increase in demand and find that pre-existing customer relationships and the relevance of the firm's technological capabilities play a role in how firms adapt to the reshuffling of demand preferences.

There is substantial evidence in the economics and management literature that market demand is positively correlated with the number of products developed for that market (Griliches and Schmookler, 1963; Schmookler, 1966; Schumpeter, 1942). This suggests that positive demand shocks should lead to the reshuffling of innovation priorities within the economy as a whole. Much of the empirical work exploring this theory has used data from the pharmaceutical industry, where innovation is both crucial for firm success while being relatively easy to measure due to the regulated nature of drug development. For example, Acemoglu and Linn (2004) show that an expected increase in a certain demographic leads to an increase in pharmaceuticals that are marketed for that demographic. In a similar vein, Dubois et al. (2015) estimate the elasticity of innovation for pharmaceuticals. They find that a 10% increase in the market size for a drug results in a 2.5% increase in the number of products for that market receiving approval from the US Food and Drug Administration ("FDA").

However, while exploring the effects of market size on the number of products available is important for consumer utility, it largely obscures the role that firms play in bringing the product to market. Because firms (rather than government agencies) are primarily responsible for developing and marketing new drugs, the aggregate change in new drugs available will be largely determined by how individual firms allocate resources. Innovation, especially in the life sciences, is often a risky and expensive endeavor. In industries where

product development takes many years, it requires managers to form expectations about the state of the world many years in the future. And for firms that make many products for different markets, changes in the expected demand of downstream consumers will lead to increased trade-offs within an innovation pipeline.

Missing from these discussions is the way in which firm boundaries may influence how firms adapt to a changing external environment, a topic that is prominent in strategic management. I argue that the boundaries of firms, and therefore the structure of their internal capital market, provide an important and still unexplored determinant of innovative activities following external shocks. The logic is as follows: in the drug development process, where costs of clinical trials increase exponentially as the product moves through development, resources become particularly constrained in the later stages of development. Therefore, as a product moves through clinical trials, firms must evaluate whether to continue investing in one product in favor of another at a similar level of development. Factors that influence this decision will include the likelihood of approval by the FDA (as is required for a product to be marketed in the United States) and the expected revenue each drug could generate (conditional on FDA approval). A sudden positive change in demand that affects one class of drug over another would therefore change the calculation a firm makes in choosing in which drug it will continue investing.

The pharmaceutical industry is especially relevant for this study due to ongoing concerns regarding efficiency and quality in R&D (see e.g., Ruffolo, 2006; Scannell et al., 2012). The costs of creating one FDA-approved drug have been increasing over the course of the decade and are now expected to average $2.6 billion (DiMasi et al., 2010, 2016). Because these costs are largely driven by the cost of failed innovations, understanding what drives firms to

continue investing in products that will eventually fail may have broad efficiency gains for the industry as a whole. This decrease in efficiency can be seen in the data. In the early aughts, firms took an average of 0.34 products per year to Phase III clinical trials (the final most expensive stage of development before FDA approval) and averaged 0.17 approvals per year. By the end of the decade, firms were conducting an average 0.5 Phase III clinical trials per year while only averaging 0.21 approvals. This suggests firms are investing more in expansive and expensive development phases while not seeing the same increase in revenue-generating outcomes.

This study will contribute to the literature on firm adaptation in the face of reshuffling of consumer demand. First, I explore how demand shocks affect resource allocation in the aggregate. Firms can adapt to demand-side changes via two channels: they can develop completely new products that are aligned with these changing consumer preferences, or they can adapt their existing routines to favor those technologies positively affected by the demand shock. This study will look exclusively at the second phenomenon. Using pipeline data from the pharmaceutical and biotechnology industry, I provide evidence that following a sudden change in expectations about future demand, firms make several adaptations to their investment protocols for product development. First, I identify the 2003 Medicare Modernization Act as a policy that changed expectations about future demand for a certain subset of pharmaceutical drugs. The expectation that Medicare Part D would increase pharmaceutical spending for certain types of drugs treating certain types of diseases is the exogenous shock that facilitates my identification strategy. Then, using a triple-difference regression, I show that the average firm response following this positive demand shock was to change its investment criteria for development projects at the most resource intensive stages

of product development. I am able to show that this change in criteria lead to a decrease in the proportion of developed products being approved, as firms find it more beneficial to take bigger risks following an increase in expected revenues. Finally, I demonstrate that even those products receiving FDA approval following the policy change spent longer in FDA review. This suggests that even those approved products did not pass smoothly through the regulatory process and could imply that they received less favorable indication (or disease) designations.

Secondly, I consider how heterogeneity among firms may lead to deviations in this average affect. Both the capital budgeting and product diversification literature suggests that the more diversified (and in this case, the more decentralized) a firm becomes, the more distortions one will see in resource allocation at the firm level. To explore my above findings in this context, I explore if large, diversified and decentralized "big pharma" firms respond differently than their smaller counterparts. After dividing the sample into these groups, I find that it is these smaller, more centralized firms that are driving the average result. Larger, decentralized pharmaceutical firms do not appear to respond to the policy shock.

This study is novel for a few reasons. While several past papers explore how industries react to changes in expected customer demand, this is one of the few to demonstrate how these changes impact managerial decisions at the intensive margin. In addition, this study explores and quantifies potential downsides of policies that suddenly shift demand expectations– specifically that they incentivize investment away from marginally more promising products, to marginally less promising products. Furthermore, this study adds to the literature on organizational structure and resource allocation, and brings empirical data to Stein's theoretical arguments of the headquarter's role in "winner picking" and "loser sticking" (Stein,

1997, 2002).

Finally, this study provides important insights regarding the pharmaceutical industry's ability to respond quickly to demand shocks. During the coronavirus outbreak of 2020, the industry faced criticism for moving too slowly to begin developing vaccines to fight the virus (Posner, 2020). This study demonstrates that, with the right incentives, certain types of firms respond fairly quickly to changing incentives to develop drugs. Furthermore, while there are likely many factors underlying the decrease in R&D efficiency in this industry (changing approval standards, the increased cost of technology, the exhaustion of the "low hanging fruit") one plausible hypothesis is that as firms predict increased market sizes (from aging demographics, expanded insurance access, or otherwise) it may be more profitable in expectation for firms to continue investing in projects that, but for these expected increases in demand, they would have terminated earlier. This study will address that hypothesis by not only exploring if firms invested more in a certain project's developments following a sudden change in market size, but will also explore if that lead to lower overall approval rates for those projects. Understanding these incentives may be the key in the face of future health threats.

3.2 Industry Setting and Hypothesis Generation

To explore how changes in expected market size may impact resource allocation decisions in innovation, I first develop a framework for how these decisions are made in equilibrium. Pharmaceutical and biotechnology companies typically have many projects under development at one time. Firm decisions on whether or not to proceed with or terminate a drug's

development plays an important role for influencing the type of projects that will eventually reach market (Jekunen, 2014). The research and development of new molecules (which can eventually become marketed drugs) is time consuming and expensive. Recent estimates put the cost of bringing a drug from infancy to approval at $2.6 billion (DiMasi et al., 2003). Additionally, drug development is a risky endeavor. Only 15% of products entering clinical trials will ultimately be approved (DiMasi et al., 2010; Thomas et al., 2016).

The research and development of new molecules can broadly be divided into two parts: discovery/research and product development. The second half of drug creation, the development phase, is the longest and most expensive part of the innovation process and is the focus of this study. It has been estimated to take an average of 6.5 years (Mestre-Ferrandiz et al., 2016). Development is broken out into three phases: Phase I, Phase II, and Phase III. Phase I is the shortest and consists of a firm testing its molecule on 20-100 healthy volunteers to confirm the safety of the molecule. If that is found to be satisfactory, the product can move to Phase II. Phase II is the first real study of the drug's effectiveness on sick volunteers. Phase III trials are often longer and more expensive versions of Phase II trials, sometimes involving up to 3,000 patients. After having completed a Phase III trial, the firm will submit a New Drug Application ("NDA") to the Food and Drug Administration for review. Only after a drug has been approved by the FDA can it be sold and marketed for that indication, or disease, in the United States.

For this study, I specifically consider the decision to move a product (defined as both the molecule and the indication it intends to treat) from Phase II to Phase III trials. The transition from Phase II to Phase III makes a particularly good setting to study a firm's risk preferences under incomplete information. Despite being the final step in drug development,

Phase III trials are still very risky. Recent evidence suggests the probability of transitioning from Phase III to submitting an NDA application is between 57-71% from 2000-2015 and can be as low as 34% for certain therapeutic categories (Wong et al., 2018). Additionally, Phase III trials are the most expensive part of the drug development process, costing a firm between $12 to $53 million dollars (Sertkaya et al., 2016). This is more than three times the cost of Phase II clinical trials (Lam, 2004).

To understand the effect of a market size shock on decision making within a firm, I first propose a model of how a firm's managers decide to take a molecule to Phase III clinical trials and then determine if an increase in market size results in a change in decision criteria. It has some similarities to the one developed by Arora et al. (2009) in that a decision to continue is a function of not only managerial subjective judgment of the likelihood of approval, but the assessment of factors like expected demand. To begin, I assume that researchers within a firm follow a multi-step Bayesian process of gaining and integrating signals about the quality (and therefore the potential revenues) of a product. These revenues will only be realized if the product is approved by the FDA, and therefore achieves "successful" Phase III trials. Importantly, "success" in a clinical trial is interpreted by the firm. It is only after submitting an NDA with the FDA that a firm can get an objective measure of the quality of their drug. Products will only continue to the next phase if the researchers receive a positive signal from the previous phase.

3.2.1 Aggregate Responses to Demand-Side Shocks

In this section, I will describe the decision-making process within a firm as gleaned from my interviews with industry professionals, including those within both small biotechnology firms and their more traditional "big pharma" counterparts. The decision to terminate a project at Phase II (that is, not continue to Phase III) is almost always made by the firm's upper management following input from the project's lead scientist. In smaller firms, these roles can be one and the same. Because the safety of the molecule is usually established by Phase II, many projects are terminated in these later stages for efficacy-related or economic concerns (Pak et al., 2015). In the empirical setting, I will simplify this interplay by referring to "the firm" as the decision maker, as is standard in the industrial organization literature.

After completing Phase II trials for a product at time t, a firm r updates its belief about the quality of molecule i for treating indication j such that $P_{ijrt} = P()$. Without loss of generality, I normalize P_{ijrt} to be between 0 and 1 and reinterpret it as a probability that this molecule i will be approved by the FDA for indication j after Phase III trials. While this is a subjective measure, I can assume that it is a function of molecule and indication characteristics such as the formulation of the drug, the mechanism of action and the indication. I assume that all firms incorporate knowledge of historic transition probabilities in their assessments of their projects.

If P_{ijrt} is judged to be greater than some value $E[K_j(T)|t]$, the firm proceeds to Phase III. $E[K_j(T)|t]$ is the firm's expectation (at time t) of the potential revenue it can achieve at time T, the time the molecule is approved for indication j (if it is approved). Here, $E[K_j(T)|t]$ can be interpreted as a threshold, and it is a function of the indication being pursued, the

number of competing products treating that indication and the costs to develop the product. The prevalence of the disease and the number of already approved drugs to treat that disease approximate the expected revenue of the product in the empirical specification. Additionally, I will assume that the costs of Phase III trials can be approximated by both the indication it is intending to treat and whether or not it is included in a cost-saving government program (such as receiving Breakthrough or Orphan Drug status). I assume that $E[K_j(T)|t]$ is an objective value shared by all firms working on the same indication j at time t. That is, every firm has roughly the same expectation of the returns they could accrue by developing a drug to treat a certain disease.

At time t, firm r faces a choice set $D = \{Continue, Terminate\}$. The firm chooses to continue when the expected quality P_{ijrt} is greater than the indication specific threshold $E[K_j(T)|t]$. While I do not calculate $E[K_j(T)|t]$ explicitly, I assume that it is between 0 and 1 and that it is decreasing in market size and increasing in the number of substitutes on the market. After Phase II trials, a firm develops its prior P_{ijrt}. Again, if $P_{ijrt} > E[K_j(T)|t]$, the firm chooses $D = Continue$ and moves on to Phase III trials. These Phase III trials are where firms gather the data to present to the FDA for approval. A firm that gets a signal of "Success" in Phase III will then submit a New Drug Application (NDA). A firm that gets a signal of "Failure" will terminate their efforts.[1]

According to the framework presented above, drugs intended to treat larger markets, all else equal, should be more likely to be taken to Phase III clinical trials. Explicitly, this implies the increase in the prevalence of indication j should lead to a decrease in the firm's

[1]Occasionally, a firm will misinterpret the signal received at the end of Phase III trials and submit an NDA application to the FDA. This is very rare (around 2% of cases in my data).

continuation threshold, as expressed formally in Equation 3.1.

$$\frac{\delta E[K_j(T)|t]}{\delta j} < 0 \tag{3.1}$$

Additionally, because an increase in j has no effect on P_{ijrt} as constructed here, one should expect more positive continuation decisions for pharmaceuticals targeting larger markets. That is, firms should be more willing to invest in these risky (and costly) Phase III trials for a product with the ability to generate greater returns. From a resource allocation perspective, this implies that when deciding how to allocate resources between two drugs under development, a firm may choose to allocate their R&D resources to the product with a lower likelihood of approval if that product has a high enough profit potential. In this study I will not consider sudden changes in the prevalence of a disease but sudden changes in the likelihood of people with that disease purchasing treatment. This will be explained further in the next section.

Hypothesis 1: Following a demand-side shock leading to increased demand for a certain subset of technologies, there will be an increase in the proportion of that class of technologies continuing to Phase III clinical trials.

Hypothesis 1 predicts that, following a demand shock, there is an increased propensity to invest in technologies that otherwise would have been terminated in the counterfactual. This implies that but-for the shock, the firm would have determined the product to be less desirable than others in its pipeline. This could be because either the risk was too high (a low probability of approval) or the benefits (expected profit) were too low. If, following the shock, the firm determines more products in this class to be desirable investments, it is due

to the increase in expected profit. By assuming that the demand-side shock only changed the expect profit to this class of products (rather than the probability of approval P_{ijrt}) it follows that products that are now receiving Phase III investment have a lower potential for approval than those in the class that would have received investment in the but-for world. This leads to Hypothesis 2.

Hypothesis 2: Following a demand-side shock leading to increased demand for a certain subset of technologies, there will be a decrease in the proportion of those affected technologies coming to market following Phase III investment.

3.2.2 Heterogeneity in Responses to Demand-Side Shocks

While Hypotheses 1 and 2 speak to the average adaptation one would expect to observe following a demand-side shock, it is likely that firm characteristics will moderate the direction and severity of the adaptation. I hypothesize that the results presented above will be moderated by a firm's capabilities in effectively reallocating resources among its development projects. By resources, I am considering everything from financial resources to human capital. Generally, strategic management scholars have found a positive relationship between a firm's ability to reallocate resources and its performance (see e.g., Teece, 2007 and Lovallo et al., 2020).

One possibility is that some firms are less able to more efficiently allocate resources following a policy change. For example, for firms with a fixed amount of resources dedicated to each therapeutic class (and particularly if those divisions are in separate cities) it may be less likely that firms can easily transfer resources between divisions quickly following a

change. For example, suppose that following a change in health policy, firms were incentivised to invest more resources in their neurology group – the therapeutic class that contains disease like Alzheimer's disease, dementia, multiple sclerosis, and sciatica. If a firm already has an active division of neurology that is already at capacity, the firm may not have the resources (lab space, scientists, etc.) to direct more research here in the short run. This could be especially true if the firm cannot easily transfer resources from another division (say, oncology) to neurology. This may be the case if the divisions are distinctly separate from each other. This could be true if, for example, the divisions are separate geographically or have different but powerful key decision makers.

In this industry, there is strong evidence in the data that the product diversification (having ongoing products within multiple therapeutic classes) within a company is strongly correlated with decentralization (having labs in multiple states and/or countries). Figure 3.1 plots the relationship between these two. As illustrated, the vast majority of firms in the sample (to be discussed in more detail in Section 3.3) specialize in developing drugs within one therapeutic division.

An example of what I will refer to as a more decentralized company is Pfizer. Pfizer has at least nine R&D locations spread across the United States and the United Kingdom. While their corporate headquarters is located in New York City, their oncology unit is in Pearl River, NY, their biotechnology unit is in La Jolla, CA, their vaccine unit is in Saint Louis, MO, and their unit for Pain and Sensory disorders is located in Cambridge, UK. I hypothesize that a decentralized company like Pfizer may be less likely to reallocate resources from, say, St. Louis to Pearl River in the short run. Pfizer is hardly unique in their R&D structure– many of the large pharmaceutical firms are decentralized. And this is uniquely

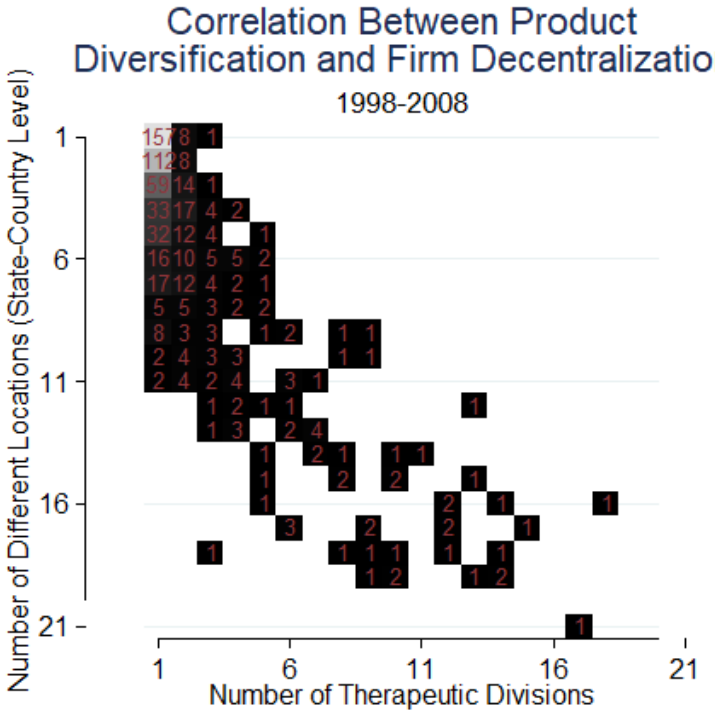

Figure 3.1: This heatmap demonstrates the positive correlation between number of product divisions and number of locations within firms in the sample. Data from BioMedTracker and Evaluate Pharma.

distinct from smaller companies, which are largely located if not on one central campus, in one city. As one would expect given evidence from Figure 3.1, Pfizer is also heavily diversified in the types of therapies it develops.

While there has been some historical research on the role of organizational structure on firm strategy (Friebel and Raith, 2010; Groves and Loeb, 1979; Harris and Raviv, 2002) and the role of decentralization in resource allocation within countries (Marschak, 1968), few papers have explored how organizational structure may impact resource allocation under changing environments. One exception is Aghion et al. (2020), who explore how decentralized vs. centralized companies fare following economic crises. They find that firms that were more decentralized before the Great Recession out-performed their more centralized peers during the crisis. However, they acknowledge that this is not initially intuitive. For example, managers in more centralized firms may be better able to make tough decisions (such as shuttering poorly performing divisions) in an economic crisis. They believe their results are driven by the important role of knowledge of the local environment that guides a more decentralized firm to weather a downturn.

The setting of this research is under very different conditions – one where firms realize the existence of new profitable opportunities and therefore must decide how to properly reallocate resources to capture them. As explored by Leiponen and Helfat (2011), the decision of where to conduct R&D across a decentralized firm is an important strategic decision that may have consequences for firm performance. And furthermore, the organizational economics literature postulates that, due to economies of coordination and reduction of transaction costs, centralized firms will have better innovation performance. In studying the effects of organizational structure on the quality of R&D output, Argyres and Silverman (2004) find

that centralized firms do better on this metric. In this study, I will explore the effects of organizational structure on the propensity of firms to allocate resources following a demand shock.

In properly formulating my hypotheses, I will turn to the literature on internal capital allocation.[2]. Early work in organizational economics (notably Williamson, 1975) posits that the role of corporate headquarters is to allocate scarce resources across its organizational units. Work by Stein (1997, 2002) demonstrates that under capital constraints, firm boundaries play an important role in how resources are allocated within a firm. In particular, he popularized the notion that headquarters are responsible for "winner picking" and "loser sticking" among divisions. Depending on the opportunities within the firm, one division may be resource constrained despite another being resource rich, and also despite the prevalence of profitable opportunities within the "poor" division. In testing Stein's theory, Gartenberg (2014) finds that the orientation of a firm's parent company leads to different types of loans being issued during the lead up to the 2007 mortgage crisis and that this led to differential performance of firms following the crash. The differences, she determines, were driven by the presence of alternative uses (or lack thereof) of capital within the firm.

Following the work of Stein, scholars have continued to explore the conditions under which corporate headquarters allocate resources efficiently. This has been referred to as the "dark side" of internal capital markets (Ozbas and Scharfstein, 2010). Using data on Compustat firms across a broad array of industries, Shin and Stulz (1998) find that firms are not efficient at moving resources to their most valuable opportunities. This finding that managers are bad at "winner picking" under diversification has also been found in work by Liebeskind

[2]For an extensive review of the recent literature and empirical findings, see Busenbark et al. (2017)

(2000), Rajan et al. (2000), Bernardo et al. (2006) and Ahn and Denis (2004). Given this, I hypothesize that an increasingly decentralized firm may be less likely to reallocate resources from one project to another in the short run. This would be demonstrated empirically as seeing no change in the propensity to take an affected class of therapies from Phase II to Phase III, despite the sudden change in expected returns on the therapy. This leads to Hypothesis 3.

Hypothesis 3: Following a demand-side shock leading to increased demand for a certain subset of technologies, there will be a greater increase in the proportion of that class of technologies continuing to Phase III clinical trials for firms that are smaller or more centralized than seen in larger, decentralized firms.

3.3 Empirical Setting and Data

As a demand shock, I will consider the passage of the Medicare Modernization Act (MMA) in the United States in December of 2003.[3] The relevant part of the bill for this research was the creation of the program that today is known as Medicare Part D. This program lead to an increase in Medicare costs by 10% in order to provide additional coverage to recipients. Prior to the creation of Medicare Part D, those covered by Medicare were only covered for pharmaceuticals used in a hospital setting. As a result, seniors spent considerably more on their prescription drugs than their employed counterparts. In 2002, the Congressional Budget Office estimated that Medicare recipients spent an average of $2,500 per person on

[3]There are several papers in the economics literature that use increases in coverage by Medicare as a proxy for an increase in demand (see e.g., Acemoglu et al., 2006; Blume-Kohout and Sood, 2013; Dranove et al., 2014; Finkelstein, 2004). The assumption in all of these cases is that when the consumer is not bearing the full cost for a pharmaceutical, they will be more likely to purchase that product.

prescription drugs. Medicare Part D sought to give both the disabled and those aged 65 and older prescription drug benefits to offset some of these costs. While enrollment in Medicare Part D is voluntary it became very popular among both Medicare recipients and private insurance companies who had the opportunity to offer plans– by 2008 there were over 1,800 different Prescription Drug Plans offering coverage through Part D (Hoadley, 2008).

While the bill was passed in December 2003, Medicare Part D coverage did not formally begin until January 1, 2006. As hoped, the implementation of this program resulted in a dramatic increase of Medicare beneficiaries enrolled in prescription drug coverage, from about 67% being enrolled in some prescription drug plan before 2006, to nearly 90% enrolled after 2006 (Yin, 2008; Duggan et al., 2008). Research on the effects of Medicare Part D on out-of-pocket spending for pharmaceuticals also suggests a positive improvement for Medicare beneficiaries. Yin (2008) estimate a decline in out-of-pocket costs of 13%, and Ketcham and Simon (2008) find a similar decline of 17%. Furthermore, research in the health-services literature also finds that Medicare Part D led to lower rates of hospitalization for seniors with conditions that could be controlled through medication (Afendulis et al., 2011).

Additional research has found that the Medicare Part D program increased utilization of prescription drugs in the home by the elderly (Engelhardt and Gruber, 2011). Lichtenberg and Sun (2007) find that the program reduced costs among the elderly by 18.4% and increased their use of prescription drugs by 12.8%. This resulted in an overall increase in prescription drug usage in the United States by 4.5%. Additionally, this increase in demand led to an increase in revenues for pharmaceutical firms (Duggan and Scott Morton, 2010). Given these favorable outcomes, economic theory suggests following Medicare Part D, firms were more likely to allocate resources to Phase III trials for prescription drug products that target

illnesses commonly faced by seniors than they were before the announcement of the program.

3.3.1 A Case Study

An example of the response to Medicare Part D Legislation can be seen in drugs formulated for in-home use targeting the treatment of Alzheimer's disease. Alzheimer's disease affects nearly only those patients 65 and older (who would qualify for Medicare and Medicare Part D) and nearly all potential therapies have been designed as small molecule capsules and tablets for daily use in the home. And the disease is not rare, therefore making it a good initial indication to explore when considering the responses of firms to Medicare Part D. Using data from Informa's BiomedTracker, I find that between 1995 and 2003 (the "pre" MMA period), 16 compounds were taken to at least Phase II clinical trials and only four of those were taken to at least Phase III (25%). In 2004 alone, immediately following the announcement of the passage of the MMA, 5 of the 6 drugs in Phase II at the time were taken to Phase III (83%). However, none of these drugs were ultimately approved.

In past studies of the effects of market size on innovation, this effect would have gone unnoticed. Because it did not lead to any new drugs for Alzheimer's disease, consumers would not have benefited. Additionally, any study that just looked at patent creation would not have seen the effect on the increase in investments in development. And finally, if firms did not increase their innovation budget, one may have seen an aggregate decrease in new products approved, as money was being shifted from other potentially more promising products to the failed trials for Alzheimer's disease.

3.3.2 Data

To rigorously explore these investment decisions, I construct a dataset that contains properties of the drug (therapeutic classes and subclasses, indication, pharmacological class, target, etc.) and the properties of the company developing the drug (public status, age, number of successful past projects). The data on pipeline dates and decisions comes from Informa's BiomedTracker.

To begin, I explore how investment in clinical trials changes at the time of the policy change. Figure 3.2 illustrates the number of Phase II and Phase III clinical trials for all firms. It is immediately apparent that the number of Phase II clinical trials have been increasing rapidly over the ten year period graphed. While the number of Phase III clinical trials has also increased, they do not appear to be increasing at the same rate as Phase II trials. Figure 3.3 confirms this. This graph illustrates the percentage of Phase II clinical trials that continue to Phase III. There is some variation over the time period, but the general trend appears to be moving downward.

However, looking only at these two charts provides only a limited perspective of how firms are behaving. A researcher who estimates innovation using clinical trial counts may conclude that firms are getting increasingly innovative over the time period, as observed by the upward trend in Figure 3.2. By looking only at Figure 3.3, one may worry that firms are becoming less capable over time, as the percentage of failed Phase II trials are increasing. In the empirical section, I will demonstrate evidence that these trends are at least partly driven by changing resource allocation strategies following the demand shock driven by Medicare Part D.

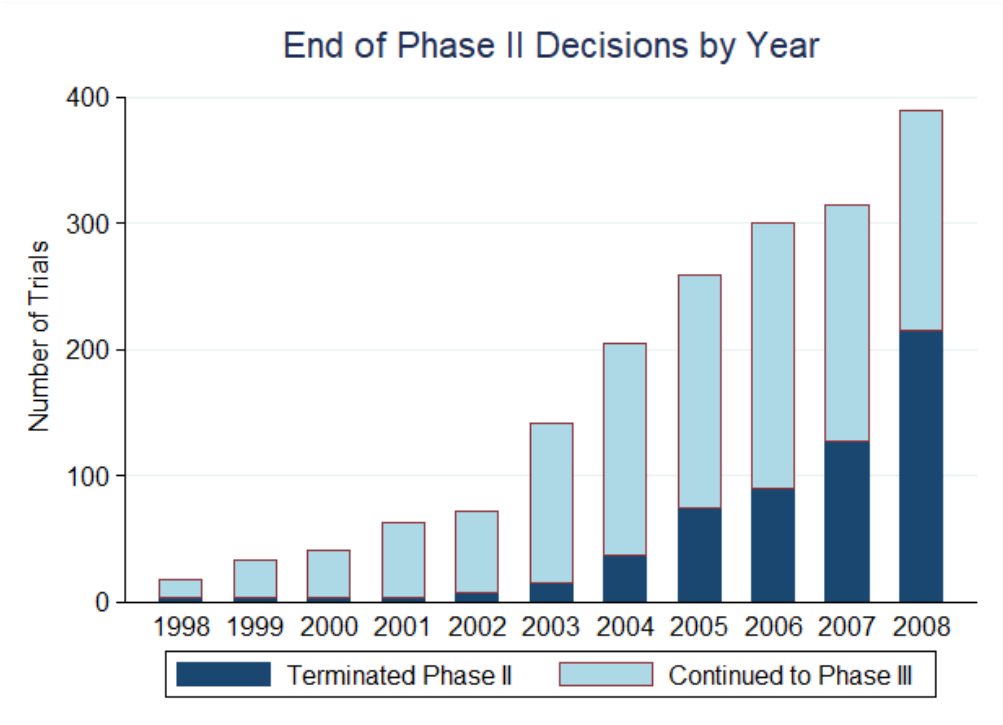

Figure 3.2: This graph illustrates the number of Phase II and Phase III clinical trials for all firms in the sample from 1998-2009.

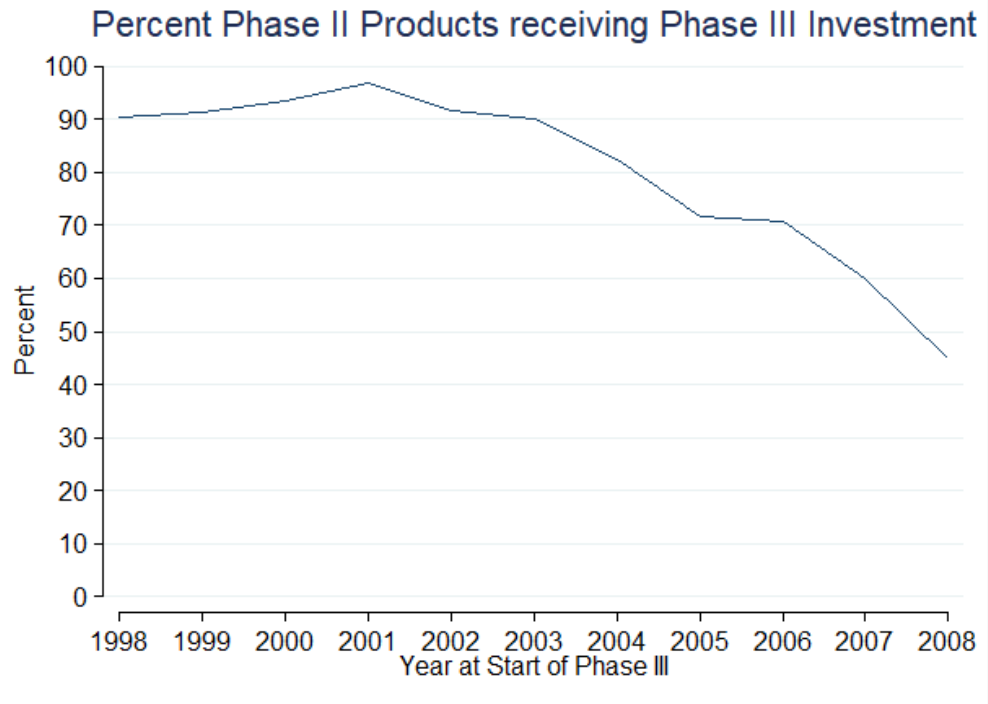

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Figure 3.3: This graph illustrates the proportion of Phase II clinical trials that continue to Phase III over time.

The collected sample spans 1998-2008 and includes companies that were active before the passage of the MMA. I choose to truncate the sample at 2008 because I want to consider only those projects that were begun prior to the announcement of the MMA, and it takes longer than 4 years for firms to take a new drug to go from discovery to Phase III trials. That is, I want to consider only how established firms treat projects already under development in response to this external change. I do not want the results to be confounded with potential changes in the early stage drug-selection strategy. Equally as important, I do not want the results to be confounded with a revenue effect. If, as studies show, pharmaceutical companies experienced increased profits from the implementation of Medicare Part D, then it could be the increase in revenues driving riskier resource allocation decisions. By truncating the period at 2008, I can obtain enough power for statistical inference while mitigating the potential effects of increased revenues. As one would expect, the results become stronger and larger as I extend the time period outward. Additionally, I find that the results are directionally and statistically robust to contractions in the time period. As a limitation, one thing I cannot control for is the possibility of cheaper financing available to firms immediately following the passage of the MMA.

The sample consists of 659 companies that were active (e.g. had a project reach Phase II) in the time period. The largest company in my data is Novartis, with 280 products that reached at least Phase II from 1998-2008, followed by GlaxoSmithKline (260 products) and then Pfizer (230 products). The mean number of products for the firms in this dataset is 26.87. They span 21 different therapeutic groups with the largest being oncology (1,627 products) followed by autoimmune/immunology (673 products). I include small molecules, biologics, and vaccines. I do not include data on the development of any generic products

Table 3.1: Descriptive Statistics
1998-2008

Companies	659
Average Age of Company in 2008	31 years
Median Age of Company in 2008	16.6 years
Divisions	
Average Number of Divisions	2.28
Median Number of Divisions	1
Maximum Number of Divisions	15

This table outlines basic statistics regarding all firms in the sample of data. Data from BioMedTracker.

or biosimilars. Table 3.1 presents additional statistics regarding the sample.

3.4 Identification and Empirical Specification

Past studies on the role of aggregate innovation (measured often in either clinical trial counts or FDA approvals) have often identified an econometric model by using a difference-in-differences analysis. Since Medicare Part D was hypothesized to increase demand for prescription drugs for the elderly, a researcher could categorize indications as either Medicare-heavy (the average age of incidence of the disease was greater than 65) or non-Medicare-heavy (the average age of onset was lower than 65). Then, using a difference-in-differences analysis, they could estimate the effect of the policy on the change in clinical trials for Medicare-heavy indications.

One critique of this method is that the parallel trends assumption may not hold, which is crucial for identification (Besley and Case, 2000). If pharmaceutical firms develop drugs

according to expected demographic trends, as suggested in work by Acemoglu and Linn (2004) and Cerda (2007), then it could be that firms were already beginning to shift resources towards pharmaceuticals for the elderly. Therefore, it is possible that development of drugs for the elderly was already beginning to outpace development for the younger demographic, and one may erroneously believe this was driven by the policy change. Fortunately, the nature of the Medicare Part D legislation provides an alternative way to explore this this issue to mitigate potential concerns about this difference-in-differences identification strategy.

There are two primary groups who purchase drugs. Hospitals purchase drugs to use for inpatient and outpatient treatment. And consumers purchase drugs to use in the home. Since drugs taken in hospitals were already covered under traditional Medicare and Medicare Part B, Medicare Part D only extended coverage to those pharmaceuticals purchased by consumers for home use. Therefore, if firms were organically increasing their rate of development for Medicare drugs external to the incentives provided by Medicare Part D, this should have been changing both in the rate they were developing drugs for hospital use by the elderly, and those designed for in-home use by the elderly.

I can exploit this policy intricacy to create a difference-in-difference-in-differences (or "triple difference") econometric specification. The first difference comes from the time period (pre or post MMA passage). The second difference comes from the difference in development between drugs of which the majority of their users will be elderly United States citizens and those for which this will not be the larger customer segment. I segment these drugs in the data by doing the following: I consider a molecule-indication dyad to be part of the Medicare relevant group if (1) it is not a pediatric, juvenile, or congenital condition (as determined by average age of diagnosis) and (2) it treats a condition unrelated to fertility or child-bearing

and (3) it is not being tested to treat a purely cosmetic issue which would likely not be covered by insurance (eg. "wrinkles", "photodamage") and (4) it is not a tropical disease.[4]

The third difference comes from the intended final purchaser of the drug: the hospital or the patient. One would expect the introduction of Medicare Part D to only incentivize development for pharmaceuticals for which patients are the end purchaser. I use the following criteria to classify the likely end purchaser of the pharmaceutical: I consider a molecule-indication dyad to be developed for patient purchase if (1) the route of administration is either topical or oral (2) the route of administration is injectable but it treats a chronic condition (eg. type 2 diabetes). An example of drugs that would not be in this segment are intravenous fluids and imaging agents.

Past literature in strategy and economics that employs the MMA as an exogenous shock has used a slightly different measurement approach. Using the publicly available Medical Expenditure Panel Survey (MEPS), researchers have scored diseases based on the proportion of survey respondents that reported having the disease and benefiting from Medicare (Blume-Kohout and Sood, 2013; Hermosilla and Wu, 2018). Then, using a difference-in-differences specification, the researchers estimate changes in the DV following the MMA passage as a function of the MMA score (a continuous value between 0 and 1). This approach has some advantages over the one employed here, namely that it identifies Medicare-relevant diseases using a continuous measure, rather than a discrete classifier. However, one downside of this measure is that, due to the nature of the MEPS data, its classification of diseases must remain relatively broad, and many disease will not be included.

[4]Tropical diseases are defined by the World Health Organization as disease that occur solely, or principally in the tropics, and are therefore uncommon in the United States (where Medicare coverage would be relevant). Examples of tropical diseases include malaria, African trypanosomiasis, Chagas disease, and dengue.

Another potential downside of past approaches is the lack of consideration for the types of drugs already covered by Medicare parts A and B. This is particularly true for cancer drugs, which constitute one of the largest therapeutic classes in the pipeline data. The vast majority of cancer treatments were already covered by Medicare Parts A and B prior to the passage of the MMA and remain covered by those programs today (Centers for Medicare and Medicaid Services, 2017). Only a few types of drugs, including anti-nausea and those related to cancer pain are covered by Medicare Part D. Without carefully accounting for the final payer of these drugs, these studies will classify many hospital-based drugs incorrectly by using only the age distribution of patients taking those drugs (which are skewed toward the elderly).

The final downside of past approaches is that pharmaceutical firms may have already been anticipating an increase in the Medicare-relevant population even before the MMA was passed. Acemoglu and Linn (2004) showed that pharmaceutical firms developed drugs based on expectations of future demographics, and so found that there was already a pre-MMA increase in the development of drugs for the elderly. Therefore, the parallel trends assumption of these prior studies may not hold. By incorporating the third difference, I can control for the fact that after the MMA, firms were incentivized to develop *only* those drugs that would be taken by the elderly *and* covered by Medicare Part D. Therefore, I can difference away any trend from an increase in drugs that generally targeted the elderly.

To model these changes in investment decisions, I assume that $Pr(Phase\ III|Phase\ II)$ takes the functional form in Equation 3.2, as is common in the consumer choice literature. Here, the choice could be interpreted as the project manager's (or CEO's) decision to invest in Phase III clinical trials or terminate the project given both the characteristics of the drug

and the state of the competitive environment.

$$\Pr(\text{Phase III}|\text{Phase II}) = \frac{exp(X\beta)}{1 + exp(X\beta)} \tag{3.2}$$

Then using a logit transformation, I can rewrite the model as using a basic triple-difference specification as is presented in Equation 3.3. I will estimate this as a first pass (column 1 of all regression tables). The dependent variable, *Pr(Phase III|Phase II)* is then the difference in the probability of continuing to Phase III for those products affected by the policy change. Empirically, this is estimated using a binary variable equal to 1 if firm r decides to invest in Phase III trials at time t for molecule i intended to treat indication j. It is equal to 0 if at time t (the end of Phase II trials) the firm terminates the development of that product. The parameter Λ represents the logit equation such that everything inside is the score. The variable *Medicare* is equal to 1 if the disease being treated is one that will be subject to any Medicare Part D reimbursement and the variable *Market* is equal to 1 if the drug will be administered at a hospital or a physician's office.

$$\begin{aligned}\Pr(\text{Phase III}|\text{Phase II}) = \Lambda(&\beta_0 + \beta_1 \text{Market}_i + \beta_2 \text{Medicare}_j + \beta_3 \text{post}_t + \beta_4 \text{Market*Medicare}_{ij} \\ &+ \beta_5 \text{Market*post}_{it} + \beta_6 \text{Medicare*post}_{jt} + \beta_7 \text{Market*Medicare*post}_{ijt} \\ &+ \epsilon_{ijrt})\end{aligned} \tag{3.3}$$

While this equation estimates the effects of the policy on investment decisions, one may be worried that it suffers from omitted variable bias. As described in the theoretical framework

above, the decision to invest in Phase III clinical trials depends on a number of factors. Most importantly, it depends on the firm's estimate of its costs of developing the drug, the potential benefits, and its subjective assessment of how likely it is to be approved. Therefore, I want to control for additional factors that may influence a firm's assessment of the project. The full regression specification then becomes

$$\begin{aligned}\Pr(\text{Phase III}|\text{Phase II}) = \Lambda(&\beta_0 + \beta_1 \text{Payer}_i + \beta_2 \text{Medicare}_j + \beta_3 \text{Post}_t + \beta_4 \text{Payer*Medicare}_{ij} \\ &+ \beta_5 \text{Payer*post}_{it} + \beta_6 \text{Medicare*post}_{jt} + \beta_7 \text{Payer*Medicare*post}_{ijt} \\ &+ \gamma X_{ijt} + \mu_t + \delta_r + \tau_j + \epsilon_{ijrt})\end{aligned} \tag{3.4}$$

Here, X is a vector of project covariates, μ_t is a vector of 10 year fixed effects and δ_r is a vector of company fixed effects. The year fixed effects are intended to control for any macro-trends in the way in which companies make decisions about Phase III clinical trials. For example, if techniques for judging the quality of drugs at Phase II get better over time, this may result in all firms pursuing fewer Phase III clinical trials over time. Year fixed effects are one way to keep from conflating these macro-level trends with the effects of the policy.

Company fixed effects are another important control in this estimation given evidence suggesting they are important for measuring firm-specific investment. Past research demonstrates there is considerable heterogeneity among firms in how they make investment decisions in clinical trials. There is a growing literature exploring how willing companies are

to devote resources to products that they have incomplete information about (Arora et al., 2009; Guedj and Scharfstein, 2004; Jekunen, 2014). Many of these differences are a function of company size, funding, and the presence of viable outside options.

The number of Phase III trials initialized by the average firm stays relatively consistent across the time period though hits its maximum just around the passage of the MMA (2003-2004). These statistics are presented in Table 3.2.

Table 3.2: Average Number of Phase III Starts within a Firm
1998-2008

	Year										
	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
All Firms	1.36	1.48	1.5	1.74	1.5	1.76	1.97	1.84	1.78	1.59	1.20
By Level of Diversification Prior to 2003											
Greater than 6 Divs	1.50	1.90	2.40	3.50	2.70	4.50	2.18	2.19	2.12	1.79	1.34
Fewer than 6 Divs	1.29	1.10	1.29	1.22	1.15	1.22	1.67	1.37	1.37	1.30	1.00

This table gives the number of Phase III clinical trial starts by firm size and year. Data from BioMedTracker.

3.5 Results

3.5.1 Implication for Firm Investment Decisions

Figure 3.4 presents a simple bar graph of the total number of Phase III trials by type of drug: those will likely be effected by Medicare Part D ("MMA Related") and those that will not ("non-MMA Related"). On the surface, it appears that the number of Phase III trials for the MMA-related drugs is growing at a faster rate than for the non-MMA drugs, and even surpasses the number by 2007. While this is suggestive of the effects of Medicare Part D, it does not control for the many factors involved in drug development.

In exploring the trends of Phase III investment by drug type and year (either MMA-relevant or Non-MMA relevant) a more nuanced picture emerges. This graph is presented in Figure 3.5. Prior to the creation of Medicare Part D, the probability that a drug in Phase II would continue to Phase III is very high, though slowly decreasing for both groups. However, following the policy change, it appears the transition probability is decreasing at a fast rate for those drugs not subject to potential revenue increases.

Results from estimation of Equations 3.3 and 3.4 are presented in Table 3.3. I find a coefficient on the difference-in-differences measure of 25.70 on the preferred specification (column 4). When calculating the marginal coefficients on the triple difference coefficient as suggested by Ai and Norton (2003), I find this translates into a treatment effect of 44%.[5] This suggests there is a substantial increase in the probability of one of the MMA-related

[5]This triple interaction effect is calculated as the discrete triple difference $\frac{\Delta^3 F(u)}{\Delta x_1 \Delta x_2 \Delta x_3}$ where $F(u) = \frac{1}{1+e^{-\beta_1 x_1+\beta_2 x_2+\beta_3 x_3+\beta_{12} x_1 x_2+\beta_{13} x_1 x_3+\beta_{23} x_2 x_3+\beta_{123} x_1 x_2 x_3}}$. Standard errors are calculated according to Cornelißen and Sonderhof (2009). The treatment effect is nearly identical when assuming a probit functional form or a linear probability model.

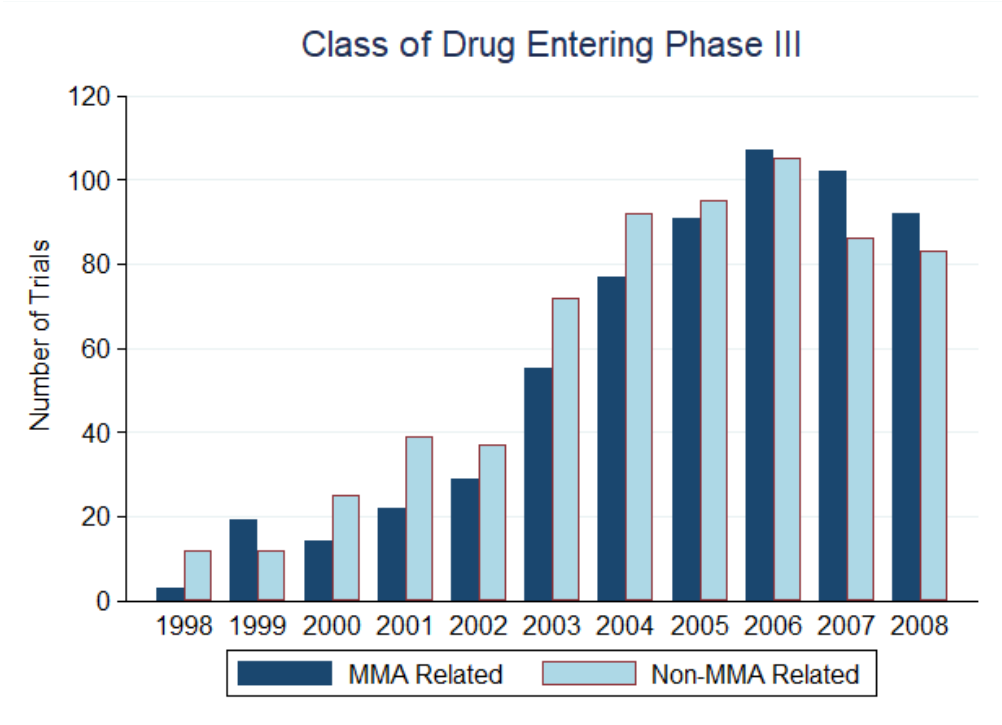

Figure 3.4: This figure presents a simple bar graph of the total number of Phase III trials by type of drug: those will likely be effected by Medicare Part D ("MMA Related") and those that will not ("Non-MMA Related"). A drug that is considered MMA Related has both of the following: the majority of users will be elderly United States citizens and the drug will be available for use in a hospital. I consider a molecule-indication dyad to be part of the Medicare relevant group if (1) it is not a pediatric, juvenile, or congenital condition (as determined by average age of diagnosis) and (2) it treats a condition unrelated to fertility or child-bearing and (3) it is not being tested to treat a purely cosmetic issue which would likely not be covered by insurance (eg. "wrinkles", "photodamage") and (4) it is not a tropical disease. I consider a molecule-indication dyad to be developed for customer purchase (e.g. NOT hospital purchase) if (1) the route of administration is either topical or oral (2) the route of administration is injectible but it treats a chronic condition (e.g. type 2 diabetes).

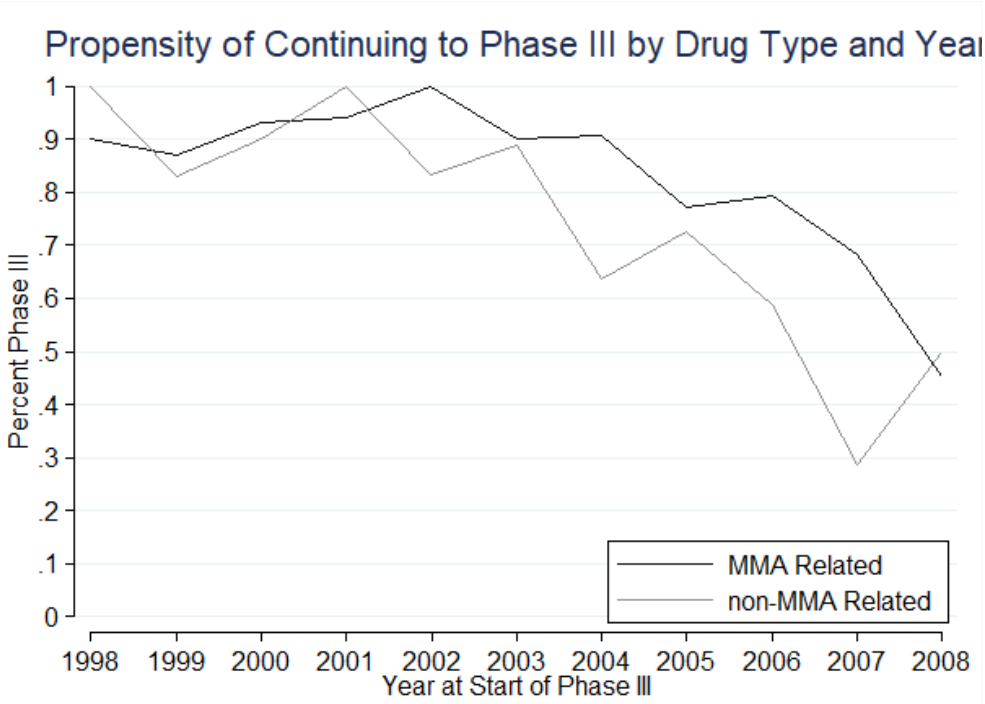

Figure 3.5: This figure presents a line graph of the average transition probability by type of drug: those will likely be effected by Medicare Part D ("MMA Related") and those that will not ("Non-MMA Related"). A drug that is considered MMA Related has both of the following: the majority of users will be elderly United States citizens and the drug will be available for use in a hospital. I consider a molecule-indication dyad to be part of the Medicare relevant group if (1) it is not a pediatric, juvenile, or congenital condition (as determined by average age of diagnosis) and (2) it treats a condition unrelated to fertility or child-bearing and (3) it is not being tested to treat a purely cosmetic issue which would likely not be covered by insurance (eg. "wrinkles", "photodamage") and (4) it is not a tropical disease. I consider a molecule-indication dyad to be developed for customer purchase (e.g. NOT hospital purchase) if (1) the route of administration is either topical or oral (2) the route of administration is injectible but it treats a chronic condition (e.g. type 2 diabetes).

drugs continuing on to Phase III following the policy change. The coefficient is significant at the 1% level under robust standard errors, clustered at the firm level (Bertrand et al., 2004). Additionally, the relevant coefficient in all specifications is positive and highly significant and is robust under contractions in the time period considered (see Appendix Table B1). This provides evidence that firms do change their later-stage resource allocation criteria in response to changes in expected demand.

3.5.2 Implication for Investment Performance

One implication of the framework developed initially is that products do not continue to Phase III for one of two reasons: (1) the firm's belief about the probability of approval is low or (2) the expected revenue that the product will generate is not high enough. Because all that has changed is the expected revenue for the firm (these products were already in development when the law was passed) and one can assume that the firm's beliefs about the probability of approval did not systematically change for any of the drugs in development following the passage of the MMA, it is likely that the relevant case is (2). This implies all else equal, one should see a decrease in the probability of approval for these drugs following the passage of the MMA. This would then imply that a firm is taking a bigger risk in their innovation pursuits and possibly allocating more resources to lower quality products.

Consider Figure 3.6, which illustrates the probability of FDA approval, given investment in Phase III clinical trials, over the time period. In general, the probability of being approved by the FDA decreases slightly, and only hovers above 50% before 2002. This underscores again how risky an investment Phase III trials can be for a firm. In breaking these out

Table 3.3: Impact of Increased Demand on Change in Probability of Investment in Phase III Clinical Trials
Logit DDD Model

Dependent Variable: Indicator equal to 1 if Received Phase III Investment				
	(1)	**(2)**	**(3)**	**(4)**
Medicare*Payer*Post	12.07***	11.24***	11.83***	25.70***
	(0.98)	(1.13)	(1.15)	(1.94)
Medicare	0.575	0.529	0.758	0.882
	(0.67)	(0.69)	(0.70)	(0.95)
Payer	12.70***	11.95***	12.82***	26.80***
	(0.78)	(0.89)	(0.95)	(1.83)
Post	-1.954**	-0.913	-1.284	-0.901
	(0.81)	(1.06)	(1.06)	(1.27)
Payer*Post	-12.00***	-11.11***	-11.69***	-25.84***
	(0.89)	(1.04)	(1.06)	(1.95)
Medicare*Post	-12.36***	-11.56***	-12.31***	-25.58***
	(0.79)	(0.97)	(1.00)	(1.74)
Medicare*Payer	-12.36***	-11.56***	-12.31***	-59.15***
	(0.81)	(0.97)	(0.99)	(3.41)
Year FE	N	Y	Y	Y
Drug Classification FE	N	N	Y	Y
Company FE	N	N	N	Y
Observations	1825	1779	1773	1365
R^2	0.11	0.40	0.47	0.61

The dependent variable is equal to 1 if a product began Phase III clinical trials given that it completed Phase II clinical trials. The variable Medicare is an indicator equal to 1 if the disease being treated is one that will be subject to any Medicare Part D reimbursement. This variable Payer is an indication equal to 1 if the drug is designed for the pharmacy, rather than hospital, market. The variable Post is an indicator equal to 1 if the Phase II trial ends after November 23, 2003, the date in which the MMA was signed into law. Note that Medicare Part D did not go into effect until January 1, 2006. Robust standard errors in parentheses and clustered at firm level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

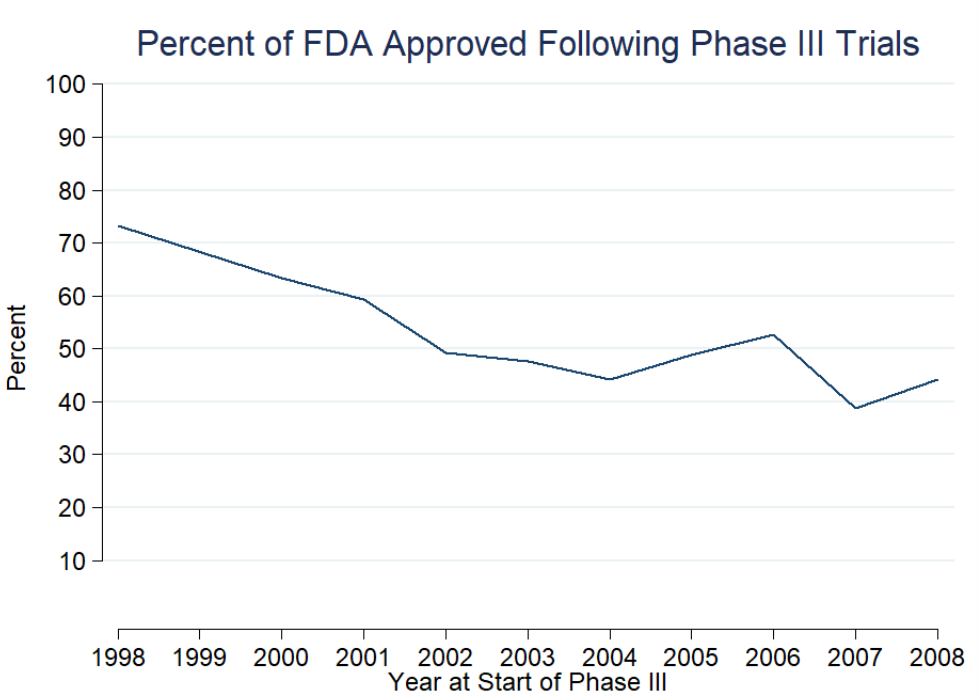

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Figure 3.6: The Probability of FDA Approval given Phase III Investment.

into MMA-relevant drugs and non-MMA relevant drugs, it is evident the proportion of approved drugs begins skewing more towards the MMA market following the passage of the law (Figure 3.7). This could be seen as confirmation of the common finding within the economics literature that as markets grow, the number of innovations catering to that market grows as well.

To test my hypothesis, I subset my sample to only those drugs that continued to Phase III trials. The dependent variable, *Pr(Approved|Phase III)*, then becomes the change in the probability of FDA approval, and is estimated using an indicator equal to 1 if the product was approved by the FDA and 0 if it was not. I then estimate the version of the triple-difference regression presented in Equation 3.5.

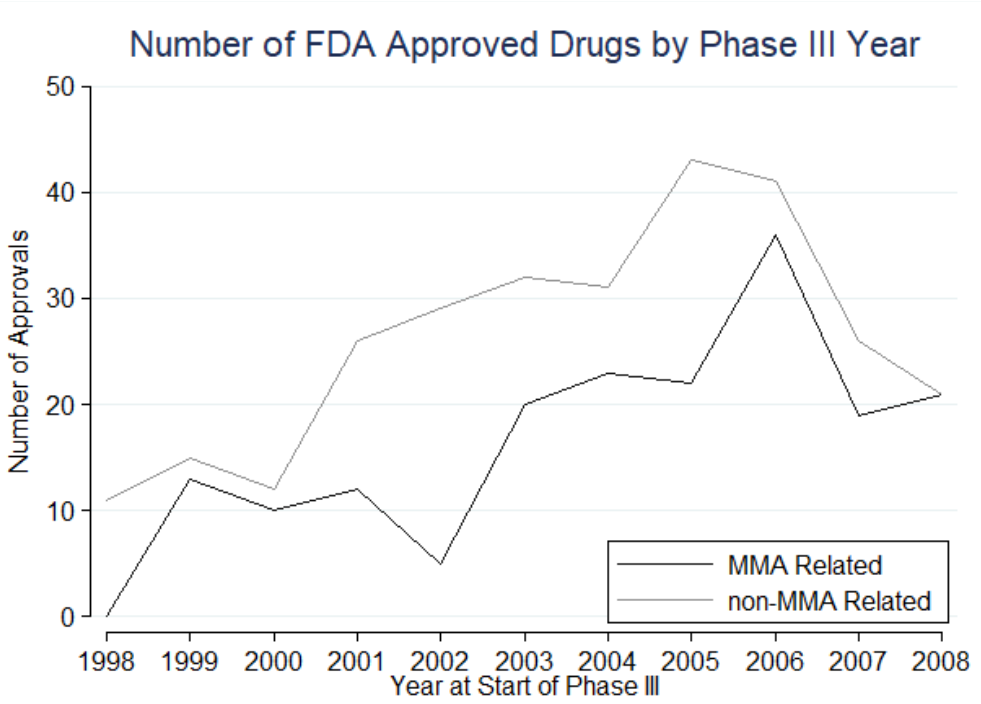

Figure 3.7: This figure presents a line graph of the number of FDA approved drugs by type : those will likely be effected by Medicare Part D ("MMA Related") and those that will not ("non-MMA Related"). A drug that is considered MMA Related has both of the following: the majority of users will be elderly United States citizens and the drug will be available for use in a hospital. I consider a molecule-indication dyad to be part of the Medicare relevant group if (1) it is not a pediatric, juvenile, or congenital condition (as determined by average age of diagnosis) and (2) it treats a condition unrelated to fertility or child-bearing and (3) it is not being tested to treat a purely cosmetic issue which would likely not be covered by insurance (eg. "wrinkles", "photodamage") and (4) it is not a tropical disease. I consider a molecule-indication dyad to be developed for customer purchase (e.g. NOT hospital purchase) if (1) the route of administration is either topical or oral (2) the route of administration is injectible but it treats a chronic condition (e.g. type 2 diabetes).

$$\begin{aligned}\Pr(\text{Approved}|\text{Phase III}) = \Lambda(&\beta_0 + \beta_1 \text{Payer}_i + \beta_2 \text{Medicare}_j + \beta_3 \text{Post} + \beta_4 \text{Payer*Medicare}_{ij} \\ &+ \beta_5 \text{Payer*post}_{it} + \beta_6 \text{Medicare*post}_{jt} + \beta_7 \text{Payer*Medicare*post}_{ijt} \\ &+ \gamma X_{ijt} + \mu_t + \delta_r + \epsilon_{ijrt})\end{aligned} \tag{3.5}$$

The results of this estimate are presented in Table 3.4. The coefficient on the difference-in-differences estimator is negative and statistically significant at the 1% level in all specifications and is robust under contractions in the time period considered (see Appendix Table B2). This lends support for the hypothesis that firms were investing in marginally lower quality drugs following the policy change, because these drugs were much less likely to be approved. When calculating the marginal effect, I find an effect of -0.47, implying a substantial decrease in the probability of approval for those drugs moving to Phase III.

These results provide a novel look at how sudden changes in demand may actually lead firms to invest in less promising technologies. That is, the empirical evidence suggests the introduction of the policy lead to the substitution away from possibly higher quality products toward lower quality products (where quality is still defined here as the probability that the drug will be approved). This can be seen by the increase is probability of undertaking expensive advanced trials, followed by the decrease in the probability of receiving approval to market the product.

As an additional test of the hypothesis that on average, lower quality or more marginally beneficial products in this class were being pursued, one can look at the trajectory of those

Table 3.4: Impact of Increased Demand on Change in Probability of Approval Following Investment in Phase III Clinical Trials
Logit Model

Dependent Variable: Indicator equal to 1 if Received FDA Approval				
	(1)	**(2)**	**(3)**	**(4)**
Medicare*Payer*Post	-2.075**	-2.032**	-2.049**	-3.134**
	(1.03)	(1.01)	(0.98)	(1.48)
Medicare	-1.203**	-1.278**	-1.024*	-1.176
	(0.58)	(0.60)	(0.61)	(0.96)
Payer	-1.764*	-1.707*	-1.505*	-2.290
	(0.97)	(0.97)	(0.90)	(1.48)
Post	-1.090*	-0.881	-1.177	-1.258
	(0.61)	(0.76)	(0.81)	(1.05)
Payer*Post	2.172**	2.140**	2.242**	3.111**
	(1.05)	(1.04)	(1.00)	(1.51)
Medicare*Post	0.732	0.838	0.838	0.969
	(0.60)	(0.59)	(0.61)	(0.77)
Medicare*Payer	1.728*	1.668*	1.561*	2.415*
	(0.95)	(0.93)	(0.84)	(1.37)
Year FE	N	Y	Y	Y
Drug Classification FE	N	Y	Y	Y
Company FE	N	N	N	Y
Observations	1265	1265	1265	939
R^2	0.02	0.48	0.52	0.58

The dependent variable is equal to 1 if a product was approved by the FDA and 0 if it was terminated during or after Phase III clinical trials. The variable Medicare is an indicator equal to 1 if the disease being treated is one that will be subject to any Medicare Part D reimbursement. This variable Payer is an indication equal to 1 if the drug is designed for the pharmacy, rather than hospital, market. The variable Post is an indicator equal to 1 if the Phase II trial ends after November 23, 2003, the date in which the MMA was signed into law. Note that Medicare Part D did not go into effect until January 1, 2006. Robust standard errors in parentheses and clustered at firm level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

products that were actually approved following the MMA. Above, I had simplified the approval process by suggesting that firms that achieve good results in Phase III will submit an NDA to the FDA and then, following the FDA's review of the data, receive approval for that indication. However, this relatively smooth process of moving from the end of clinical trials to approval does not always happen. In addition, even if the drug is approved for some subset of an indication, it may not be as broad as the firm had initially hoped for when they filed the NDA. In the previous analyses, I had considered *any* approval related to that molecule-indication to be a successful approval. This could have been overstating a firm's success because their drug may have actually been approved for a much less desirable market than they had hoped for (for example, as a third line, rather than a first line, treatment for cancer).

While I do not have data on how the exact nature of FDA approval differs from the firm's first drug or biologic application, I will explore the following as a possible proxy. I will rely on the fact that the FDA maintains a strict review timeline process as directed by the Prescription Drug User Fee Act (PDUFA). PDUFA, passed in 1992, allowed the FDA to collect application fees from pharmaceutical firms in exchange for meeting review timeline benchmarks. Under PDUFA, the FDA has ten months to review an NDA or BLA (six months if the product received priority review).

If a firm's application is not approved by the FDA after the set timeline, the firm will receive a Complete Response Letter (CRL) from the FDA.[6] In this case, the firm has the option to redo some clinical trials and collect new data that will satisfy the concerns of the

[6]The FDA did not begin using CRLs for small molecules until 2008, to replace what had previously been either "Approvable" letters or "Non-approvable" letters. They had been standard for biologics since 1998.

FDA. If the firm or the FDA determines the deficiencies are insurmountable, the firm will withdraw the NDA and terminate the project. According to my interviews with industry experts, even if a firm is able to get an approval for this drug, it will often be for a smaller subset of an indication, or for a population that does not respond to anything else on the market. Sometimes a firm will receive many CRLs for one drug, as they keep repeating the process of collecting new data and resubmitting the application. While not only harmful to firm value (which usually declines with every CRL) this is incredibly costly in time and resources. It can cost pharmaceutical firms up to $8 million for every extra *day* that a drug is in Phase III clinical trials (Miseta, 2013), so having to redesign and execute new trials is an unfortunate outcome, even if the firm does eventually receive FDA approval.

For my identification strategy in this analysis, I will assume that "lower quality" NDAs will ultimately take longer to get eventual FDA approval, likely because it will require more back-and-forth with the FDA to reach a consensus regarding for who the drug can be approved. I can do this by collecting information on the first filing date of the NDA and the eventual date of approval. If it is true that "lower quality" drugs targeting the Medicare segment were being taken further in clinical trials, it may also be the case that even those that were approved received designations for indications that were not as broad as originally intended. While the FDA can grant itself review extensions, it is unlikely that they will systematically grant themselves review extensions primarily on the MMA-relevant class post 2003.

The model I use is similar to that presented in Equations 3.4 and 3.5, except that I consider only approved products and explore the time it took (in days) to move from the filing of an NDA to FDA approval. The econometric equation I will estimate is presented

below. Since the dependent variable is continuous, I use a standard OLS difference-in-differences style regression presented in Equation 3.6.

$$\begin{aligned}\text{Log(Days to Approval)} = \beta_0 &+ \beta_1 \text{Payer}_i + \beta_2 \text{Medicare}_j + \beta_3 \text{Post} + \beta_4 \text{Payer*Medicare}_{ij} \\ &+ \beta_5 \text{Payer*post}_{it} + \beta_6 \text{Medicare*post}_{jt} + \beta_7 \text{Payer*Medicare*post}_{ijt} \\ &+ \gamma X_{ijt} + \mu_t + \epsilon_{ijrt}\end{aligned} \tag{3.6}$$

Results are presented in Table 3.5. The positive and statistically significant coefficient (though only at the 5% significance level) in all specifications suggest that firms pursuing MMA-relevant drugs following Medicare expansion spent considerably more time under review by the FDA. This provides some evidence that even for products that were approved in this class, they may have not received the most desirable designations.[7]

3.6 Organizational Structure and Resource Allocation

In this analysis, I test Hypothesis 3 by reconducting the above analyses on a sample of firms that are more diversified and a sample of less diversified firms. A crucial component of this analysis is in deciding a cutoff for in which to classify firms as more or less diversified. As possibilities, I consider (1) those firms in the top 90% in number of therapeutic divisions in which they have been active and (2) those firms with a presence in multiple states and/or countries. While the results are robust to both methods, I will present results for method

[7]It is also possible that this result suggests that firms were more careless with their applications (perhaps because they were hoping to beat competitors to market?)

Table 3.5: Impact of Demand Shock on Change in Time Spent Under FDA Review for Approved Products

Dependent Variable: Log(Number of Days from Application to Approval)			
	(1)	**(2)**	**(3)**
Medicare*Payer*Post	0.988**	1.030**	0.940**
	(0.40)	(0.41)	(0.40)
Medicare	0.328*	0.254	0.219
	(0.18)	(0.18)	(0.18)
Payer	0.855**	0.899**	0.739**
	(0.36)	(0.38)	(0.37)
Payer*post	-1.127***	-1.204***	-1.137***
	(0.38)	(0.40)	(0.39)
Medicare*Post	-0.413**	-0.331	-0.354*
	(0.20)	(0.20)	(0.20)
Medicare*Payer	-0.838**	-0.843**	-0.723*
	(0.37)	(0.38)	(0.38)
post	0.336*	-0.0138	0.0168
	(0.18)	(0.20)	(0.19)
Therapeutic Group	Y	Y	Y
Approval Year FE	N	Y	Y
Drug Classification FE	N	N	Y
Observations	1024	1024	1024
R^2	0.145	0.227	0.249

The dependent variable measured in days between NDA submission and FDA approval. The number of observations is lower than in Table 3.4 because not all approvals had retrievable NDA dates. The variable Medicare is an indicator equal to 1 if the disease being treated is one that will be subject to any Medicare Part D reimbursement. This variable Payer is an indication equal to 1 if the drug is designed for the pharmacy, rather than hospital, market. The variable Post is an indicator equal to 1 if the Phase II trial ends after November 23, 2003, the date in which the MMA was signed into law. Note that Medicare Part D did not go into effect until January 1, 2006. Robust standard errors in parentheses and clustered at firm level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Table 3.6: List of Companies Active in Highest Number of Therapeutic Classes 1998-2003

Company Name	Number of Active Divisions prior to 2003
Abbott Laboratories	6
Allergan	9
Astellas Pharma	7
AstraZeneca	9
Bausch + Lomb	8
Bristol-Myers Squibb	6
DRI Capital Inc.	9
Eli Lilly	7
Endo International	6
GlaxoSmithKline	10
Johnson & Johnson	10
Merck & Co.	10
Merck KGaA	7
Novartis	9
Otsuka Holdings	7
Pfizer	9
Roche	10
Sanofi	10

This table lists all companies flagged as "highly diversified" in the analyses and gives the number of therapeutic divisions in which the firm was actively developing products prior to 2003. Data are from BioMedTracker.

(1) in Table 3.7. The list of companies classified as most diversified by this method (6 or more divisions) are listed in Table 3.6.

After splitting the sample and rerunning the triple-difference regressions separately, I find compelling support for Hypothesis 3. The coefficient on the relevant coefficient, *Medicare*Payer*Post* is positive and significant only for that sample consisting of firms that are arguable more centralized and focus on fewer therapeutic classes than the sample with the large, diversified/decentralized firms.

Table 3.7: Impact of Increased Demand on Change in Probability of Investment in Phase III Clinical Trials and Probability of Approval Logit Model

Dependent Variable: Indicator equal to 1 if Received Phase III Investment

	Fewer than 6 Divisions		6 or More Divisions	
	(1)	**(2)**	**(3)**	**(4)**
Medicare*Payer*Post	12.95***	27.11***	-1.106	-1.351
	(1.49)	(2.32)	(1.58)	(1.85)
Year FE	Y	Y	Y	Y
Drug Classification FE	N	Y	N	Y
Company FE	N	Y	N	Y
Observations	739	739	1001	1001

Dependent Variable: Indicator equal to 1 if Received FDA Approval

	Fewer than 6 Divisions		6 or More Divisions	
	(1)	**(2)**	**(3)**	**(4)**
Medicare*Payer*Post	-3.026*	-17.40***	-1.620	-2.407
	(1.68)	(2.09)	(1.62)	(1.72)
Year FE	Y	Y	Y	Y
Drug Classification FE	N	Y	N	Y
Company FE	N	Y	N	Y
Observations	505	342	760	587

The dependent variable is equal to 1 if a product began Phase III clinical trials given that it completed Phase II clinical trials. The variable Medicare is an indicator equal to 1 if the disease being treated is one that will be subject to any Medicare Part D reimbursement. This variable Payer is an indication equal to 1 if the drug is designed for the pharmacy, rather than hospital, market. The variable Post is an indicator equal to 1 if the Phase II trial ends after November 23, 2003, the date in which the MMA was signed into law. Note that Medicare Part D did not go into effect until January 1, 2006. Robust standard errors in parentheses and clustered at firm level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

There is some reason to be concerned that the changing nature of Medicare reimbursement for oncology services at this time may be biasing the results. Because many all oncology services will be classified as "Non-MMA", it may be that part of the move away from Non-MMA therapies toward MMA therapies may be mostly driven by less enthusiasm for investing in Phase III clinical trials for cancer. After dropping all oncology projects and re-estimating Equations 3.3 through 3.6, I find that the direction and statistical significance of the results stay unaltered. These results are reported in Appendix Tables B3-B5.

3.7 Discussion

This study explores how a firm's investment strategy responds immediately following changing expectations in future demand. It differs from past studies in the literature in that it focuses not on the direct effect on the quantity of products reaching a market but rather on how it changes the allocation of resources across an R&D department. When exploring these effects in the aggregate, I find that when expectations about future demand suddenly shift, firms increase their investments in products that are less likely to be approved, all else equal. Using a standard economic model of investment decisions, I demonstrate why this change in criteria may actually result in fewer approved products (or more "failed" products) as firms substitute resources away from higher quality products to lower quality ones. This hypothesis is substantiated by my empirical results. Empirically, I find that firms increase their propensity to invest in a certain segment of products after they believe there will be an increase in demand from that segment. Additional empirical evidence demonstrates that because of this, firms have lower total rates of approval than they would have in the

counter-factual scenario. This may be one reason for decreased efficiency in pharmaceutical R&D.

As an additional contribution, this study contributes to work on firm structure, decentralization, and product diversification and furthers the conversation on how organizational structure may lead to differing strategies following a positive shock. While there are known benefits to decentralization, this study addresses some of the downsides of this structure when there is a sudden change in priorities. While I observe smaller, centralized firms reallocating resources towards the newly higher valued products, I find no evidence that their larger counterparts were able to do the same.

One limitation of this study is that I cannot address whether or not this change in behavior is either "good" strategy or "bad" strategy. There are reasons to believe that firms were better off following the policy despite the effects on innovation. This is because even if a firm brings fewer products to market following a change in criteria, those products that they do develop may bring in more revenue, and therefore actually increase returns to the firm. Duggan and Scott Morton (2010) find some evidence that revenues grew for those Medicare-intensive drugs already on the market, however, there has been no attempts to measure the causal effect of Medicare Part D on total value captured by the firm. However, like much of the capital allocation literature, understanding the causal nature of allocation and firm performance is outside the scope of this study.

However, the empirical results suggest one reason firms may not have behaved optimally. By investing in Phase III trials for riskier molecules, firms were tying up scarce non-monetary resources (lab space, scientists) for potentially more successful molecules. One industry publication stresses the importance of proper resource allocation by noting that "If doomed

drugs can dodge Phase III, you save that money to reinvest in other potentially more successful compounds" (Lam, 2004). From a consumer welfare perspective, the interpretation is also mixed. On the one hand, these analyses suggest consumers may have had fewer new therapies available following the passage of the MMA. On the other hand, because these resources were being devoted to more novel innovations (though using a very conservative definition of novel), some fraction of consumers may have indeed benefitted.

This study merely scratches the surface of how policy shocks may impact a firm's innovation strategy. While I provide evidence that it may effect a firm's resource allocations in the short run, these changes may also affect the future trajectory of innovation, organizational learning and long run firm performance. I will leave these issues to future research.

Chapter 4 Old Wine in a New Bottle: Market Effects of Product Repurposing

4.1 Introduction

The COVID-19 pandemic has drawn increased attention to how pharmaceuticals are discovered, developed and brought to market. As firms and government agencies try to quickly develop an effective therapy, one strategy is receiving fresh attention: that of drug repurposing. Drug repurposing (or repositioning, reprofiling, or re-tasking) is being pursued in this pandemic because it is both quicker and less risky than the traditional drug discovery process. Repurposing involves taking a drug that is already approved or has been heavily studied for another disease (or "indication") and testing its therapeutic abilities in COVID-19 patients. So far, over twenty compounds that have already completed Phase I clinical trials have been identified as potential therapies, and many of the drugs being considered as possible candidates are those already approved for other indications (Andersen et al., 2020; Shah et al., 2020). These include older drugs that have already penetrated the over-the-counter market, such as the active compound in the heartburn drug Pepcid (Borrell, 2020). However, even recently developed drugs, including the Ebola vaccine, are being explored for

their potential to treat the disease (Niarchos, 2020). This differs from developing a drug "from scratch" in that the organization can bypass the discovery and preclinical process and often the human safety trials. By repurposing an already approved drug, an organization and shave years off the drug development process and save millions (to billions) of dollars.

The repurposing of drugs has often been a function of serendipity. This was true in the case of Thalidomide, the notorious drug once used to treat morning sickness in expectant mothers.[1] Decades later, it was found to be an effective treatment of multiple myeloma and later, leprosy (Oprea and Mestres, 2012; Singhal et al., 1999). Oftentimes, successful repurposing can be a revenue boon for the developing firm, as was the case with Viagra, which was initially approved to treat angina (Novac, 2013). However, repurposing old, off-patent drugs to treat new diseases can also benefit consumers as well. If an off-patent drug is repositioned to treat a new disease, the developing firm cannot charge monopoly prices for its use. So given the high prices of pharmaceutical drugs the possibility of drug repurposing as a welfare-enhancing strategy receives considerable attention from public policy scholars and consumer advocacy groups. Indeed, there is currently an expanding amount of public awareness about the possibility that new cures could be found in already established drugs (Fedson and Rordam, 2015; Harris, 2018). Following recent outbreaks of deadly viruses, there has been increased effort from the scientific community to test old drugs for treating respiratory viruses (BenevolentAI, 2020; Mullin, 2014; Senanayake, 2020). Academic institutions have also taken an interest in this endeavor (Oprea et al., 2011). The Broad institute at MIT has created specific resources to facilitate the discovery of new uses for old drugs.

[1]Thalidomide was heavily marketed for treatment of morning sickness in the 1950s though was never FDA approved for treatment. Once it was discovered to cause severe birth defects, this led to increased regulation of the pharmaceutical industry resulting in the current regulatory process present in the United States today.

Recently, scientists there tested over 4,000 drugs on human cancer cells and determined that nearly 50 had undiscovered anti-cancer properties (Corsello et al., 2020).

One scenario that has received less attention by journalists and academics is the repurposing of a drug that is still under patent protection. There are several reasons why a pharmaceutical company may actively seek to repurpose a branded, on-patent drug for a new indication. With the high cost of bringing a brand new molecule to market and evidence of slowing R&D productivity in traditional drug discovery (Pammolli et al., 2011), repurposing an already approved drug for a new market can be cost efficient while simultaneously benefitting underserved patient populations. Furthermore, because the molecule has already been deemed safe and its pharmacokinetic properties well understood, firms can benefit from shorter and cheaper Phase I and II clinical trials, as all the firm must do is prove the drug's effectiveness in treating the new disease (Pushpakom et al., 2019). This is considered a winning proposition for both suppliers and patients. Finally, it is considered an effective lifecycle management strategy for a pharmaceutical company. With the additional approval comes three additional years of exclusivity for the drug, making it one of the most pursued line extension strategies (Tiene, 2017).

While there are clear revenue benefits to a firm that repurposes a patented drug, there is also the possibility further benefits, in the form of spillover demand into a drug's other approved indications. This question of the market effects of product expansion has important implications for a firm and a competitor's strategy. There are obvious, and heavily studied, reasons why a company may want to differentiate a product by increasing the number of functions that product can perform. By doing so, the product's value may increase to the initial consumers who value both functions and the product will attract new consumers

who especially value the second function. However, this study differs from other product proliferation studies in that it will explore the effects of a product expanding into a new market that is orthogonal to the initial one. That is, I will explore products for which its repurposing for a different use will likely not increase the value to the consumers using the product for the initial use, though it will allow the firm to capture demand from a new market. This would be akin to, for example, a firm expanding a product's ability to be used in China after being developed initially for use in the United States. While this change would likely not increase the value of the product to U.S consumers, this increase in aggregate demand for the product could impact demand in the United States through indirect channels.

This chapter will look explicitly at the case of repurposing of oncology drugs for other uses within oncology. Focusing on this therapeutic class is ideal for this project due to the amount of repurposing of patent protected drugs that occurs within this group. In 2014, over half of marketed oncology drugs treated multiple indications. It is predicted that by the end of 2020, the number of oncology drugs treating multiple indications will be three times greater than those approved for one indication (Mestre-Ferrandiz et al., 2015). And while many of the headline stories in drug repurposing focus on one drug that may treat two very different diseases, most repurposing occurs among indications that are similar therapeutically (Baker et al., 2018). Importantly, these approvals for new cancers are often granted sequentially, allowing us to observe the sales of drugs competing in that disease both before a competitor receives a new approved disease and afterward. Furthermore, there have been calls for companies to consider exploring their repurposing opportunities in cancer given the limited therapies available and the higher likelihood that one drug can effectively treat

several different tumor types (Gupta et al., 2013; Pantziarka et al., 2014).

The repurposing of oncology drugs to treat new types of cancer may result in changes to demand patterns for not just the new indication but also among the indications for which the drug was previously approved. If I observe changes to demand in the market which had no new entrants, then repurposing may also hold strategic implications for a firm and its competitors. This will further the conversation on the strategic benefits of product proliferation and this specific case of drug repurposing. In this study, I find strong evidence that as firms find new approvable indications for one cancer drug, it leads to increased sales of that drug for treatment of the initially improved indication. Furthermore, I find that competing drugs treating the initial disease and are in the same chemical subgroup also receive a small but positive boost in demand following their competitor's repurposing. I do not find evidence that these demand spillovers are a result of increased advertising or decreased pricing by close competitors as they anticipate the effects of repurposing. Further analysis suggests that these are gains from business stealing of competitors in other chemical subgroups. These findings align with theories of information and advertising spillovers.

4.2 Prior Literature and Regulatory Setting

4.2.1 Product expansion, repurposing and business stealing

This article contributes to the literatures on product expansion, business stealing, and pharmaceutical repurposing. Questions regarding the role of product expansion on firm and competitor outcomes have been explored to some extent in the product proliferation litera-

ture. Much of this literature is interested in how product strategies impact firm performance. In particular, this study has similarities with those exploring the effects of within-industry product proliferation – the case where a firm sells two products to different submarkets within the same industry (Barroso and Giarratana, 2013). For example, Siggelkow (2003) explores the effects of product diversification within one industry. In looking at the performance of mutual fund families, he finds that there are performance benefits to those firms that "focus" on one fund category. He postulates that one reason for this could be that focused companies attract people with similar interests and values therefore leading to a well-defined company culture and image.

However, in a different study exploring technology start-ups Stern and Henderson (2004) find that those that diversify the products they offer within a business unit tend to fare better so long as the competitive landscape remains relatively stable. They argue that these benefits are likely due to learning effects and experience accumulation as employees explore different approaches and master new skills that are crucial to survive in a high-tech landscape. While early research has explored the benefits of product proliferation as it relates to economies of scope (Markides and Williamson, 1994) or risk-reduction (Hill and Hansen, 1991), more recent studies in this literature have explored issues of within-industry diversification from the lens of resource development and managerial cognition. (One noted exception is Li and Greenwood (2004), who explore how increased diversification may facilitate multi-market contact and collusion among firms, leading to increased performance as measured by rate of return.) However, there is limited research exploring if and how product proliferation can impact consumer demand. This is an important and overlooked potential mechanism for which product proliferation may lead to improved firm performance.

This chapter will also add to the literature on firm competition and business stealing. When a new product successfully enters the market, that product has captured market share by either expanding demand (Cao et al., 2018), stealing demand from competitors (Bernheim and Madsen, 2017), or some combination of the two (Davis, 2006). In the industrial organization literature, entry that leads to business stealing is considered to be socially inefficient and has therefore generated a long and productive research agenda (Mankiw and Whinston, 1986). This research suggests that industries likely to have inefficiently excessive entry are those with large fixed costs to entry (including costly R&D) and low marginal costs (Berry and Waldfogel, 1999) and products that are somewhat substitutable.

Much of this empirical literature in product business stealing explores the entry of firms creating (somewhat) homogenous goods including radio stations and movie theaters. Initially, this requirement may seem ill-suited to describe the cancer drug market, for which competitors must show improved safety and efficacy over the current therapy protocol to receive FDA approval. However, I assert that the cancer drug market is more like the radio stations market, the setting of the influential empirical study of business stealing by Berry and Waldfogel (1999).

Like radio stations, cancer patients can only consume one drug at a time and while there is some diversification among radio stations (including the types of music played or the quality of the hosts) they are likely not substantial differences in preference orderings for most consumers, making them largely substitutable. And while the narrative offered by drug developers that there are large differences in safety and efficacy among the different cancer therapies, there is increasing concern among industry experts that the increased efficacies of each new drug are too marginal to make them significantly superior to their counterparts

(Hanahan, 2014; Leaf, 2014; Prasad, 2020). Recently, oncologists themselves have argued that new entrants to the cancer market offer limited benefits. For example, when Fojo et al. (2014) survey 71 recently approved drugs treating solid tumors, they find a median improvement in longevity of only 2.1 months. And Raza (2019) has argued that the illusion of improved rates of cancer survival over the past few decades are due to earlier detection, rather than improved therapies.

This chapter also contributes to the literature on the competitive effects of drug repurposing.[2] Presently, much of the academic literature on drug repurposing considers the case where the drug to be repurposed is off-patent, and therefore unable to acquire monopoly rents due competition from generic drugs. Because there is little incentive for pharmaceutical companies to explore new indications for off-patent drugs, economists and public policy scholar have debated ways to encourage scientists and drug developers to undertake this sort of welfare-enhancing research (Walson, 2012). The interested reader should refer to Roin (2014) for an in-depth analysis of this "public policy failure" (Roin, 2014, p. 40).

This study is one of the first studies that, to my knowledge, explores the effects of repurposing drugs that are still under patent protection. In this case, many of the benefits derived from the reduced R&D risk of repurposing apply to this situation as well. Several scholars within the industry have stressed the substantial costs and benefits to the firm that chooses to focus its R&D efforts on repurposing already approved and/or heavily studied drugs for new indications is a strategy that carries less risk that studying de novo molecules (Ashburn and Thor, 2004; Novac, 2013). By exploring other opportunities for approved

[2]In the literature, drug repurposing can refer to the research of new indications for drugs that are either already approved or failed in late stage (efficacy based) clinical trials. Here, I will only consider the repurposing of drugs that have already been FDA approved.

drugs, companies can skip the discovery and preclinical phase of R&D, saving hundreds of millions of dollars (Sahoo, 2007). Furthermore, companies can harness already obtained knowledge about the safety of the drug and its efficacy in a different disease, potentially lowering the likelihood of a late-stage failure. However, there is no research yet that explores the spillover and competitive effects of drug repurposing which could provide post-approval benefits to the firm as well.

4.2.2 Regulatory environment in the U.S

The current regulatory environment faced by pharmaceutical companies in the United States can be traced to the passage of the Drug Price Competition and Patent Term Restoration Act in 1984, informally known as the "Hatch-Waxman" Act. The Act purported to provide a delicate balance between easing the pathway for generic entry and continuing to provide incentives for innovation (Grabowski, 2007). Under Hatch-Waxman, upon approval the FDA grants each new drug regulatory protection lasting for five years (known as *data exclusivity*) which runs concurrently with patent protection. During this data exclusivity period, regardless of the status of the underlying patent(s), no generic entry may occur. At the conclusion of data exclusivity branded products are protected only by their patents; this period running from the cessation of data exclusivity to patent expiration is commonly referred to as market exclusivity.

Important for the current setting is the ability by firms to obtain three additional years of data exclusivity for reformulations, which include: (a) reformulating the molecular entity; (b) changing the manner of delivery; or (c) adding a new indication. Specifically, I am interested

in the third type of reformulation focused on adding a new indication or repurposing. This process includes additional clinical testing and another submission to the FDA for approval but this is generally viewed as less expensive than the original approval.

Critically, the above discussion pertains only to chemical-based or small molecule drugs. The Biologompetitics Products Cion and Innovation Act which was passed in 2009 governs biologic-based or large molecule drugs. Biologic-based drugs receive 12 years of data exclusivity (as opposed to the five-years for chemical-based drugs) but are ineligible for additional data exclusivity protection for a new indication unless there are changes to the structure of the biologic product that alter safety, purity or potency.

4.3 Theoretical Propositions

Consider two firms, Firm A and Firm B, that sell branded drugs, Drug A and Drug B within the same 4-digit Anatomical Therapeutic Chemical (ATC4) market, respectively.[3] While a drug may be assigned to only one ATC code, approved treatments for a specific disease may include drugs from several different ATC groups. Let's assume that at time t = 0, both drugs (Drug A and Drug B) treat the same indication, j. Firm A and Firm B compete with each other in the market to garner patients (i.e., via price and/or direct-to-consumer advertising) and by encouraging physicians to prescribe (i.e., via detailing or the practice of sending sales representatives to physician offices).

Now, let's consider what happens if at time $t = 1$, Drug B receives FDA approval for a new indication $k \neq j$, which is in a different ATC4 therapeutic market. Drug B is now

[3]The ATC classification system, designed by the World Health Organization, divides drugs into groups according to their anatomical annotation (`https://www.whocc.no/atc_ddd_index/`).

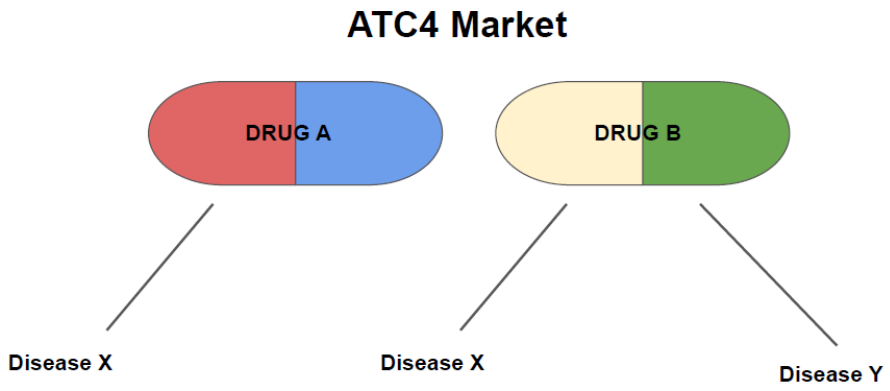

Figure 4.1: A Diagram of the Research Question

approved to treat indication j and indication $k \neq j$ while Drug A remains treating only indication j. See Figure 4.1. While sales of Drug B will increase due to the treatment of indication $k \neq j$, this research focuses on what, if anything, happens to both sales of Drug B and Drug A for the treatment of indication j at time $t = 1$. I consider four plausible competing explanations as to what may happen in the market.

Proposition 1: No Impact. The repurposing of Drug B into a new market to treat indication $j \neq k$ has no effect on the market for indication j. I will consider this the baseline case which implies that, *ceterus paribus*, physicians and patients do not prescribe or request Drug A any differently. That is, when treating indication j, doctors do not prescribe Drug A or Drug B at different rates than they had prior to the repurposing of Drug B.

Proposition 2: Business stealing from Firm B. The repurposing of Drug B into indication $k \neq j$ spills over and increases the sales of Drug B for treating indication j thereby lowering the sales of Drug A for treating indication j. This outcome could result for a number of reasons. First, Firm B increases its advertising and marketing efforts for indication $k \neq j$ or similarly, receives press coverage. This heightened awareness by physicians (and

consumers) allows them to more easily recall Drug B's name and benefits resulting in an increased propensity to prescribe Drug B for indication j. The effects of pharmaceutical advertising have been shown to be effective both in doctors Larkin et al. (2017)) and in patients (e.g., Sinkinson and Starc, 2019). Moreover, these spillover effects are theorized to be a driver behind brand extensions and are often observed empirically in other consumer product markets (e.g., Aaker, 1996; Balachander and Ghose, 2003; Sahni, 2016). For example, advertising spillovers help explain why demand increases for original flavor yogurt when a firm increases its advertising for a new flavor.

Secondly, a halo effect might be created around Drug B because it now treats multiple indications, has gone through additional clinical testing, and multiple FDA approval processes. Drug B may also benefit from peer effects as other physicians begin to prescribe the drug to treat indication $k \neq j$. These behavioral effects may make a physician feel more confident and comfortable about Drug B thereby making them more likely to prescribe it over Drug A for indication j. In either case, this would cause a business stealing effect from Drug A to Drug B.

Proposition 3: Competitive pre-emption by Firm A. The repurposing of Drug B into indication $k \neq j$ leads to an increase in the sales of Drug A but a decline in sales of Drug B to treat indication j, ceterus paribus. This could happen if Firm A, anticipating an increase in advertising and marketing by Firm B, strategically responds by either increasing their advertising and marketing or lowering the price for Drug A. The likelihood that a firm retaliates via increased advertising and marketing is well documented in the economics and marketing literature (e.g., Gatignon et al., 1989). Furthermore, if Firm B is focused on

increasing advertising and marketing for its new indication $k \neq j$, Firm A could use this distraction to better target physicians specializing in indication j. These effects have been explored in the literature on scarce resource allocation and product cannibalization (e.g., Roberts and McEvily, 2005).

Proposition 4: Market-level halo effects. Finally, it is possible that when Drug B is repurposed for indication $k \neq j$ that both Drug B and Drug A experience increases in sales in the treatment of indication j. This would suggest that the halo effects created by Drug B as it expands to treat indication $k \neq j$ spills over into the entire class of drugs treating indication j. For example, if a physician learns that Drug B has been shown to be safe and efficacious for a new indication, $k \neq j$, she may become more comfortable prescribing Drug A to treat indication j because she associates that class of drugs as a whole as safe and effective.

This kind of spillover would be predicted by the literature exploring the impact of information and peer effects on sticky demand. Much of this literature explores the effects of marketing, endorsements, and media depictions on sales of the relevant product and spillovers to sales of other products. For example, Garthwaite (2014) finds that book endorsements lead to business stealing from other book titles and that demand also spills over into other books written by the endorsed author. In the pharmaceutical industry, the setting of this study, there is a growing literature that explores demand spillovers; scholars have shown that demand for one drug can be influenced by new information, new publicity, or an increase in advertising for another drug (Sinkinson and Starc, 2019). Additionally, Shapiro (2018) finds that demand for any antidepressant increases when one firm increases its advertising. This

suggests that new information (or simply an increased prevalence of information) about one antidepressant makes consumers more likely to take any antidepressant.

4.4 Empirical Methodology and Data

4.4.1 Modeling drug repurposing and firm sales

When a firm receives approval for a new indication, I expect to see sales of the drug increase. However, one may also see increased sales of the drug for its prior approved indications as well. This could happen if there were spillover effects due to the announcement of the approval for the new indication. To explore this, I consider the following regression specification. For drug i treating indication j in quarter t, I explore the effect of sales for indication j when the firm receives a new approval for indication $k \neq j$.

$$\begin{aligned} \log(\text{Quantity})_{ijt} = \alpha_0 &+ \beta_1 \text{Competitors}_{ijt} + \beta_2 \text{Own Drug Repurposed}_{ijt} \\ &+ \beta_3 \log(\text{Lag Ad-spending})_{ijt} + \beta_4 \log(\text{Price})_{ijt} + \beta_5 \text{Off-Patent}_{ijt} \\ &+ \text{Year FEs} + \text{Indication FEs} + (\text{Indication x Year FEs}) + \epsilon_{ijt} \end{aligned} \tag{4.1}$$

where the dependent variable, *Quantity*, is the log of total standard units sold. Standard units are determined by IQVIA and are meant to equate pills, tablets, capsules and liquid doses. *Competitors* is a continuously updated count of the number of competing drugs for an indication within a therapeutic market. I expect the sign of β_1 to be negative; as the number of competitors increase, they will begin to steal market share from incumbents. *Own Drug*

Repurposed is an indicator equal to 1 if drug i treating indication j is approved for another indication $k \neq j$, zero otherwise. β_2 is the coefficient of interest and I expect a positive sign if there is spillover effect to other indications treated by drug i.

Lag advertising includes direct promotion to physicians (otherwise known as detailing), journal advertising and direct-mail advertising. Consistent with prior literature, β_3 is expected to be positive. Price is the log of the price of drug i and β_4 is expected to be negative. To correct for the endogeneity of price, I use mean and median price of drugs within the 3-digit ATC therapeutic market as instruments and implement a 2SLS procedure.[4] The F-statistic on the first stage regression rejects the hypothesis of weak instruments. *Off-Patent* is an indicator equal to 1 if drug i is subject to generic competition in time t. Again, consistent with the literature, I expect β_5 to be negative.

Finally, I include year and indication fixed effects along with an interaction between the two to control for factors that vary within an indication over time. This is to control for external factors that lead to changing rates of cancer treatment by type (location). For example, there is evidence that rates of breast cancer were increasing over the period (Schneider et al., 2014; Siegel et al., 2012). This could be for several reasons, including increased early detection or a population that is living longer. By including indication fixed effects, I can control for these external trends of treatment by type of cancer. The F statistic on the first stage regression rejects the hypothesis of weak instruments. The variable *Off-Patent* is an indicator equal to 1 if the drug has come off patent and is now subject to generic competition. I expect β_5 to be negative, as generic entry is shown to have a strong negative impact the sales of its branded drug counterpart (Berndt, 2002; Grabowski et al., 2014).

[4]Results are robust to building instruments within the 2-digit ATC level.

4.4.2 Modeling drug repurposing and competitor sales

Next, I model the impact of competitor repurposing into a new indication, $k \neq j$, on focal drug i sales in indication j. Competitors are defined as firms selling drugs within the same ATC4 therapeutic market. For example, in the breast cancer market focused on aromatase inhibitors (ATC4 L2B3) the drugs Femara (Novartis), Arimidex (AstraZeneca), and Aromasin (Pfizer) are all direct competitors. However, they do not compete directly with Fareston and Nolvadex, which are estrogen modulators also approved to treat breast cancer. In this case, interest is in the effect a repurposing of Arimidex has on sales of Femara. This can be explored more generally in the following specification:

$$\begin{aligned} \log(\text{Quantity})_{ijt} = \alpha_0 &+ \beta_1 \text{Competitors}_{ijt} + \beta_2 \text{Own Drug Repurposed}_{ijt} \\ &+ \beta_3 \text{Competitor Drug Repurposed}_{ijt} + \beta_4 \log(\text{Lag Ad-spending})_{ijt} \\ &+ \beta_5 \log(\text{Price})_{ijt} + \beta_6 \text{Off-Patent}_{ijt} + \text{Year FEs} + \text{Indication FEs} \\ &+ (\text{Indication x Year FEs}) + \epsilon_{ijt} \end{aligned} \tag{4.2}$$

where all the variables remain the same as in Equation 4.1 except *Competitor Drug Repurposed* which is defined as an indicator equal to 1 if competitor drug i treating indication j is approved for another indication $k \neq j$, zero otherwise. The coefficient β_3 thus represents the possibility of a spillover from competitor repurposing on the sales of focal firm drug i treating indication j.

In Equation 4.2, the "treated" sample contains a drug-indication dyad within an ATC4

therapeutic market that is also approved for an indication for which the expanding drug has also been previously approved. For example, Treanda is a drug in ATC4 therapeutic market L1A0 first approved for chronic lymphocytic leukemia before receiving an additional approval for indolent non-Hodgkin's lymphoma in October 2008. In this case, the "treated" sample consists of the sales of competing drugs in ATC4 therapeutic market L1A0 that also treat chronic lymphocytic leukemia but not non-Hodgkin's lymphoma. Excluded are sales of any drugs that treat chronic lymphocytic leukemia approved after October 2008 and any drugs treating chronic lymphocytic leukemia that are not in ATC4 therapeutic market L1A0, of which there are four.

4.4.3 Data

I am fortunate to have access to a range of unique and comprehensive data sets that provide me with disaggregate level data that allows me to track variables by drug (i), therapeutic market or indication (j), in quarter (t). Data on FDA approvals by molecule and disease come from BioMedTracker, a competitive intelligence and investment analytics database developed by the Business Intelligence Division of Informa PLC. Data on sales by molecule spanning 2002-2010 are from IMS. Data is limited to those drugs in the IMS sales data that can be matched to the BioMedTracker indication and regulatory approval data. Furthermore, because I am interested in sales at the drug-indication level, this further limited the sample. All drugs that had only one indication approved are included, as it is assumed that all United States sales of these drugs are for the one approved indication. To include those drugs with more than one indication, I relied on an IMS dataset that summarizes prescribing behavior

for each drug. In divvying up the sales from the IMS data into sales by drug and indication, I calculated the percentage of prescriptions by indication for that drug in that year and applied this to the IMS sales data to calculated the total amount of sales by indication.

Prior to 2002 (the year the data begins), there were 70 unique molecules approved within the L1, L2, and L3 ATC drug classes with several molecules treating more than one disease. For example, Taxol was approved to treat ovarian cancer in 1992, breast cancer in 1994, and non-small cell lung cancer in 1999. A list of all indications and the number of drugs approved for treatment prior to 2002 is presented in Table 4.1. While the majority treat a type of cancer, other related conditions (including endometriosis, uterine fibroids, and HPV) are also within the L-class of drugs.

Furthermore, there is some heterogeneity in the way with which different ATC classes grow over time. For example, the largest class of drugs, the Alkylating agents (L1A0) saw no new FDA approvals between 2002-2010. This is likely because it is one of the older classes of cancer drugs, many of which were already off patent or coming off patent during the relevant time period. In contrast, the A-Neo Protein Kinase Inhibitors (L1X4) while still a relatively small subgroup saw considerable growth during the time period. Despite having received only one FDA approval prior to 2002, by 2010 there were 8 total approvals. See Table 4.2 for a timeline of approvals by ATC4 group.

Table 4.1: Full List of Indications with Approval
Pre-2002

Indication	Number Approved
Actinic Keratoses	1
Acute Lymphocytic Leukemia (ALL)	3
Acute Myelogenous Leukemia (AML)	2
Acute Promyelocytic Leukemia (APL)	2
Adrenocortical Cancer	1
Bone Complications (including bone metastases)	1
Bone Marrow Transplant and Stem Cell Transplant	1
Brain Cancer (Malignant Glioma; AA and glioblastoma (GBM))	2
Breast Cancer	11
Chronic Lymphocytic Leukemia (CLL)	3
Chronic Myelogenous Leukemia (CML)	3
Colorectal Cancer (CRC)	3
Cushing's Syndrome	1
Cutaneous T-Cell Lymphoma (CTCL) - NHL	2
Endometriosis	4
Hairy Cell Leukemia	1
Hematologic Cancer	1
Hodgkin's Lymphoma	4
Human papillomavirus (HPV) Treatment (Antiviral)	1
Kaposi's Sarcoma	2
Multiple Myeloma (MM)	3
Multiple Sclerosis (MS)	3
Non-Small Cell Lung Cancer (NSCLC)	3
Ovarian Cancer	4
Pancreatic Cancer	1
Prostate Cancer	10
Renal Cell Cancer (RCC)	1
Rheumatoid Arthritis (RA)	1
Sickle Cell Anemia	1
Skin Cancer - Basal Cell Carcinoma (BCC)	1
Small Cell Lung Cancer (SCLC)	1
Solid Tumors	1
Testicular Cancer	1
Uterine Fibroids	3

This table presents a list of all indications and the number of molecules approved for their treatment prior to 2002. Data from BioMedTracker.

Table 4.2: Number of Approvals by ATC4 Code
Through 2010

ATC4 Code	pre-2002	2002	2003	2004	2005	2006	2007	2008	2009	2010
L1A0 Alkylating Agents	15	15	15	15	15	15	15	15	15	15
L1B0 Antimetabolites	12	12	12	15	16	18	18	19	19	19
L1C0 Vinca Alkaloids	15	15	15	16	17	20	20	20	20	21
L1D0 Antineoplas. Antibiotics	5	5	5	5	5	5	5	5	5	5
L1X1 Adj. Prep for Cancer Therapy	1	1	1	1	1	1	1	1	1	1
L1X2 Platinum Compounds	4	5	5	5	5	5	5	5	5	5
L1X3 Antineoplastic MABS	1	1	1	1	1	2	2	2	3	3
L1X4 A-Neo Protein Kinase Inh.	1	2	3	3	3	4	7	7	8	8
L1X9 All Other Antineoplastics	12	12	12	12	12	13	14	14	15	16
L2A2 Cytostatic Progestogens	1	1	1	1	2	2	2	2	2	2
L2A3 Cyto Gonad Hormone Analog	9	9	9	9	9	9	9	9	9	9
L2B1 Cyto Anti-Oestrogens	2	2	2	2	2	2	2	2	2	2
L2B2 Cyto Anti-Androgens	3	3	3	3	3	3	3	3	3	3
L2B3 Cytostatic Aromatase Inhibitor	4	4	4	4	4	4	4	4	4	4
L2B9 Other Cyto Hormone Antagist	0	1	2	2	2	2	2	3	3	3
L3A1 Colony-Stimulating Fact.	1	2	2	2	2	2	2	2	2	2
L3A9 Other Immunostim.	3	3	3	3	3	3	3	4	4	4
L3B1 Interferons Alpha	1	1	1	1	1	1	1	1	1	1
L3B2 Interferons Beta	2	3	3	3	3	3	3	3	4	4

This table presents a list of all FDA-approvals by ATC4 Classes L1, L2, and L3 through 2010. Data from BioMedTracker.

There is considerable heterogeneity in the proportion of sales captured by an ATC4 class during the time period as illustrated in Table 4.3. Demand for branded Alkylating agents (L1A0) shrunk over time as these drugs faced increased competition by generic manufacturers and new technologies in other classes. Class L1X4 grew as expected given the large increased of approved drugs joining the sample. But demand for drug classes that did not see new entrants over the time period also grew. For example, the Cytostatic Aromatase Inhibitors (L2B3) saw substantial demand increases despite a lack of new entrants.

4.5 Empirical Results

4.5.1 Impacts of drug repurposing on focal firm sales

As a firm receives a new indication approval for an already approved drug, one expects to see all sales of the drug increase, due to new prescriptions for the drug to treat the newest approved disease. However, one may also see increased sales of the drug for its other approved indications as well. This would happen if there were spillover effects from the announcement of the new approval, as explained in Proposition 2. To explore this, I look at sales of exapanded drugs by indication over time. Here, I am constrained to those drugs which have the data by indication.

Table 4.3: Quantity Sold by ATC4 Code
2002-2010

ATC4 Code	2002	2003	2004	2005	2006	2007	2008	2009	2010
L1A0 Alkylating Agents	17,258	19,997	13,853	10,229	10,722	8,832	7,088	5,859	5,329
L1B0 Antimetabolites	52,864	54,215	39,311	35,812	34,184	28,199	25,893	21,441	21,321
L1C0 Vinca Alkaloids	3,801	3,112	2,910	2,573	3,086	3,125	2,339	2,356	2,344
L1D0 Antineoplas. Antibiotics	208	195	156	143	121	81	62	58	49
L1X1 Adj. Prep for Cancer Therapy	32	29	22	19	20	23	23	20	16
L1X2 Platinum Compounds	1,573	1,920	1,701	1,065	948	936	929	654	184
L1X3 Antineoplastic MABS	30	35	36	40	63	144	107	92	221
L1X4 A-Neo Protein Kinase Inh.	14,006	20,223	20,558	17,920	15,192	18,014	18,696	20,020	23,999
L1X9 All Other Antineoplastics	9,960	9,770	9,101	7,494	6,989	6,676	8,406	8,043	6,979
L2A2 Cytostatic Progestogens	16	8	18	857	3,934	5,685	5,413	5,503	5,125
L2A3 Cyto Gonad Hormone Analog	1,579	1,436	1,257	1,179	1,095	998	998	686	615
L2B1 Cyto Anti-Oestrogens	68,462	26,554	7,353	3,336	1,199	342	302	242	276
L2B2 Cyto Anti-Androgens	37,027	29,872	27,757	24,611	25,296	25,681	25,137	13,769	1,521
L2B3 Cytostatic Aromatase Inhibitor	37,150	50,418	82,610	114,747	138,234	149,175	156,324	155,259	116,421
L2B9 Other Cyto Hormone Antagist	54	119	125	133	154	161	162	180	231
L3A1 Colony-Stimulating Fact.	807	962	1,190	1,356	1,649	1,667	1,648	1,689	1,630
L3A9 Other Immunostim.	15,123	17,378	19,558	21,357	22,498	22,465	23,514	25,389	27,956
L3B1 Interferons Alpha	10	7	7	6	5	3	0	0	0
L3B2 Interferons Beta	11,312	11,412	10,564	11,152	11,860	10,326	10,597	10,590	10,801

This table presents sales by ATC4 code. Sales data from IMS.

Table 4.4 presents regression results from Equation 4.1. The dependent variable across all four models is *Quantity* or the log of total standard units sold by firm i, treating indication j, in quarter t. Standard errors are clustered at the drug-indication level. The coefficients on *Price* and *Off-Patent* are negative, as expected. Likewise, the coefficient on *Lag Advertising* is positive, again, as expected. Across all four models the coefficient on the variable of interest, *Own Drug Repurposed*, is positive and significant at the 1 percent level. This suggests that sales for indication j increase when the firm receives a new approval for indication $k \neq j$. In other words, there are positive spillovers within a drug when it receives additional approvals for new indications. In my prior rubric, the sales of Drug B treating indication j increase after Drug B receives approval to treat indication $k \neq j$.

4.5.2 Impacts of repurposing on competitors

In the previous section I determined that when Drug B was repurposed to treat indication $k \neq j$, there were positive spillovers in the treatment of indication j. Are these spillover effects self-contained to Drug B or do these spillovers impact competitor drugs that also treat indication j? I define direct competitors as those drugs within the same ATC4 therapeutic market that have been approved by the FDA for the same indication. For example, in the breast cancer market (ATC4 market L2B3) the three aromatase inhibitors Femara (Novartis), Arimidex (AstraZeneca), and Aromasin (Pfizer) are all direct competitors. Thus, I am interested in whether a repurposing of Arimidex into a new indication has any spillover effects on Femara or Aromasin in the aromatase inhibitor market.

Table 4.5 presents regression estimates from Equation 4.2. The dependent variable across

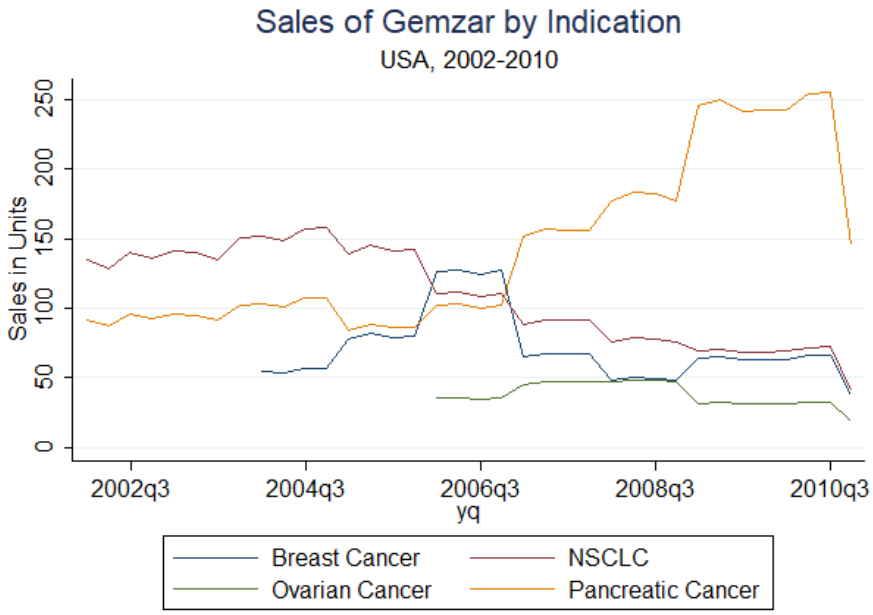

Figure 4.2: Sales data from IMS.

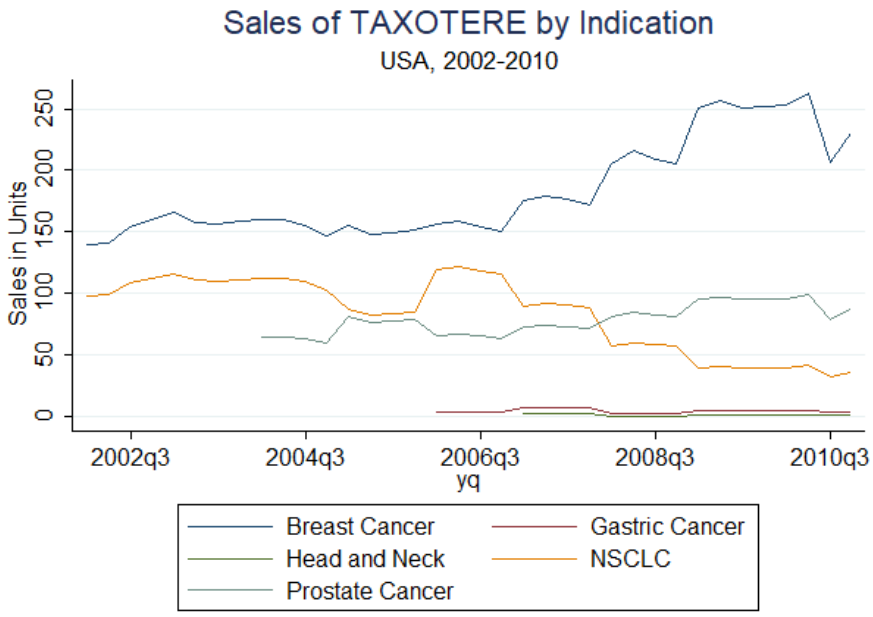

Figure 4.3: Sales data from IMS.

Table 4.4: Effect of Drug Repurposing on Quantity Sold
2002-2010

Dependent Variable: Log(Quantity Sold)				
	(1)	**(2)**	**(3)**	**(4)**
log(Price)	-0.829***	-0.844***	-0.726***	-0.758***
	(0.07)	(0.07)	(0.08)	(0.08)
Own Drug Repurposed	2.125***	2.206***	2.077***	1.927***
	(0.23)	(0.23)	(0.51)	(0.50)
Number of Competitors		0.304**	-0.0878	0.131
		(0.14)	(0.16)	(0.15)
log(Lagged Ad Spending)			0.362***	0.302***
			(0.06)	(0.05)
Off Patent				-1.396***
				(0.25)
Indication FE	Y	Y	Y	Y
Year FE	Y	Y	Y	Y
Indication x Year FE	Y	Y	Y	Y
Observations	3153	3153	2327	2327
R^2	0.643	0.644	0.709	0.731
First-stage F-stat	14.68	14.63	12.78	13.40

Robust standard errors in parantheses are clustered at the Drug-Indication level.

* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

all four models remains *Quantity* or the log of total standard units sold by firm i, treating indication j, in quarter t. Standard errors are clustered at the drug-indication level. All coefficients on the controls continue to have the expected sign. The coefficient on the variable of interest, *Competitor Drug Repurposed*, is positive and significant. This suggests that as a firm repurposes their drug in market $k \neq j$, this leads to an increase in sales of their competitors in the original market j. In the context of the above example, as Arimidex expands into market $k \neq j$, sales of Femara increase in market j.

Combined with the results in the prior section, it appears that as a drug is repurposed into market $k \neq j$, there are positive spillovers to the both the focal drug and competitor drugs within the original market j. Thus, Proposition 1 is not supported and while I see an increase in sales of Drug B for indication j, they do not appear to come at the cost of sales of Drug A. As such, Proposition 2 is also not supported.

4.5.3 Strategic preemption by competitors

While both the sales of Drug B and Drug A have been shown to increase for the treatment of indication j, they could be doing so for different reasons. With the expansion of Drug B into the treatment of indication $k \neq j$, it is possible that Firm A engaged in some type of strategic preemption. To investigate this possibility, I consider two additional analyses exploring the effect of a drug's repurposing on price and advertising spend of their competitors. First, I explore if the acquisition of a newly approved indication leads competitors to lower their price. In Table 4.6, Model 1 I re-estimate Equation 4.2 replacing the dependent variable with $log(Price)_{ijt}$ or the log of drug price for indication i, in market j at time t. The variable

Table 4.5: Effect of Competitor Repurposing on Quantity Sold
2002-2010

Dependent Variable: Log(Quantity Sold)				
	(1)	**(2)**	**(3)**	**(4)**
log(Price)	-0.858***	-0.868***	-0.764***	-0.800***
	(0.07)	(0.08)	(0.08)	(0.08)
Own Drug Repurposed	2.399***	2.442***	2.433***	2.300***
	(0.28)	(0.27)	(0.61)	(0.53)
Competitor Drug Repurposed	0.602*	0.538*	1.168***	1.258***
	(0.32)	(0.32)	(0.34)	(0.33)
Number of Competitors		0.272*	-0.173	0.0494
		(0.14)	(0.17)	(0.16)
log(Lagged Ad Spending)			0.381***	0.320***
			(0.06)	(0.05)
Off Patent				-1.463***
				(0.25)
Indication FE	Y	Y	Y	Y
Year FE	Y	Y	Y	Y
Indication x Year FE	Y	Y	Y	Y
Observations	3153	3153	2327	2327
R^2	0.642	0.643	0.713	0.736
First-stage F-stat	14.63	14.58	12.77	13.40

Robust standard errors in parantheses are clustered at the Drug-Indication level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

of interest is *Competitor Drug Repurposed* and the coefficient is expected to be negative if firms preemptively act by lowering price.

Instead of changing price, firms could decide to increase their advertising expenditures, which has been shown to be effective both in doctors (e.g., Larkin et al., 2017) and in patients (e.g., Sinkinson and Starc, 2019). In this case, as Drug B expands to treat indication $k \neq j$ (along with the original indication j), Firm A increases their advertising spend on Drug A for the treatment of indication j. I explore this possibility in Table 4.6, Models 2 and 3 where I again re-estimate Equation 4.2 replacing the dependent variable with *Advertising* and *Lag Advertising*, respectively. The variable of interest is *Competitor Drug Repurposed* and the coefficient is expected to be positive if firms preemptively act by increasing advertising.

Results are presented in Table 4.6. The coefficients on the control variables are as one would predict. The coefficient estimates for *Off-Patent* are worth mentioning as they may seem counterintuitive. In Model 1, I see that effect of generic entry has a positive effect on price. This effect is well documented in the literature (Frank and Salkever, 1997; Regan, 2008); firms often raise price to capture increased rents from the price-insensitive customers who prefer branded products. In Models 2 and 3, I see negative effects on advertising; as generics enter the market, firms begin to decrease advertising since substitution laws will allow insurance companies to move patients to generic products.

Table 4.6: Effect of Competitor Repurposing on Price and Advertising 2002-2010

Dependent Variable:	Log(Price)	Ad Spending	Lagged Ad Spending
	(1)	**(2)**	**(3)**
log(Price)		-0.232***	-0.255***
		(0.05)	(0.06)
Number of Competitors	0.347**	0.552***	0.791***
	(0.17)	(0.13)	(0.16)
Own Drug Repurposed	2.271***	-0.0694	0.293
	(0.22)	(0.26)	(0.54)
Competitor Drug Repurposed	0.949***	-0.342***	-0.560***
	(0.26)	(0.11)	(0.19)
Off Patent	0.332***	-0.341***	-0.723***
	(0.23)	(0.09)	(0.16)
Indication FE	Y	Y	Y
Year FE	Y	Y	Y
Indication x Year FE	Y	Y	Y
Observations	3153	3153	2327
R^2	0.470	0.437	0.530
First-stage F-stat		14.55	13.36

Robust standard errors in parantheses are clustered at the Drug-Indication level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

I do not see, in any of the models, the coefficients for the variable of interest, *Competitor Drug Repurposed*, respond in a way that is predicted above. It suggests that the demand expansion for Drug A as Drug B is repurposed into indication $k \neq j$ is not due to preemptive activities by Firm A. In short, Proposition 3 is not supported. Interestingly, the coefficients were both the opposite of what would have been predicted. In Model 1 I see that the price of Drug A increases as Drug B expands into indication $k \neq j$. Additionally, in Models 2 and 3, it appears that advertising expenditures decline. Combined with my prior results, an interesting picture is beginning to emerge for Drug A as Drug B is repurposed. That is, one observes increases in demand and price and decreases in advertising for Drug A in the treatment of indication j as Drug B expands into indication $k \neq j$. In the next section I discuss a scenario that can lead to this result.

4.5.4 Business stealing from distant (non-market) competitors

Thus far, I have documented both an expansion of Drug A and Drug B for the treatment of indication j as Drug B expands into market $k \neq j$. This supports a halo effect for the entire class of drugs that treat indication j. In other words, doctors or patients may have increased demand for a class of drugs given the positive news surrounding alternative approved uses for just one of the drugs. Importantly, this kind of spillover effect is supported in the literature (e.g., Garthwaite, 2014; Shapiro, 2018; Sinkinson and Starc, 2019). This implies, however, that the results are implying either an increase in new consumers or from business stealing from among other drugs that treat the same indication but are in a different class of drugs (i.e., the halo effect does not extend to them).

Recalling that the focus of this study is on markets that treat cancer, it is sensible to assume that most rationale people diagnosed with cancer are likely to seek treatment. As such, I believe it is less likely that this increase in demand is coming from patients who would not have otherwise been treated for their cancer. This leaves us with the possibility that this class of drugs is stealing business from other classes of drugs that treat the same indication. For clarity, consider the following five drugs: Femara (Novartis), Arimidex (AstraZeneca), Aromasin (Pfizer), Fareston (Kyowa Kirin) and Nolvadex (AstraZeneca). The first three drugs are aromatase inhibitors while the last two drugs are anti-estrogens; all five drugs treat breast cancer. Importantly for this analysis, the first three drugs are in ATC4 therapeutic market L2B3 and the last two drugs are in ATC4 therapeutic market L2B1.

To test whether business stealing is occurring from other classes of drugs that treat the same indication, I re-estimate Equation 4.2 in Table 4.7. The variable of interest is *Same Indication/Different Class Repurposed* and an indicator that equals 1 if a drug treats the same indication as drug i but resides in a different therapeutic class than the drug being repurposed. In the above example, if Femera (ATC4 L2B3) was repurposed, then the variable would equal one for the two drugs in market ATC4 L2B1 (i.e., Fareston and Nolvadex). In the complete specification, Model 3, the coefficient on the variable of interest is negative and significant at the one percent level, suggesting that the demand expansion I documented previously is coming at the expense of these more distant or non-market competitors.

Table 4.7: Effect of Competitor Repurposing on Quantity Sold
2002-2010

Dependent Variable: Log(Quantity Sold)				
	(1)	**(2)**	**(3)**	**(4)**
log(Price)	-0.763***	-0.747***	-0.792***	-0.773***
	(0.08)	(0.08)	(0.08)	(0.07)
Own Drug Repurposed	2.570***	2.081***	2.425***	1.973***
	(0.35)	(0.30)	(0.31)	(0.28)
Same Indication/Same Class Competitor Drug Repurposed	0.818**		0.847***	
	(0.33)		(0.31)	
Same Indication/Different Class Competitor Drug Repurposed		-0.583**		-0.500**
		(0.26)		(0.24)
Number of Competitors	-0.0491	-0.00521	0.123	0.166
	(0.16)	(0.16)	(0.15)	(0.15)
log(Lagged Ad Spending)	0.353***	0.352***	0.304***	0.302***
	(0.05)	(0.05)	(0.05)	(0.05)
Off Patent			-1.299***	-1.255***
			(0.27)	(0.26)
Indication FE	Y	Y	Y	Y
Year FE	Y	Y	Y	Y
Indication x Year FE	Y	Y	Y	Y
Observations	2346	2346	2346	2346
R^2	0.714	0.714	0.731	0.731

Robust standard errors in parantheses are clustered at the Drug-Indication level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

4.5.5 Does drug repurposing impact firm performance?

The extent to which these demand changes impact firm performance should be reflected in focal firm equity performance. As such, I follow McWilliams and Siegel (1997) and use an event-study analysis to compute cumulative abnormal returns (CAR). I estimate a market model over a period of 250 days prior to the event date, $t = 0$, defined as the approval date by the FDA for a new indication. Over a three-day event window (t-1 to t+1) I find an average CAR of 1.52 percent, significant at the 1 percent level. When I multiply this by market capitalization data from Compustat this translates into approximately $1.4 billion.

I argue that this monetized value of the abnormal return represents the unexpected change in the discounted value of future cash flows of the focal drug, Drug B. These cash flows are anticipated to come from several sources. First, there will be the direct impact on the focal firm, Firm B, as they repurpose Drug B for a new indication, $k \neq j$. Second, given the regulatory structure in place, a new indication provides three additional years of data exclusivity thereby directly increasing the value Drug B in treating the original indication j. Finally, as discussed above, there can be positive spillovers for Drug B in treating the original indication j as well as increases in sales due to business stealing from firms outside of the ATC therapeutic market that sell drugs for indication j.

4.6 Robustness Tests

One possible concern of this study is that the results I am seeing are capturing unobservable changes of use within the ATC-4 class over time and that these results unrelated to one class

member's repurposing. To explore this further, I re-estimate the regression specifications using a set of "placebo" indications within the relevant ATC-4 class. These placebo groups include all indications within the relevant ATC-4 class that are unrelated to the newly repositioned focal drug. For example, consider Erbitux, a drug initially approved for the treatment of colorectal cancer which was later approved in 2006 to treat Head and Neck cancer. Since Erbitux resides in ATC class L1X3, I would initially have been interested in the growth of sales for colorectal cancer for both Erbitux and its competitors in class L1X3 following the drug's reposition.

To test the robustness of my findings, I consider what happens to sales of unrelated drug-indications within the relevant ATC class. A finding of positive sales growth among unrelated indications would suggest that the above findings were driven by factors beyond the effects of repurposing. To do this, I create a placebo "treatment" group where a drug is treated if it is approved for indication $l \neq j \neq k$ but in the same ATC4 class as drug i that expanded into indication k. I then rerun Equation 4.2 on this new "treatment" group. Results are presented in Table 4.8. The small and statistically insignificant coefficients on *Placebo Competitor* suggest that the key results are not driven by unobserved changes within the competitor class.

4.7 Concluding Remarks

This article provides fresh insight into how an increase of a product's scope can change demand for both it and its close competitors. This study looks specifically the repurposing of a pharmaceutical drug, that is, the case where a company finds new uses for an already

Table 4.8: Effect of Competitor Expansion on Quantity Sold
With "Placebo" Competitors
2002-2010

Dependent Variable: Log(Quantity Sold)				
	(1)	**(2)**	**(3)**	**(4)**
log(Price)	-0.778***	-0.790***	-0.790***	-0.738***
	(0.07)	(0.07)	(0.07)	(0.07)
Placebo Competitor	-0.153	-0.114	0.143	-0.129
	(0.20)	(0.20)	(0.19)	(0.21)
Number of Competitors		0.222	0.390***	0.153
		(0.14)	(0.15)	(0.15)
Off Patent			-1.095***	-1.208***
			(0.23)	(0.26)
log(Lagged Ad Spending)				0.295***
				(0.05)
Indication FE	Y	Y	Y	Y
Year FE	Y	Y	Y	Y
Indication x Year FE	Y	Y	Y	Y
Observations	3278	3278	3278	2346
R^2	0.641	0.641	0.659	0.734

Robust standard errors in parantheses are clustered at the Drug-Indication level.

* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

approved therapy. I find that as the company provides proof of additional uses it not only leads to increased sales for its original uses, but that this excess demand spills over to its closest competitors. Additional exploration suggests that this excess demand is from business stealing from its competitors further away in compound similarity.

These findings certainly have implications for drug development and the strategies of pharmaceutical firms. While the approval of a new use for an already marketed drug does not generate as much attention as the approval of a new molecule, I find that these supplementary approvals appear to make doctors and patients more likely to choose that therapy for its other approved diseases than they were prior to the supplementary approval. Furthermore, their close competitors appear to also achieve some benefits from this. One hypothesized reason would be that additional approvals to even one drug in the class leads to greater legitimacy of that chemical subgroup.

While I believe these results will generalize to industries beyond the pharmaceutical industry, it will be important to better understand when these positive demand spillovers do and do not apply to increases in product scope. I will leave these issues to future research.

Appendices

Appendix A

A.1 Data Description

The main data source used in this study comes from BioMedTracker, a competitive intelligence and investment analytics database developed by the Business Intelligence Divison of Informa PLC. BioMedTracker is a subscription service marketed to pharmaceutical companies and investment analysts seeking a centralized service tracking product development and regulatory events in the industry.

To access and clean the data for this study, I used BioMedTracker to search for any drug development events that occured between 1990 to present day. While this study uses the date of completition of Phase II clinical trials as the relevant date for most analyses, because the BioMedTracker database does not always have complete date information about every drug, by searching for any event this allowed me to collect information on any drug developed by any company with *any* date-based information. I then dropped any generic products. This resulted in a dataset of over 41,000 drug-indication observations.

If a product was missing information on the date in which is Phase II trials ended and it began Phase III clinical trials, I used the start of Phase III clinical trials as the relevant date. For those that did not continue to Phase III and had a missing end of Phase II date, I used

additional sources including EvaluatePharma, ClinicalTrials.gov, and textual information from BioMedTracker to search for and fill in missing dates. In total, I supplemented dates for 3,230 projects.

A.2 Variable Definitions and Construction

Dependent Variable

Pr(Phase III | Phase II). This is a binary variable equal to 1 if the molecule i went to Phase III trials for indication j given it had been in Phase II. As described in the framework above, Phase III trials are often just larger (but much more expensive) versions of Phase II trials. By conditioning on Phase II participation, one can control for some of the selection effects occurring up until Phase II. In particular, molecules beginning Phase II are generally considered safe in the therapeutic dose.

Independent Variables

Post-rejection. This is the coefficient of interest: an indicator equal to 1 if the project (on a unique molecule) completes Phase II clinical trials following an FDA rejection. I consider only those projects using a different molecule to mitigate any effects from direct knowledge spillovers. To explore the effects of rejection over time, I will first consider only the projects immediately following failure, and then consider the effect on several projects in the future.

Leading Indication. This is an indicator equal to 1 if the indication being pursued is the "leading indication" for that drug. Firms designate leading indications to be the one they believe is most promising for the molecule, and therefore, it is the project to first begin

extensive clinical trials. One would expect a higher probability of continuation for products containing leading indications, all else equal.

Number of Indications. This is a count of the number of indications a firm is pursuing for the molecule. As described previously, a firm expecting to benefit from knowledge spillovers may be less likely to terminate following Phase II. In the estimation, I consider the product of *Leading Indication* and *Number of Indications* as measuring the full potential for knowledge spillovers.

ODA. This is an indicator equal to 1 if the drug has received an Orphan Drug designation. Because designated orphan drugs accrue additional benefits (like shorter Phase III trials and tax credits on R&D expenditures), a firm may be more likely to pursue a drug with that designation than the same drug not receiving a designation. However, orphan drugs by definition are targeting smaller markets, which may make them less desirable than a molecule targeting a large but under-served population. Orphan drugs constitute 12.6% of drug-indication pairs in this sample.

Fasttrack. This is an indicator equal to 1 if the drug has been designated for fast-track approval by the FDA. These drugs are potentially of higher quality and will often have shorter Phase III trials and faster review times (Thaul, 2008). They also may command higher revenues because they are serving an unmet need. To receive a Fast-track designation, the drug must both address a serious or life-threatening condition and address an unmet medical need. I expect the coefficient on this variable to be positive and significant. 12.2% of this sample contains drugs with Fast-track status.

Breakthrough. This is an indicator equal to 1 if the drug has received a Breakthrough Therapy Designation. Products receiving a Breakthrough Therapy Designation have dis-

played clinical evidence to provide noted improvement over already marketed therapies. Like Fasttrack products, benefits include shorter clinical trials, shorter regulatory review times, and increased interaction with the FDA. Preliminary evidence suggests products receiving a Breakthrough Therapy Designation have shorter clinical development times by nearly 30% (Chandra et al., 2019). Breakthrough designations are difficult to obtain, and constitute 4.4% of this sample. I expect the coefficient on breakthrough drugs to be positive and significant.

Num Competitors. This is the number of approved drugs on the market to treat indication j at time t. Because there is a strong first-mover advantage in this industry, many firms consider their expected market share when considering the upside of investment.

Past Experience. This is a cumulative count of total Investigative New Drug Applications (INDs) that firm r has filed at time t. This controls for a firm's experience level, given past research has demonstrated that less experienced firms can be less likely to terminate development projects (Guedj and Scharfstein, 2004) and that past experience is valuable for clinical trial success (Danzon et al., 2005; Macher and Boerner, 2006). INDs are usually filed right before a firm conducts Phase I clinical trials. This is similar to a measure employed by Allain et al. (2016) to control for experience between pharmaceutical firms in their study on the timing of molecule licensing.

Avg Approval Phase III. This is the average probability of approval for a drug in its therapeutic class as collected and reported by BioMedTracker. Drugs with historically higher average probabilities of approval should be more likely to continue to Phase III trials, all else equal. This will fall out of the specifications containing indication fixed effects.

Molecule Type. This is a vector of fixed effects for 20 different types of molecule

formulations, ranging from traditional small molecules, to peptides and gene therapies.

Indication. This is a vector of 546 indication fixed effects. Because an indication is directly linked to demand, these fixed effects (along with the number of competitors) will proxy for potential revenue. A firm can expect to sell more drugs if they are developing a drug for a more common indication.

Year. This is a vector of fifteen year-specific fixed effects for the year at the end of Phase II clinical trials. These control for any macro-trends in the way in which companies make decisions about Phase III clinical trials. For example, if techniques for judging the quality of drugs at Phase II get better over time, this may result in all firms pursuing fewer Phase III clinical trials over time. Year fixed effects mitigate the possibility of conflating these macro-level trends with the effects of the treatment.

Drug Classification. This is a vector of fixed effects for three types of drug classifications: new molecular entities (NMEs), NDAs and sNDAs, biologics, and vaccines.

Company. This is a vector of 1,571 company fixed effects including both pharmaceutical and biotechnology companies. These control for unobserved heterogeneity in initial risk attitudes for firms in my sample. This is important given past research on the heterogeneity among firm capabilities in innovation (Arora et al., 2009; Eggers, 2012), capabilities in termination (Guler, 2018), and the potential for resource redeployment (Lieberman et al., 2017). Additionally, research exploring investment decisions on characteristics of pharmaceutical firms has demonstrated certain firms are inherently more risk averse than others (Guedj and Scharfstein, 2004).[1]

[1]See Appendix A.3 for an analysis demonstrating a positive correlation between firm experience and the capability of "failing fast" in this sample.

A.3 Ability to Terminate as a Capability

In this paper, I provide evidence that large failures driven by feedback external to the firm can impact a firm's future innovation investment decisions. In particular, I show that they terminate future projects earlier and this leads to higher rates of approval for those projects that they do pursue. These findings may suggest that the ability to know when to terminate is a dynamic capability that, if executed properly, could free up firm resources for other projects. Therefore I want to explore the evidence that the ability to recognize early on that a project will not be successful is a dynamic capability that can be acquired and cultivated. The acquisition of capabilities has long been of interest to strategy scholars (Barney, 1991; Ethiraj et al., 2005) and very recently, scholars have become interested in the "capability to terminate." In what may be the first paper to explore this capability, Guler (2018) notes that the detection of failure itself is a capability often unaccounted for in literature on organizational learning. Using data on venture capital firms, she finds firms with a higher termination capabilities are also higher performers. To observe if this holds within the pharmaceutical industry, I explore associations between termination capabilities and innovation performance.

To analyze the associations between firm performance and the ability to terminate early, one must first determine how to measure this capability. For this analysis, I examine how long it takes a specific firm to terminate a project trial for a product in which they determined to be unsuccessful. To do this, I consider all projects that reach at least Phase II clinical trials. Recall that by Phase II, the firm has already determined that its product is not toxic

to a small sample of healthy volunteers, but are looking to collect data on safety and efficacy for sick volunteers. The choice to consider projects that made it at Phase II is largely one of necessity because the data is more complete beginning in Phase II. As the dependent variable in an OLS regression, I calculate how long it takes, in days, for the firm to terminate this project. To measure firm performance, I consider the number of FDA approvals the firm has within the disease class at the year of termination. I then classify high performing firms as those that have a number of approvals above a certain threshold in that disease class in that year. The estimated ordinary least squares model is presented in Equation A.1.

$$\log(\text{Time to Termination}|\text{Phase II}) = \alpha_0 + \beta\text{Capability} + \Theta X + \tau_m + \Phi_j + \mu_t + \epsilon_{ijrt} \quad \text{(A.1)}$$

Here, X is again vector of Project-time controls, and τ_m, Φ_j, and μ_t represent fixed effects for molecule type, indication, and year respectively.

I consider four different measures for a firm's capabilities at time t in a given therapeutic class. I first consider the log of the number of approvals the firm has in the relevant therapeutic class at start date of Phase II clinical trials (column 1). Secondly I consider an indicator for whether or not, at time t, the firm is in the top 75% of firms by number of FDA approved drugs in that class (column 2). Column 3 employs an indicator for firms in the top 90% by therapeutic class. And finally, in column four I look at whether or not the firm is public, and therefore likely has more aggregate experience and success in taking drugs through clinial trials.

In addition to these measures of firm capabilities, X is a vector of project characteristics

that include indicators for whether or not the drug has received any beneficial status from the government (Orphan Drug, Fasttrack, or Breakthrough), the number of indications it is pursuing, and whether or not it is the first indication to enter Phase II trials (if it is targeting multiple indications). All of these factors could potentially impact a firm's incentives to terminate a project, all else equal. Molecule Type, Drug Classification, and Indication are all product-level fixed effects. Also included is a vector of year fixed effects for the year of termination. This should control for any macro-level conditions or information that incentivised firms to terminate.

Table A1 presents the results from this estimation, under the four different measures of a high performing firm. These estimates provide some evidence that there is an association between firm performance (as measured in FDA approved products) and its ability to terminate a project more quickly. Specifically, a 1% increase in approved molecules for that therapeutic class leads to a 2.5% reduction in days in advanced clinical trials. Firms in the top 75% of the distribution of FDA approvals for a therapeutic class spend nearly 8% less time in clinical trials, and those in the top 90% spend over 10% less time. Public firms in general spend 12% fewer days in advanced clinical trials. In addition, the coefficients on all other variables coincide with what one would expect. Molecules that have beneficial status (Orphan Drug, Breakthrough Designation, or Fasttrack Designation) spend a longer time in clinical trials all else equal, likely because the benefits of approval are greater or the costs of development are lower. Leading indications and molecules with multiple indications also spend significantly longer, likely because the learning benefits of clinical trials are greater for these products.

While these findings cannot be interpreted causally, they add additional evidence to the

Table A1: Time to Termination
2000-2018

	Dependent Variable: Log(Number of Days in Phase II)			
	(1)	**(2)**	**(3)**	**(4)**
Capability Definition:	*log(Approvals)*	*Top 75%*	*Top 90%*	*Public*
Capability	-0.0242***	-0.0766***	-0.104***	-0.120***
	(0.01)	(0.02)	(0.03)	(0.03)
ODA	0.252***	0.293***	0.292***	0.299***
	(0.05)	(0.04)	(0.04)	(0.04)
Breakthrough	0.302**	0.270**	0.259**	0.261**
	(0.15)	(0.12)	(0.12)	(0.12)
Fasttrack	0.347***	0.327***	0.324***	0.325***
	(0.06)	(0.04)	(0.04)	(0.04)
Lead Ind*Num Inds	0.0616**	0.0687***	0.0695***	0.0716***
	(0.03)	(0.02)	(0.02)	(0.02)
Constant	5.221***	5.503***	5.635***	5.486***
	(0.43)	(0.40)	(0.40)	(0.40)
Indication FE	Y	Y	Y	Y
Year FE	Y	Y	Y	Y
Molecule Type FE	Y	Y	Y	Y
DrugClass FE	Y	Y	Y	Y
Observations	4582	6058	6058	6058
R^2	0.353	0.342	0.343	0.343

The dependent variable is the log of the number of days a product was in Phase II clinical trials before voluntary termination by the firm. Capabilities are measured as follows: (1) The log of the number of approvals the firm has in the relevant therapeutic class at start date of Phase II clinical trials; (2) An indicator for whether or not, at time t, the firm is in the top 75% percent of number of FDA approved drugs in that class; (3) An indicator for the top 90% of number of FDA approved drugs in that class; (4) Whether or not the firm is public, and therefore likely has more experience taking drugs through clinical trials. Robust standard errors in parentheses.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

results presented by Guler (2018) showing the ability to terminate quickly may be a dynamic capability associated with a competitive advantage. Furthermore, it supports findings by Guedj and Scharfstein (2004) that younger firms (who have possibly not yet developed this capability) will hold onto innovation projects longer for lack of a better outside option.

A.4 Effect of Failure Given Capabilities

One characteristic of the pharmaceutical and biotechnology industries is the tendency for firms to gravitate towards specializing in certain therapeutic areas. For example, large pharmaceutical firm Allergan does the majority of its research in ophthalmology and neurology, while small biotechnology firm SillaJen Biotherapeutics specializes exclusively in oncology. Even large and historically successful pharmaceutical firms can terminate research for diseases in which they grow to believe they lack capabilities. In 2018, the pharmaceutical company Pfizer garnered attention when they terminated all of their projects for Alzheimer's Disease, laying off over 300 people in their neuroscience division. In a statement, the company described it as "an exercise to re-allocate spending across our portfolio, to focus on those areas where our pipeline, and our scientific expertise, is strongest" (Reuters, 2018).

There has been some recent significant research on the role that failure may play on future firm behavior depending on whether or not the failed product was within a class in which the firm had experience. Using data from the mutual fund industry, Eggers and Suh (2019) find that failure in domains in which the firm is particularly inexperienced results in retreat from creating new products in this domain, and toward those which they have more experience. Conjointly, they find that failure in areas where the firm has experience does

not cause these changes, likely because the firm may have a better understanding of what caused the failure.

In this analysis, I explore if the effect of an FDA rejection is more pronounced on projects in which the firm has had significant experience. To do this empirically, I create a variable that flags the therapeutic class where the firm has most success. Recall that the data divides up indications into 20 therapeutic classes. To determine where a firm is likely most capable, I consider all of its Phase III clinical trials prior to receipt of the CRL and calculate the percentage of those that were approved by class. I assume the two therapeutic classes in which firms have the most approvals are their specialties. In the event of a tie, the specialty is flagged as the therapeutic category with the highest percentage of Phase III clinical trials that were approved. For example, this algorithm indicated Merck & Company's specialties to be "Infectious diseases" (where they had 11 approvals prior to their CRL) and "Autoimmune/immunology" (six approvals). FDA rejections for drugs in a firm's specialty class account for roughly half of all rejections in the data. Table A2 displays the list of therapeutic classes with the corresponding number of firms in my sample that have it flagged as their specialty.

To test this, I re-estimate Equation 2.1 but with the addition of an interaction term for if the firm's FDA rejection was within a therapeutic class in which the majority of its approvals are from. Table A3 displays the estimated coefficients.

These results do not completely coincide with those found in Eggers and Suh (2019) who argue that "negative feedback in experienced domains... will not lead to a significant adjustment" (312) because organizations can rationalize those failures as aberrations. In Table A3, the coefficients on *Post-rejection x specialty* are slightly positive though statistically in-

Table A2: Number of Companies by Specialty

Therapeutic Class	Number of Companies
Allergy	10
Autoimmune/immunology	50
Cardiovascular	47
Dermatology	14
ENT/Dental	1
Endocrine	52
Gastroenterology	17
Hematology	32
Infectious disease	70
Metabolic	25
Neurology	102
Obstetrics/Gynecology	3
Oncology	121
Ophthalmology	26
Orthopedics	2
Psychiatry	34
Renal	5
Respiratory	11
Rheumatology	6
Urology	6

This table counts the number of companies in the sample that have the specified therapeutic class as their specialty given the following algorithm: I assume the two therapeutic classes in which firms have the most approvals are their specialties. I also consider all of a firm's Phase III clinical trials and calculate the percentage of those that were approved by class. In the event of a tie, the specialty is flagged as the therapeutic category with the highest percentage of Phase III clinical trials that were approved. Therapeutic Class is defined by BioMedTracker.

Table A3: The Probability of a Product in Phase II Continuing to Phase III When Rejection is for Therapeutic Class in Firm's Specialty
2000-2018

	Dependent Variable: Continue to Phase III		
	(1)	**(2)**	**(3)**
Post-rejection x specialty	0.0915	0.0631	0.0509
	(0.06)	(0.06)	(0.06)
Post-rejection	-0.112***	-0.0950***	-0.0994***
	(0.04)	(0.04)	(0.04)
Indication FE	N	Y	Y
Year FE	Y	Y	Y
Molecule Type FE	Y	Y	Y
Drug Classification FE	Y	Y	Y
Company*Therapeutic Class FE	N	N	Y
Observations	5938	5938	5938
R^2	0.275	0.395	0.554

The dependent variable is equal to 1 if a product began Phase III clinical trials. Post-rejection is an indicator equal to 1 if it was the next product to finish Phase II following the receipt of a CRL for a different molecule in the therapeutic category for which it has the most FDA approvals. Specialty class is an indicator equal to 1 if the rejection was for a project within one of the two therapeutic classes in which firms have the most approvals at time t. Robust standard errors in parentheses and clustered at the Company*Therapeutic Class level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

significant. This suggets that a firm's experience or capabilities may not insulate it from the average effects of rejection on firm behavior. Given the setting of this study, this effect is not entirely surprising. A firm likely expects occasional poor performance in the mutual fund industry, where they have little control over external forces. However, in this study, firms submit an application to the FDA explicitly because they (and outside analysts) believe it will be approved. This tension between beliefs and reality will likely cause a bigger response from the firm regardless of whether or not the rejection was within a therapeutic class in which they had considerable experience.

A.5 Timing of Termination Following Rejection

If the effect seen on future investment decisions following FDA rejection was a function of only financial considerations, it is plausible that firms would begin terminating Phase II clinical trials very shortly after the FDA rejection. Recall that the mechanism for the effect proposed here is that following rejection, firms become less likely to continue in investing in a product after seeing the Phase II data. To explore this rigorously, I analyse if the time that terminated projects spent in Phase II after FDA rejection is statistically equivalent to the time spent in Phase II clinical trials before rejection, *ceteris paribus*.

To test this, I consider how long it took a firm to terminate a project in Phase II trials, provided that it was eventually terminated. I subset the data to those eventually terminated Phase II clinical trials and calculate the log of the number of days spent in Phase II clinical trials. I then run a regression with *Log(Days in Phase II)* as the dependent variable and an indicator equal to 1 if the project was the next Phase II termination immediately following

the FDA rejection. The fixed effects and relevant controls from the previous regressions are also included. Results are presented in Table A4.

The coefficients on *Post-rejection* are all statistically insignificant from zero, suggesting that there was no observable difference in the time to terminate Phase II projects just following rejection from the FDA. In addition, the coefficients on the controls are directionally as one would expect. For example, the coefficient on *Lead Ind*Num Inds* is positive. If a firm is pursuing other indications for the same molecule, it will be more likely to hold onto a project longer due to the possibility of acquiring additional information about the molecule to be applied to other indications.

A.6 Exploring the Effect of Phase III Terminations following Abnormal Returns

In exploring the effects of phase III failures on future investment in product development, I had considered all failed trials that had lasted longer than a certain threshold of time. However, the endogeneity problems described in Section 2.5.2 could still be of concern in this case and perhaps driving the "non-result" seen in Table 2.9. In this section, I will test the robustness of this result by looking at those trials that lasted over 50% of the average length of time within the class *and* resulted in abnormal negative returns to the company's stock. As described in Section 2.5.2, those failures that lead to a signifcantly large drop in a company's value may be plausibly the most "surprising", both to investors and the firm.

To probe the robustness of the Phase III failure results, I first limit the sample to only

Table A4: Time Terminated Projects are in Phase II Following FDA Rejection
2000-2018

	Dependent Variable: log(Days in Phase II)		
	(1)	**(2)**	**(3)**
	1 Product Later	2 Products Later	3 Products Later
Post-Rejection	-0.00519	0.110	-0.0336
	(0.15)	(0.12)	(0.12)
ODA	0.0923	0.0931	0.0930
	(0.12)	(0.12)	(0.12)
Breakthrough	-0.215	-0.220	-0.216
	(1.04)	(1.04)	(1.04)
Fasttrack	0.0874	0.0900	0.0870
	(0.14)	(0.14)	(0.14)
Lead Ind*Num Inds	0.0367***	0.0366***	0.0367***
	(0.01)	(0.01)	(0.01)
Num Competitors	0.00130	0.00132	0.00130
	(0.00)	(0.00)	(0.00)
Past Experience	-0.0168***	-0.0168***	-0.0168***
	(0.00)	(0.00)	(0.00)
Constant	8.474***	8.525***	8.500***
	(0.68)	(0.68)	(0.67)
Year FE	Y	Y	Y
Molecule Type FE	Y	Y	Y
DrugClass FE	Y	Y	Y
Company*Therapeutic Class FE	Y	Y	Y
Observations	3054	3054	3054
R^2	0.724	0.724	0.724

Post-rejection is an indicator equal to 1 if it was the next 1, 2 or 3 products to finish Phase II following the receipt of a CRL and is not the same molecule as the failed product. Robust standard errors in parentheses and clustered at Company*Therapeutic Class level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

those publically traded firms and the failed Phase III trials that lasted over 50% of the average length of time within the class. By including only those failed trials that plaubily lasted the full length of time, the amount spent on the drugs development will be nearly in line with those drugs that received a CRL. This allows for a closer "apples to apples" analysis of the differential effects of failure and rejection.

To build a dataset of surprising terminations, I use stock market data from CRSP and consider only Phase III terminations that resulted in statistically significant negative abnormal returns. This results in a sample of 23 terminations. Then, using this sample of terminations, I estimate regression Equation 2.3, where *Post-termination* = 1 if molecule i treating indication j was the next project in the pipeline to finish Phase II clinical trials. Table A5 displays the results. As in Table 2.9, the coefficient statistically insignificant from 0, suggesting no change in propensity to continue investing following these surprising Phase III failures.

Table A5: The Probability of a Product in Phase II Trials Continuing to Phase III Following Voluntary Phase III Termination
Terminations that resulted in Statistically Significant Decrease in Returns

	Dependent Variable: Investment in Phase III			
	(1)	**(2)**	**(3)**	**(4)**
	Next Project	Next 2 Projects	Next 3 Projects	Next 4 Projects
Post Termination	0.0897	0.0613	-0.0675	0.00937
	(0.23)	(0.11)	(0.11)	(0.11)
Project-time Controls	Y	Y	Y	Y
Year FE	Y	Y	Y	Y
Molecule Type FE	Y	Y	Y	Y
DrugClass FE	Y	Y	Y	Y
Company*Therapeutic Class FE	Y	Y	Y	Y
Observations	6284	6284	6304	6284
R^2	0.660	0.660	0.657	0.660

The dependent variable is equal to 1 if a product began Phase III clinical trials.
Post-termination is an indicator equal to 1 if it was the next product to complete Phase II clinical trials following the voluntary late termination of a Phase III trial. I define a late termination as one that lasted longer than the average for its therapeutic class. Robust standard errors in parentheses and clustered at the Company*Therapeutic Class level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Appendix B

Table B1: Impact of Increased Demand on Change in Probability of Investment in Phase III Clinical Trials
Logit DDD Mode
2000 - 2008

Dependent Variable: Indicator equal to 1 if Received Phase III Investment	**(1)**	**(2)**	**(3)**	**(4)**
Medicare*Payer*Post	11.71***	11.24***	11.83***	25.70***
	(1.01)	(1.13)	(1.14)	(1.94)
Medicare	0.617	0.529	0.758	0.882
	(0.68)	(0.69)	(0.70)	(0.95)
Payer	12.31***	11.95***	12.82***	26.80***
	(0.83)	(0.89)	(0.94)	(1.82)
Post	-1.771**	-0.913	-1.284	-0.901
	(0.82)	(1.06)	(1.06)	(1.27)
Payer*Post	-11.61***	-11.11***	-11.69***	-25.84***
	(0.95)	(1.04)	(1.05)	(1.95)
Medicare*Post	-0.503	-0.268	-0.233	-0.378
	(0.79)	(0.81)	(0.82)	(1.10)
Medicare*Payer	-12.01***	-11.56***	-12.31***	-25.58***
	(0.86)	(0.97)	(0.99)	(1.72)
Year FE	N	Y	Y	Y
Drug Classification FE	N	Y	Y	Y
Company FE	N	N	N	Y
Observations	1779	1779	1773	1365

The dependent variable is equal to 1 if a product began Phase III clinical trials given that it completed Phase II clinical trials. The variable Medicare is an indicator equal to 1 if the disease being treated is one that will be subject to any Medicare Part D reimbursement. This variable Payer is an indication equal to 1 if the drug is designed for the pharmacy, rather than hospital, market. The variable Post is an indicator equal to 1 if the Phase II trial ends after November 23, 2003, the date in which the MMA was signed into law. Note that Medicare Part D did not go into effect until January 1, 2006. Robust standard errors in parentheses and clustered at firm level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Table B2: Impact of Increased Demand on Change in Probability of Approval Following Investment in Phase III Clinical Trials
Logit Model
2000 - 2008

Dependent Variable: Indicator equal to 1 if Received FDA Approval	**(1)**	**(2)**	**(3)**	**(4)**
Medicare*Payer*Post	-2.053*	-2.153**	-2.217**	-2.738*
	(1.08)	(1.08)	(1.08)	(1.55)
Medicare	-1.042*	-1.118*	-0.892	-0.930
	(0.62)	(0.64)	(0.65)	(1.05)
Payer	-1.522	-1.578	-1.390	-2.155
	(0.99)	(1.00)	(0.93)	(1.53)
Post	-0.937	-0.938	-1.224	-1.109
	(0.63)	(0.78)	(0.83)	(1.13)
Payer*Post	2.141*	2.199**	2.353**	2.755*
	(1.11)	(1.10)	(1.08)	(1.54)
Medicare*Post	0.814	0.935	0.917	0.730
	(0.64)	(0.63)	(0.64)	(0.84)
Medicare*Payer	1.390	1.489	1.416	2.227
	(0.98)	(0.97)	(0.89)	(1.48)
Year FE	N	Y	Y	Y
Drug Classification FE	N	Y	Y	Y
Company FE	N	N	N	Y
Observations	994	994	994	846

The dependent variable is equal to 1 if a product was approved by the FDA and 0 if it was terminated during or after Phase III clinical trials. The variable Medicare is an indicator equal to 1 if the disease being treated is one that will be subject to any Medicare Part D reimbursement. This variable Payer is an indication equal to 1 if the drug is designed for the pharmacy, rather than hospital, market. The variable Post is an indicator equal to 1 if the Phase II trial ends after November 23, 2003, the date in which the MMA was signed into law. Note that Medicare Part D did not go into effect until January 1, 2006. Robust standard errors in parentheses and clustered at firm level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Table B3: Impact of Increased Demand on Change in Probability of Investment in Phase III Clinical Trials
Logit DDD Mode
Dropping Oncology Projects

Dependent Variable: Indicator equal to 1 if Received Phase III Investment				
	(1)	**(2)**	**(3)**	**(4)**
Medicare*Payer*Post	12.13***	11.00***	12.11***	26.55***
	(0.95)	(1.34)	(1.37)	(2.00)
Medicare	0.396	0.330	0.560	0.500
	(0.66)	(0.73)	(0.76)	(0.98)
Payer	13.24***	12.15***	13.48***	27.87***
	(0.74)	(1.01)	(1.08)	(1.95)
Post	-1.919**	-1.209	-1.521	-1.348
	(0.81)	(1.17)	(1.17)	(1.41)
Payer*Post	-12.58***	-11.35***	-12.37***	-27.12***
	(0.84)	(1.15)	(1.18)	(2.07)
Medicare*Post	-0.0408	0.168	0.171	0.0790
	(0.78)	(0.84)	(0.86)	(1.09)
Medicare*Payer	-12.49***	-11.40***	-12.66***	-26.40***
	(0.81)	(1.22)	(1.24)	(1.80)
Year FE	N	Y	Y	Y
Drug Classification FE	N	Y	Y	Y
Company FE	N	N	N	Y
Observations	1341	1303	1297	963

The dependent variable is equal to 1 if a product began Phase III clinical trials given that it completed Phase II clinical trials. The variable Medicare is an indicator equal to 1 if the disease being treated is one that will be subject to any Medicare Part D reimbursement. This variable Payer is an indication equal to 1 if the drug is designed for the pharmacy, rather than hospital, market. The variable Post is an indicator equal to 1 if the Phase II trial ends after November 23, 2003, the date in which the MMA was signed into law. Note that Medicare Part D did not go into effect until January 1, 2006. Robust standard errors in parentheses and clustered at firm level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Table B4: Impact of Increased Demand on Change in Probability of Approval Following Investment in Phase III Clinical Trials
Logit Model
Dropping Oncology Projects

Dependent Variable: Indicator equal to 1 if Received FDA Approval	**(1)**	**(2)**	**(3)**	**(4)**
Medicare*Payer*Post	-2.583**	-2.539**	-2.487**	-3.564**
	(1.06)	(1.05)	(1.02)	(1.52)
Medicare	-1.056*	-1.165*	-0.913	-1.354
	(0.61)	(0.65)	(0.66)	(1.12)
Payer	-1.764*	-1.728*	-1.460	-2.350
	(0.97)	(1.00)	(0.92)	(1.59)
Post	-1.179*	-1.267*	-1.483*	-1.666
	(0.62)	(0.75)	(0.80)	(1.15)
Payer*Post	2.383**	2.319**	2.414**	3.077*
	(1.10)	(1.10)	(1.07)	(1.59)
Medicare*Post	1.199*	1.310**	1.193*	1.246
	(0.63)	(0.63)	(0.63)	(0.86)
Medicare*Payer	1.674*	1.653*	1.483	2.780*
	(0.97)	(0.98)	(0.90)	(1.54)
Year FE	N	Y	Y	Y
Drug Classification FE	N	Y	Y	Y
Company FE	N	N	N	Y
Observations	808	808	808	685

The dependent variable is equal to 1 if a product was approved by the FDA and 0 if it was terminated during or after Phase III clinical trials. The variable Medicare is an indicator equal to 1 if the disease being treated is one that will be subject to any Medicare Part D reimbursement. This variable Payer is an indication equal to 1 if the drug is designed for the pharmacy, rather than hospital, market. The variable Post is an indicator equal to 1 if the Phase II trial ends after November 23, 2003, the date in which the MMA was signed into law. Note that Medicare Part D did not go into effect until January 1, 2006. Robust standard errors in parentheses and clustered at firm level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Table B5: Impact of Increased Demand on Change in Probability of Investment in Phase III Clinical Trials and Probability of Approval
Logit Model
Dropping Oncology Projects

Dependent Variable: Indicator equal to 1 if Received Phase III Investment				
	Fewer than 6 Divisions		6 or More Divisions	
	(1)	**(2)**	**(3)**	**(4)**
Medicare*Payer*Post	11.68***	27.98***	-14.27***	-14.39***
	(2.14)	(3.13)	(2.25)	(1.43)
Year FE	Y	Y	Y	Y
Drug Classification FE	N	Y	N	Y
Company FE	N	Y	N	Y
Observations	413	287	562	555

Dependent Variable: Indicator equal to 1 if Received FDA Approval				
	Fewer than 6 Divisions		6 or More Divisions	
	(1)	**(2)**	**(3)**	**(4)**
Medicare*Payer*Post	-1.876	-0.771	-3.326*	-3.885**
	(1.74)	(2.02)	(1.73)	(1.80)
Year FE	Y	Y	Y	Y
Drug Classification FE	N	Y	N	Y
Company FE	N	Y	N	Y
Observations	331	200	477	477

The dependent variable is equal to 1 if a product began Phase III clinical trials given that it completed Phase II clinical trials. The variable Medicare is an indicator equal to 1 if the disease being treated is one that will be subject to any Medicare Part D reimbursement. This variable Payer is an indication equal to 1 if the drug is designed for the pharmacy, rather than hospital, market. The variable Post is an indicator equal to 1 if the Phase II trial ends after November 23, 2003, the date in which the MMA was signed into law. Note that Medicare Part D did not go into effect until January 1, 2006. Robust standard errors in parentheses and clustered at firm level.
* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

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