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A Road Untaken: What Makes Entrepreneurs Promote Breakthrough Innovation?

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Abstract

This paper examines the strategic conditions that drive entrepreneurial innovators to pursue novel innovation rather than innovation that is closer to existing technologies. To an increasing extent, startups commercialize innovation in a cooperative setup. Because radical breakthrough innovation is more difficult to communicate than its incremental counterpart, entrepreneurial innovators may avoid breakthrough innovation for which the cost of developing credible information is exceedingly high. In the context of the Orphan Drug Act (ODA), this study uses a difference-in-difference approach to measure whether entrepreneurs are more likely to bring novel innovations to the market when the policy change unexpectedly lowers the cost of obtaining information that will convince investors through a small market test. Using a new measure of the novelty of innovation and a detailed panel dataset of therapeutic molecules, this empirical study finds that biotech startups bring more breakthrough drugs to markets affected by ODA. This research also finds that in ODA-affected areas, entrepreneurs are more likely to make partnerships with pharmaceutical partners, but the timing of the partnership is delayed to the advanced development stage for startups to create credible evidence of novel drugs. Taken together, the results of this study suggest that the cost of convincing investors prevents entrepreneurs from marketing novel innovation and that a public policy can moderate inefficiency in the "market for ideas" by decreasing the information friction.

KEY WORDS: technology commercialization strategy (TCS), innovation, entrepreneurship, R&D alliance, information asymmetry, biotechnology, the pharmaceutical industry

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"Many investors want to finance drugs that depend on proven mechanisms. Once a novel pathway survives clinical studies, investors are herded into financing projects targeting the same mechanism, leaving other pioneering projects overlooked,"
a manager from a San Francisco-based biotech company

1. Introduction

What types of innovation do startups bring to market through partnership? To an increasing extent, entrepreneurs have commercialized their inventions in a cooperative setup. Entrepreneurs license technological intermediaries to large incumbent firms to access partners' well-established commercialization assets (Teece 1986, Pisano 1991, Gans and Stern 2003, Arora, Fosfuri et al. 2004). The market transaction of an immature technology, however, requires a costly exchange of information between two organizations (Williamson 1979, Hegde 2011, Tadelis and Zettelmeyer 2011, Hermosilla and Qian 2013). In particular, radical breakthrough innovation is often more difficult to communicate than its incremental counterpart because of a lack of available information necessary for valuation (Henderson 1993, Sorescu, Chandy et al. 2003, Hsu 2004, Rothaermel and Deeds 2004, Pisano 2006, Litov, Moreton et al. 2012, Marx, Gans et al. 2014, Alvarez-Garrido 2015). When it is nearly impossible to convey credible information about the prospect of novel innovation, startups may avoid pursuing radically novel projects even when they are capable of undertaking such innovations. My research aims to understand what constraints entrepreneurs face in seeking to commercialize novel innovations and how they overcome these pitfalls using policy incentives.

I use a difference-in-difference approach to measure whether entrepreneurs are more likely to bring novel innovations to market when a policy change unexpectedly helps them to convince partners of the prospect of novel technologies. The empirical context analyzed in this paper is the Orphan Drug Act (ODA). The act originally aimed to facilitate the development of treatments for rare diseases. Interestingly, small drug developers have found that the policy incentives ease the development of "proof-of-concept" products of novel drugs that may attract partners (Howell 2015). Using a new measure of the novelty of innovation and a panel dataset of therapeutic molecules, this empirical study examines whether biotech startups are more likely to market breakthrough drugs in areas affected by ODA. This research finds that in ODA-affected areas, entrepreneurs hold novel projects longer before contracting with licensee partners and generate more revenue streams from pursuing novel innovation. I note that the goal of this paper is not to evaluate the direct impact of ODA on orphan drug development. Rather, this research provides new insight into a positive externality of ODA: the act reduces information asymmetry between entrepreneurial innovators and large incumbent firms seeking to collaborate for novel innovation.

For example, consider the case of Remicade that was initially approved as an orphan drug but soon became a blockbuster drug. Centocor, Inc, a biotech company founded in 1979, developed Infliximab, one of the first drugs based on monoclonal

antibody (mAb) that intervenes in tumor necrosis factor (TNF) to moderate inflammatory responses. The company believed that Infliximab could be used to treat a series of autoimmune diseases. However, the company could neither afford to conduct costly independent clinical studies nor find a financing partner without having prior evidence. Alternatively, the company developed Infliximab as a treatment for the Crohn's disease, a rare inflammatory disorder. By doing so, the firm took advantage of the incentives provided by ODA. Moreover, because the rare disease affected only a small number of patients, the company did not need to recruit many patients for clinical studies, which generated considerable cost savings. When Infliximab was approved as Remicade in 1998, Johnson & Johnson immediately recognized its potential to treat other—more common—inflammatory diseases, such as rheumatoid arthritis and psoriatic arthritis. Two years later, as an independent subsidiary of Johnson & Johnson, Centorcor, Inc, expanded the drug's labels to treat more than eight disorders. Remicade became the first anti-TNF biologic therapy to treat one million patients worldwide, and it is considered one of the most successful orphan drugs. The Remicade example demonstrates how a biotech startup can convince a large partner of the value of a radical drug by showcasing it in a small market using ODA incentives.

Why should we care about the novelty of entrepreneurial innovation? The significant impact of breakthrough innovation on social welfare is well documented (Schumpeter 1942, Rothaermel 2000, Fleming 2001, Katila 2002). Moreover, entrepreneurs have better capabilities and incentives to bring radical innovations to market (Anderson and Tushman 1990, Henderson and Clark 1990, Cohen and Klepper 1996, Cohen and Klepper 1996, Tripsas 1997, Sosa 2009). However, as many small startups draw upon market mechanisms to bring their innovations to market, failure in the "market for ideas" may distort the incentives of entrepreneurial innovators. Prior research studying market inefficiency has primarily focused on the danger of unwanted spillovers (Arrow 1962, Gans, Hsu et al. 2008, Katila, Rosenberger et al. 2008). This study suggests that the enormous costs of transferring information to a partner can also be a source of market inefficiency. The empirical findings have practical implications for startups and policy makers regarding how to moderate the problem of translating the prospect of radical breakthrough innovations. Moreover, this research traces the entire stream of revenues generated from novel technologies beyond the initial commercialization success and thus provides novel insight into the long-term effect of pursuing novel innovation on the growth of an individual firm.

In addition, this study has methodological and therapeutic implications. With few exceptions (Chatterji and Fabrizio 2014, Teodoridis 2014), the direction of entrepreneurial innovation has been overlooked as a result of measurement challenges. Investigating the types of commercialized innovations is even more difficult because one cannot use patent data: filing a patent does not necessarily mean that a patent holder commercializes the technology. This empirical study brings a new measure of the novelty

of marketed technologies based on the originality of the scientific mechanisms behind a drug.

More importantly, less attention has been devoted to types of innovation because prior research has analyzed the commercialization choices of entrepreneurs through the lens of the sequential decision-making process: a startup innovates and then decides whether to market its technology and, if so, how to do so. In reality, however, entrepreneurs consider external factors that affect profit generation from the beginning in determining which projects to advance and ultimately bring to market. In this sense, the innovation and marketing decisions of entrepreneurs are endogenous to environmental conditions (Pinch and Bijker 1987, Lounsbury and Glynn 2001, Kuan 2015). My findings support the view of entrepreneurial decision making in the context of technology commercialization.

This research joins the growing literature on technology commercialization strategies (TCSs). In particular, several recent studies focus on the dynamics of TCSs in which entrepreneurs alternate between different commercialization modes to acquire complementary assets (Wakeman 2010, Hsu and Wakeman 2013, Marx and Hsu 2013) or to develop information that is necessary for partnerships (Marx, Gans et al. 2014). My research aims to add new causal evidence of the dynamics of TCS, thereby connecting TCS research to the literature on radical breakthrough innovation.

This paper proceeds as follows. Section 2 discusses related literature and derives testable hypotheses. Section 3 describes the empirical context and provides a brief scientific background. Section 4 introduces the data, and Section 5 explains the methodology. Empirical results are presented in Section 6. Section 7 concludes the paper.

2. Theory and Hypotheses

A sheer volume of studies on economics and innovation indicates that market outcomes depend on the quality of information available (Greenwald, Stiglitz et al. 1984, Myers and Majluf 1984, Tadelis and Zettelmeyer 2011) and that breakthrough innovations are more vulnerable to value translation problems than are innovations closer to the existing knowledge base (Alvarez-Garrido 2015). This research suggests that entrepreneurs promoting novel innovations have an additional burden in using the market mechanism for commercialization. Thus, changes in environmental factors affecting the cost of convincing may impact the types of innovations transferred in the "market for ideas."

This section first discusses why startups pursuing novel innovation find it more difficult to persuade incumbent partners than their counterparts developing technologies reliant on the existing scientific base. I then review the TCS literature and discuss the dynamic strategies that startups use to overcome these constraints. I derive a series of testable hypotheses by drawing upon the previous research.

2.1 Challenges of developing partnerships for novel innovation

Novel breakthrough innovations are vulnerable to information asymmetry problems. A developer knows the value of her novel technology better than anyone else but often fails to convey this information to a potential partner. Why does this value translation problem occur?

First, large incumbent firms often lack the scientific understanding necessary to evaluate radical new technologies. Many technologies outsourced from entrepreneurial innovators are at the scientific frontier, which could disrupt how an industry operates. In contrast, the strength of incumbent players lies in the deeper understanding of existing technologies and markets. For example, when biotechnology emerged in the 1980s and 1990s, many pharmaceutical companies, most of which had developed drugs based on small chemical molecules, struggled to evaluate the potential of biotechnology-based drugs (Pisano 2006, Hughes 2011, Werth 2013). Even today, biotech firms are considered to have a better understanding of the new technology than large partners do, which accounts for the increasing trend of inter-firm collaboration. When a partner has insufficient knowledge to understand a technology subject to partnership, distinguishing true information from cheap talk is difficult and thus leaves a company vulnerable to a "lemons" problem (Akerlof 1970, Pisano 1997, Mirowski and Van Horn 2005). In this case, previous evidence on performance is critical to convince less informed parties of the prospect of a technology. By nature, however, a radically breakthrough innovation lacks a precedent performance record, making most of the communication efforts of startups unverifiable.

Second, incumbent firms do not have the proper metrics to evaluate the potential of radical technologies. Initially, disruptive technologies perform poorly on dimensions that are currently valued by incumbent partners and consumers (Christensen and Bower 1996, Christensen 2013, Marx, Gans et al. 2014). Consider the case of Pixar. Since its foundation, Pixar visited Disney annually in pursuit of a partnership, but Disney constantly declined the offer for ten years. "Even today there is no electronic process that produces anything close to 'Snow White quality' and there is little reason to believe there ever will be," wrote Frank Thomas, a filmmaking giant at Disney, "and old-fashioned animation has more control and more freedom, and also offers a greater range of expression." Disney clearly believed that Pixar's three-dimensional (3D) computer animation technologies could not match Disney's capabilities, particularly in the aspects that Disney believed were valued by consumers of animation (Price 2009).

In addition to asymmetric information, the high costs involved in novel innovation also make partnerships challenging. The development of radical technologies involves high levels of uncertainty and, thus, high failure rates because of their unique and unprecedented nature. The low probability of success may not justify the costly investments required for the commercialization of a new technology.

Moreover, incumbent firms internally have greater costs of integrating radical technologies because of the fear of cannibalization of existing competences. A firm pursuing radical innovation must adopt both new knowledge and new organization processes (March 1991, Chandy and Tellis 1998, Sorescu, Chandy et al. 2003). Moreover, resources that have been concentrated on existing pipelines should be redistributed or dismissed, which creates resistance within a firm (Kelly and Amburgey 1991, Tripsas and Gavetti 2000). An influential line of research classifies innovations as competence-destroying (those requiring new organizational skills to successfully commercialize) and competence-enhancing (those that build upon existing know-how) innovations (Marx, Gans et al. 2014). New entrants have greater incentives to pursue competence-destroying innovations, whereas established incumbent firms tend to support innovations that sustain or reinforce their existing portfolio (Levinthal and March 1993, Christensen and Bower 1996). When the smartphone market was emerging, for example, LG electronics decided not to enter into the smartphone market, stating "feature phone forever" as its informal slogan. This decision was not reversed until the eventual parent company of LG replaced most of the executive board members of the mobile phone division and ended a long-term partnership with a consulting partner.

Although both information asymmetry and high costs explain the difficulty of commercializing novel innovation through partnership, the latter does not necessarily distort the incentives of players in the "market for ideas." However, the former factor can create inefficiency in the market. Thus, it is important to analyze the causal impact of reduced information asymmetry on the incentives of entrepreneurial innovators capable of novel innovation.

One challenge of using ODA is that the act affects startups' choices simultaneously through two channels. A small market test using the ODA incentives partially solves the information asymmetry problem, but the incentives also decrease the development costs associated with radical innovation. I use a series of empirical tests to distinguish the impact of reduced information asymmetry from the impact of cost reduction.

2.2 Technology commercialization strategies and types of technological innovation

Inspired by the seminal work of Teece (1986), the TCS literature examines the determinants of the commercialization choices of entrepreneurial innovators between independent market entry and collaboration with incumbent partners. Although partnership with incumbent firms allows entrepreneurs to tap into well-established complementary assets in a timely and cost effective manner, the transfer of technologies at early stages also presents the risk of unwanted knowledge spillover (Arrow 1962, Caves, Crookell et al. 1983, Katila, Rosenberger et al. 2008). According to several TCS studies, the more significant incumbent firms' complementary assets are for commercialization and the stronger protection the intellectual property regime provides,

the more entrepreneurial innovators perceive cooperative commercialization choices as attractive (Gans and Stern 2003, Arora, Fosfuri et al. 2004, Gans, Hsu et al. 2008).

Some recent studies note that prior research does not reflect the dynamics of TCS. The commercialization of a technology is not a static game. Rather, startups "switch back" between independent market entry and cooperation with incumbents to either acquire essential assets and skills or develop convincing information with which to persuade potential partners (Wakeman 2010, Hsu and Wakeman 2013, Marx and Hsu 2013). In particular, Marx, Gans, and Hsu (2014) find that when entrepreneurial innovation involves a disruptive technology, startups initially pursue market entry before switching to a cooperative commercialization strategy to reduce the high integration cost for incumbent firms.

The example of Pixar and Disney demonstrates the use of initial market entry in pursuit of future partnership. When Pixar had repeatedly failed to attract the attention of Disney, Lucasfilm suggested a partnership with Pixar to generate the famous scene in Star Trek where the Enterprise spaceship crewmembers practice battles using a virtual simulation machine. The Star Trek scene created by Pixar became the first movie scene that adopted rigorous 3D computer animation technology. Soon after the successful debut of Pixar, the technology division of Disney began seriously considering the potential of 3D technology. Several years later, Disney finally partnered with Pixar to use disruptive technology to produce animation (Price 2009).

However, the independent market entry of a startup is not a feasible option in many high-tech sectors, as advanced development and commercialization require capital-intensive processes and tacit knowledge. For example, a biotech firm rarely can afford to conduct a standard Phase III clinical trial alone. The sponsor of a clinical study must recruit a large number of patients—more than 3,000 in some Phase III clinical trials. Moreover, such a company must monitor whether multiple testing regions apply the same trial protocols and make judgments about the efficacy and safety of tested drugs based on information collected on a regular basis. This task is not easy for a small entrant firm to conduct independently. The vast costs of independent market entry, together with the challenge of partnering with incumbent firms, leave limited commercialization options to startups developing breakthrough innovations.

When an external factor enables startups to conduct small-sized market tests independently, however, startups can develop credible information regarding a novel technology at an affordable cost (Howell 2015). ODA provides a variety of incentives and guidance for developers of treatments for rare diseases, and small startups take advantage of this act to test novel drugs in small clinical trials targeting small markets for rare diseases. Therefore, this context serves as an useful setting to explore the impact of information friction on the types of innovation delivered by entrepreneurs.

Hypothesis 1-1. Entrepreneurial firms are more likely to develop radical breakthrough innovations, as an institutional change reduces communication challenge associated with novel innovation.

One challenge of using ODA in this study is that the act affects the incentives of drug developers through multiple channels. Specifically, distinguishing the impact of the decrease in information asymmetry from the impact of cost reduction is challenging. Two mechanisms may impact entrepreneurs' behaviors in different ways. If an information friction problem is the main reason that firms seek orphan designation, we should observe that the molecules developed by the applicants are novel and are thus difficult to communicate. By contrast, cost reduction leads firms to develop "marginal" drugs that would not have been developed otherwise because of excessively high uncertainty or mediocre economic value. Such marginal drugs are not necessarily novel. Moreover, if the cost reduction channel is the main driver, there should be no difference in the magnitude of impact between distinct groups facing different level of information asymmetry problems.

To distinguish the impacts stemming from different channels, I compare the behaviors of US-based biotech firms and EU-based biotech firms. I argue that the act affects two groups through different mechanisms: the former mainly through the information asymmetry mechanism and the latter through the cost reduction mechanism.

The regional variation in the timing of the ODA enactment across the two regions justifies this approach. ODA has existed since 1983 in the US, allowing US firms to benefit from the cost reduction led by the act. If an US firm wanted to take advantage of cost benefits to advance marginal drugs, it could apply for orphan status in the US without waiting for adoption of ODA by the EU. Although the additional cost reduction may still impact the incentives of US firms, the cost reduction impact is relatively marginal compared with the impact on EU firms. By contrast, because the EU introduced the act in 1999, EU-based firms should observe a relatively dramatic decrease in drug development costs at that time. In summary, the cost reduction channel has a more significant impact on EU firms than on US firms.

However, the information friction channel has greater effects on US firms. Although both US-based biotech firms and EU-based ones can reduce the value translation problem using the ODA incentives, it is the group of US firms that *ex ante* suffers more from the information asymmetry problem in the EU market. Compared to the European counterparts, US firms have relatively little contact with either the European Medicine Agency (EMA) or pharmaceutical companies headquartered in the EU. Networks, reputations, geographic distance, distinct regulatory environment, and language and cultural barriers all create disproportionate obstacles for US firms compared with EU firms in the European market. The EU version of ODA enables

foreign firms entering the EU market to reduce the initially higher level of information friction.

Figure 2 depicts the differential impact of ODA on US-based firms and EU-based firms. I predict that a group of firms that has experienced greater communication challenges is more likely to develop novel drugs as a result of the ODA. An assumption behind the next hypothesis is that the EU version of ODA affects US firms more through the information asymmetry channel rather than through the cost reduction channel and affects EU firms more through the cost reduction channel than through the information asymmetry channel.

Hypothesis 1-2. A group of firms disproportionately affected by information friction is more likely to pursue novel innovation as a response to ODA.

Meanwhile, the availability of small market tests led by ODA also affects the ways in which startups and incumbent partners collaborate. Startups often transfer technological intermediates in an early development stage to finance the projects. This approach does not cause a problem when startups and incumbent partners can correctly estimate the value of technologies at the early stage. For example, when two firms collaborate to develop technologies that are closer to the existing scientific base, both parties have sufficient information available for valuation. For the transfer of radical technologies, however, transactions at the early development stage involve a greater level of conflicts on valuation, and thus, may lead to negative effects on market outcomes stem from a lack of information. When a startup is given the change to showcase a complete form of novel innovation at affordable cost, it can better convince partners of the prospect of a radical technology. Thus, a startup developing novel innovation has an incentive to engage in a series of advanced-stage developments of a new innovation. John Lewicki, the head of the research and development department at OncoMed Pharmaceuticals, addresses this point clearly: [2] the novel drug company wants to "hold onto the (novel) drugs as long as possible and create as much value as we can before partnering our products with large pharmaceutical companies," and "this takes a lot of money."

Hypothesis 2-1. As the Orphan Drug Act eases startups to generate an advanced form of "prototype products," entrepreneurial innovators are more likely to advance their drug development projects longer before contracting with partners.

Understanding the change in partnership practice helps us answer the following question: who should conduct market testing of radical technologies? From a startup's perspective, conducting initial market testing by itself is beneficial because the market

[2] OncoMed Pharmaceutical is a clinical-stage biotech company that seeks to develop an innovative cancer therapy based on cancer stem cell research.

test outcomes reduce information friction and thus help put the firm in a superior bargaining position during a partnership negotiation. This capability also benefits a large partner because it has access to more information at the time of a partnership deal. Moreover, from the social welfare perspective, having startups play important roles in developing radical technologies lead to an efficient market allocation among alliance partners. Startups have a better understanding of disruptive innovations and more incentives to develop such innovations (Schumpeter 1942, Grossman and Hart 1986, Aghion and Tirole 1995). It may result in better outcomes in the market for technology transfer. Therefore, the next hypothesis investigates the impact of ODA on the performances of the "market for ideas."

Hypothesis 2-2. Startups promoting novel innovations are more likely to find partners, as the Orphan Drug Act improves the transferability of the novel technologies.

Finally, I examine how ODA affects long-term commercialization performances of pursuing novel innovation. A firm's expected returns from investing in a particular type of knowledge arise not only from its current product building on this knowledge but also from the entire stream of potential products in the future that may exploit this knowledge (Toh and Polidoro 2013). Do startups promoting radical innovation make profitable and sustainable revenue streams? How do external conditions impact the compensation? The third hypothesis seeks answers to these questions.

Hypothesis 3. The Orphan Drug Act leads startups to generate greater and sustainable revenue streams from pursuing radical innovation.

A contribution of this paper is that the empirical study traces the entire stream of revenues generated from breakthrough innovation beyond the initial commercialization success. This work deepens our understanding of the process through which a startup expands an initially marketed technology to multiple markets to recoup R&D costs accrued in early development stages.

3. Empirical Context

3.1 Drug approval process

A series of strict regulatory procedures and requirements governs the pharmaceutical sector to guarantee the efficacy and safety of approved drugs. Typically, it takes 12 to 18 years for a therapeutic molecule to obtain marketing approval from a regulatory agency such as the Food and Drug Administration (FDA) in the US. Although I mainly discuss the drug approval process in the US in this section, the general procedures are similar for other regions, including the EU.

Figure 1 depicts the drug approval process in the US. A drug developer first identifies a therapeutic molecule or a target that may treat one or multiple disorders. It takes 2–8 years to optimize a lead molecule. With the lead molecule, a company then conducts preclinical studies including animal studies to test the basic safety and efficacy of the molecule, which requires approximately 5-year-long examinations. When the drug candidate survives all the required preclinical studies, the developer submits an Investigational New Drug (IND) application to FDA to conduct clinical studies.

Clinical trials consist of three phases. A Phase I study tests the general safety of a drug candidate with 20–100 healthy volunteers. A Phase II study validates the efficacy of a drug with 100–300 patients who suffer from an initially targeted disease. Finally, in a Phase III trial, trial sponsors perform randomized and controlled multicenter trials to finally confirm the safety and efficacy of a drug with 1,000–3,000 patients. Each phase takes approximately 1.5 years, 2 years, and 3 years, respectively. When a drug has undergone all clinical studies, the developer then submits a New Drug Application (NDA). It takes a year for FDA to review all the procedures and the outcomes to finally approve the marketing of a drug. Failure rate is considerably high in this sector. Only 16% of drugs tested in clinical trials successfully reach to the approval stage.

In many cases, a developer seeks to expand the label of an approved drug beyond the initially targeted disease indication, which is called label expansion (Shineman, Alam et al. 2014). The re-purposing of existing drugs requires another set of clinical studies. But the risks and costs related to the label expansion are much lower than those of developing a brand-new molecule because the safety and efficacy of an existing drug have previously been proven.

3.2 Orphan Drug Act (ODA)

ODA was first enacted by the US in 1983 to facilitate the development of treatments for rare diseases. In the past, most rare diseases remained “orphans” because market sizes were too small to justify the costly development of medications. To intervene in this market failure problem, the policy provided orphan drug developers a variety of incentives, including 50% tax benefits associated with clinical trial costs, regular guidance meetings with the FDA and market exclusivity. The considerable success of the act encouraged the EU and other countries to adopt similar legislation (Lichtenberg and Waldfogel 2003, Cheung, Cohen et al. 2004, Yin 2008). The EU’s adoption of ODA in 1999 marked the greatest change since the enactment of ODA by the US. This research examines the marginal impact of the enactment of ODA by the EU because there were few biotech startups when the US adopted the act in 1983.

To take advantage of the incentives provided by ODA, a drug developer must file an application that states 1) which molecule is used, 2) which disease indication is targeted, and 3) why the molecule is the best therapy for the specific rare disease. An applicant must validate that the target disease satisfies the criteria for a rare disease. In the US, a rare disease is defined as one that affects fewer than 200,000 people each year.

When a regulatory agency approves the application and grants the molecule an orphan designation, the developer can enjoy the ODA incentives to develop the designated molecule as an orphan drug (Grabowski 2005).

Currently, there are 7,000 rare diseases worldwide, affecting around 30 million patients in the US and 350 million worldwide. Approximately 95% of rare diseases lack a single FDA-approved treatment. Nearly 360 orphan drugs have been marketed, and 2,500 compounds have been granted orphan designation so far. The marketed orphan drugs include well-known drugs such as Gleevec, Rituxan and Humira. Some orphan drugs have had enormous success. Rituxan, for example, was granted orphan status for the treatment of B-cell Non-Hodgkin's lymphoma. With expanded use for other types of cancer and rheumatoid arthritis, the drug had sales of $5.24 billion in 2010, becoming the world's second most profitable drug (EvaluatePharma 2013).

Recently, an interesting controversy surrounding the expansion of orphan drugs for multiple indications has arisen. Some advocates of ODA are concerned that drug developing firms are abusing the ODA incentives to develop drugs that potentially cure a broad range of indications, including non-orphan diseases that would thus have been developed without the ODA benefits (Wellman-Labadie and Zhou 2010, Stephens and Blazynski 2014). In the following statement, FDA recently admitted that this gamesmanship exists:

> [...Nevertheless, controversy has existed over some drug manufacturers exploiting the ODA by marketing orphan-approved drugs for non-orphan use or by monopolizing drug markets. Recently, the FDA has issued final regulations that seek to clarify the ODA in an attempt to ameliorate these problems. ... The FDA believes that drug companies were previously seeking out the narrowest possible orphan subsets "to avail themselves of orphan-drug benefits when the overall approved use is not an orphan use." ...]

Others argue that it is the potential of label expansion of orphan drugs that motivates drug developers to invest in orphan drug development (Johnson 2014). From this perspective, the re-purposing of a novel orphan drug for non-rare indications may increase social welfare, by benefitting both patients who suffer from rare diseases and those from common diseases.

4. Data

I develop a panel dataset that includes the detailed development and commercialization histories of therapeutic molecules. The dataset includes all drug development projects across the globe from 1980 to 2014. I combine multiple sources to develop this dataset.

The study primarily draws upon the Pharmaproject database to collect the list of pharmacological research projects and associated characteristics. I collect the unique drug ID; drug name; originator; licensees; target disease indications; related patent numbers; and dates of main events such as dates of entry, patent application, licensing agreement, approval, and expansion to new disease indications. Additionally, the dataset comprises detailed molecule-specific characteristics including the mechanism of action, route, origin, weight, molecule structure (the number of hydrogen bond (H.Bond) donors, H.Bond acceptors, and rotatable bonds), diffusion speed within a human body (logP), whether a molecule is patented, and whether it is a New Chemical Entity (NCE). The database is widely used by researchers in life science as well as in innovation and management (Metrick and Nicholson 2006, Alcacer, Cantwell et al. 2007, Sorescu, Chandy et al. 2007, Blume-Kohout and Sood 2008, Adams and Brantner 2010, Berndt and Trusheim 2012).

I complement the database with clinical trial data and orphan designation data. The clinical trial data are collected from clincialtrial.gov. The US orphan designation data is obtained from the FDA website, and the EU data is from the EMA website. The final dataset includes a detailed history of each drug candidate, including both successful drugs and discontinued drugs, from entry to approval and label expansion (or discontinuation in the case of discontinued products).

Table 1 presents summary statistics. The original data includes 49,890 unique therapeutic molecules that underwent testing between 1983 and 2014. There are 2,481 available MOAs. 12% of 1,189 existing disease indications are rare diseases. Diseases are categorized into 15 disease categories, including alimentary/metabolic, blood and clotting, cancer, cardiovascular, dermatological, genitourinary, hormonal, immunological, infectious disease, musculoskeletal, neurological, parasitic, respiratory and sensory disorders. 42% of the tested drugs belong to disease categories disproportionately affected by the ODA. Small biotech firms develop 57% of the therapeutic molecules in the dataset. Note that I do not consider established biotech companies such as Amgen and Genentech small biotech firms. The first-generation biotech firms possess complementary resources, experience and reputation that are equivalent to those of large pharmaceutical companies.

5. Empirical Study Design

5.1. Methodology

I use a difference-in-difference (DiD) approach to test the main hypotheses. The unit of analysis is at the therapeutic molecule and disease category level. To formalize the DiD method and to facilitate statistical interference, I estimate the following equation:

$$Y_{ijt} = \alpha_j + \gamma_t + X_i'\mu_i + \beta_0 Affected_{ij} + \beta_1 AfterODA_{it} + \beta_2 Affected_{ij} * AfterODA_{it} + \varepsilon_{ijt}$$

where Y_{ijt} represents the outcome variable (the novelty of innovation, an indicator of whether it is licensed, the timing of the first licensing deal, and market expansion outcomes), i indexes individual therapeutic molecules ($i \in \{1, ..., 49{,}890\}$), j indexes disease categories ($j \in \{1, ...,15\}$), and t indexes year ($t \in \{1983, ..., 2014\}$). *AfterODA* is a binary variable equal to 1 if a molecule entered for testing after 2000 and 0 otherwise.

Affected is a binary variable equal to 1 if a molecule is developed to treat disease categories disproportionately affected by ODA and 0 otherwise. I use the nature of rare diseases to determine the treatment group and the control group. As shown in Figure 3, most rare diseases are either genetic disorders or abandoned disorders for economic reasons, generally falling into the categories of blood and clotting disorders, cancers, infectious diseases and parasitic diseases. The four categories are the treatment group in my study, and the other eleven categories are assigned as the control group.

The coefficient of interest is β_2. The coefficient captures the difference in the outcome variables of the treatment group relative to the control group. β_0 and β_1 explain any effect caused by shocks specific to the treated disease categories and by the shocks that occur concurrently with ODA, respectively. I include disease category fixed effects and year fixed effects. $\mathbf{X}_i$ is a vector of control variables. Errors are clustered at the disease category level.

I use a triple DiD method to test *Hypothesis 1-2*. With a triple difference estimator, I compare the evolution of the gap between the group of firms suffer from a greater level of information asymmetry and its counterpart in the treatment group to the evolution of the gap in the control group. The estimated formula is as follows:

$$Y_{ijkt} = \alpha_j + \gamma_t + X_i'\mu + \beta_0 Affected_{ij} + \beta_1 AfterODA_{it} + \beta_2 LessInfo_{ik} + \beta_3 Affected_{ij} * AfterODA_{it} + \beta_4 Affected_{ij} * LessInfo_{ik} + \beta_5 AfterODA_{it} * LessInfo_{ik} + \beta_6 Affected_{ij} * AfterODA_{it} * LessInfo_{ik} + \varepsilon_{ijkt}$$

where $LessInfo_{ik}$ is an indicator variable that equals 1 if a molecule is originated by a group of firms that suffer more from information asymmetry (*H1-2*), i.e., US firms. Molecule-specific controls are included. As the dependent variable is a binary variable, I run binomial logit regressions for *H1*.

To test the second hypothesis upon the propensity and the timing of licensing contracts, I perform a survival analysis using a Cox proportional hazard model. The model requires two dependent variables. One is an indicator that equals 1 if an event of interest occurs and 0 otherwise. The other variable measures the time difference between the entry of an observation and the realization of an event of interest. I construct the latter variable by measuring the time difference between the entry of a molecule and the date of

the first licensing contract associated with the molecule. The estimated regression formula is the same as that for *H1-1*.

I use the same DiD formula to test the third hypothesis, which examines the trajectories of label expansions for additional disease indications beyond the initially targeted disease. Naturally, the dependent variable is a count variable. Thus, I test the outcomes with Poisson regressions and negative binomial regressions.

5.2. Variables

Dependent variables

Novelty of innovation (H1) I measure the novelty of drugs using the originality of the mechanisms used by drugs. A drug intervenes in the human body through a specific mechanism. For example, angiogenesis-inducing cancer drugs block the oxygen delivery channels to tumor cells to induce the natural death of cancerous cells. Some mAb-based cancer drugs deliver toxins directly to the problematic cells. Most allergy medications block histamine receptors to reduce the level of histamine absorbed in the body. These mechanisms are called Mechanism Of Actions (MOAs). MOA is not only a widely used term among drug developers and researchers in related fields (Danzon 2000, Higgins and Rodriguez 2006, Toh and Polidoro 2013) but also an important measure of the novelty of drugs, as indicated in the following Nature article.

> "As a productivity year I'd give [2014] a 3 out of 3," says Chris Milne, Director of Research at the Tufts Center for the Study of Drug Development in Boston, Massachusetts, USA. In terms of innovation, however, Milne ranked the 2014 approvals only "a 2 out of 3." The reasons being, drug companies seek approvals for agents that act on *the same proven targets and indications.* For example, among four drugs approved for type 2 diabetes, two are second- and third-in-class sodium-glucose cotransporter 2 inhibitors to treat type 2 diabetes and the other two are fourth- and fifth-in-class glucagon-like peptide 1-receptor agonists. "There is some of that herd mentality here," he notes (Mullard 2015).

I identify each MOA used by a therapeutic molecule. I then sort molecules by MOA, disease category and entry date to generate a sequence number. If the number is 1, then the molecule introduces a brand-new mechanism to treat a disease category for the first time. 2 indicates that a drug is the second one adopting a novel mechanism. In that sense, the sequence number is used as a "novelty score."[3] In addition, I construct a binary variable that assigns a value of 1 to the first five drugs that use a novel mechanism and 0 to the others, to take into account that several drug developers often compete on a novel

[3] Note that an MOA is not subject to patenting. Although patents offer strong protection for pharmaceutical inventions, patents do not award exclusionary rights over the scientific principles underlying drugs.

mechanism so one might not say the first one precedes the second one. The reported regression results use the binary variable as the dependent variable. I conduct robustness checks by adjusting the number of drugs that use a brand-new mechanism—1, 3, 5 and 7—and by using the novelty score itself as a dependent variable. The empirical results are robust to the modifications.

Probability and timing of partnership (H2) I use a Cox proportional hazard model to examine changes in the timing *(H2-1)* of partnership agreements and the probability of making a partnership *(H2 -2)*. The analysis requires two dependent variables. One is an indicator variable for whether an event of interest—a licensing deal, in this case—occurs. I construct a binary variable that assigns a value of 1 if a molecule is subject to at least one licensing agreement and 0 otherwise. The other dependent variable measures the time difference between the entry of a project and the first partnership contract. The Pharmaproject database traces conference presentations, press, patent filings, websites, and personal contacts to identify the entry of new therapeutic molecules. I use the date that each molecule first appears in the database as the entry date. I sort all licensing agreements related to a therapeutic molecule by dates and select the earliest deal. Then, I calculate the time difference between the entry date and the date of the first licensing contract.

Market expansion (H3) As shown in Figure 1, a drug developer can generate a subsequent stream of revenues by re-purposing a previously approved drug. Firms pursuing label expansion must determine which additional diseases to target and conduct a required set of clinical trials. The Pharmaproject database reports the approvals of label expansion as well as the approved date of the statement. I construct a count variable that quantifies the market expansion events related to each drug.

Independent variables

Affected This binary variable equals 1 if a molecule is developed to treat diseases within blood and clotting, cancer, infectious disease or parasitic categories and 0 otherwise.

AfterODA This binary variable equals 1 if a molecule entered after 2000 and 0 otherwise.

LessInfo To clarify the channels through which ODA impacts the novelty of entrepreneurial innovation, *H1-2* compares the size of the impact between the group of firms that initially have a greater level of information friction and the group that is less vulnerable to information asymmetry. I restricted the sample to a group of biotech firms in the EU or the US and construct a firm-level group dummy variable that assigns a value of 1 to US firms and 0 to others. Because EMA and European pharmaceutical companies have less reputation or information about US biotech firms compared to EU counterparts,

the reduction of information asymmetry led by ODA should have stronger impact on US firms than EU firms.

Control variables

Molecule-specific characteristics I control for whether a molecule is patented and whether it is a new chemical entity (NCE). Previous literature documents that patents affect the technology commercialization modes of entrepreneurs. Also, FDA and EMA provide a series of fast-track drug approval processes for NCEs to facilitate the introduction of the disruptive innovations to market. Additionally, I control the route, origin, drug diffusion rate (logP), weight and structure (H.Bond donors, H.Bond acceptors and rotatable bonds) of each therapeutic molecule.

6. Results

6.1. Novelty of innovation (*H1*)

Figure 4 presents the trend of the novelty of entrepreneurial innovation over time. The decrease in novelty over time is not surprising, as firms repeatedly use pre-existing MOAs. In the treated disease categories, the rate of decreasing speed is higher. However, after ODA, the novelty of drugs in treated categories springs back and catches up the level of novelty in control categories.

Table 2 shows the DiD estimates of the novelty of drugs developed by biotech startups. In the logit regression in Column (5), the coefficient of ODA dummy is –-0.801, which gives the odd ratios exp (-0.801) = 0.45. Firms are 63% less likely to develop drugs based on a novel mechanism after ODA. A switch from the control disease categories to the treated disease categories yields a change in log odds of (-0.801 + 0.321) = -0.48. The ratio of these two odds ratios is the coefficient of interest in my study. The coefficient of the interaction term is 0.321, generating the odd ratios exp(0.321) = 1.38. Firms within the treated categories are two times more likely to adopt new mechanisms to develop drugs.

Both causal impact and selection into the affected categories can explain the increase in the novelty of entrepreneurial innovation. On one hand, the enactment of ODA encourages firms to develop radically novel molecules that they would not have advanced otherwise. On the other hand, firms developing novel MOAs may decide to target the disease categories that are disproportionately affected by the act. To separate these two mechanisms, I replicate the estimation in Table 2 using the Phase I clinical trial starting dates instead of molecule entry dates. As shown in Figure 1, it takes approximately 6 to 8 years for a newly studied molecule to enter into clinical studies. Moreover, the list of pre-clinical studies by FDA or EMA varies over disease categories It means that drug developers cannot easily switch from one category to another to run

clinical trials. Thus, if the novelty of drugs entering into phase I clinical trials increases sharply after ODA, then the impact is causal rather than driven by selection.

Table 3 presents the estimation. The coefficient of the interaction term is not only greater but also more significant than that in Table 2. The ratio of the odds ratios in Table 3 ranges from 4.74 to 5.16. According to Column (5), the probability that a firm adopts a new mechanism to develop a drug falls from 0.78 to 0.09 after ODA. However, in the treated disease categories, the probability increases from 0.09 to 0.80, recovering the original level prior to ODA. It suggests that firms in the treated categories are approximately eight times more likely to advance novel drugs to phase I clinical trials than are firms in the control categories.

Next, I test *H1-2* to investigate the heterogeneous impact of the EU ODA on firms across region. ODA simultaneously reduces information asymmetry and drug development costs. Thus, I compare the responses of US firms and EU firms to the act, assuming that ODA affects US firms primarily through the information asymmetry channel and affects EU firms through cost reduction. The trend of novelty by firm region in Figure 5 supports my prediction. In the control disease categories, the novelty of drugs developed by both EU firms and US firms steadily decreases, and no difference between the two groups emerges. In the treated categories, however, US firms bring more novel drugs to market than EU firms do.

Table 4 shows the outcomes of triple DiD estimations. The coefficient of interest is one of $Affected_{ij} * AfterODA_{it} * LessInfo_{ik}$. It accounts for the evolution of the gap between US firms and EU firms in the treated categories compared with the control categories. The ratio is approximately 2 and is significant across all columns. According to Column (5), the coefficient of the triple interaction term gives odd ratios exp(0.919) = 2.507. This result indicates that, in the affected disease categories, approximately 6% of EU firms adopt novel mechanisms to develop drugs, while 13% of US firms choose to introduce novel drugs as a result of the ODA by the EU. Alternatively, I restrict my samples to the molecules developed by US firms and those by EU firms to separately run DiD regressions with the restricted samples. Columns (6) and (7) suggest that that ODA causes US developers to adopt more radical technologies but have no such impact on EU firms.

6.2. Collaboration practice (*H2*)

I employ survival analysis to examine the practice of collaboration and the probability of entering into a partnership. Figure 6 presents the cumulative density functions of the survival functions. In the empirical context, “survival” means that at least one licensing agreement is made on a subject molecule. Panel (c) in Figure 6 shows that in the ODA-affected group, firms have a higher probability of signing licensing deals. Table 5 echoes this prediction. The coefficient of the interaction terms indicates that the odd ratio is exp(0.133) = 1.14. After the ODA, molecules in the treated disease categories have a 6% higher probability of being licensed.

Meanwhile, the probability density function of the affected group continually lags behind its counterpart density during the period of 1,800 days since entry. It suggests that developers in the affected group postpone the timing of the first licensing deal to create as much information as possible before entering negotiations. To statistically confirm the difference in the timing of licensing deals, I run a two-sample Kolmogorov-Smirnoff test. The test yields D = 0.0555 and p-value = 0.00006637, rejecting the null hypothesis. The finding is consistent with the prediction in *H2-1*.

6.3. Market expansion (*H3*)

Finally, Table 6 shows the DiD estimates of label expansion (i.e., re-purposing of drugs). By expanding the label of approved drugs, developers are allowed to sell drugs in other disease markets beyond the initially targeted disease. Thus, the re-purposing of an approved drug is an important means of generating sustainable revenues from investing in a technology. The Poisson regression yields a significant and positive coefficient of the interaction term. Exp(0.245) = 1.28 indicates that, when other predictor variables are held constant, the molecules in the affected group are extended for use in 28% more disease indications. The size of the impact appears even greater when I restrict the scope to molecules adopting novel MOAs only in Column (4) - Column (6).

The dataset includes many molecules that are never extended to other disease indications. Thus, I run negative binomial regressions and confirm that the size and the significance of the coefficients remain the same. Figure 7 shows that, among novel drugs entered after ODA, molecules in the treated disease categories are expanded to treat three more disease indications on average than those in the control categories.

7. Discussion and Conclusion

Breakthrough innovations significantly improve social welfare as well as the growth of individual firms, yet relatively little is known about what leads entrepreneurial firms to commercialize novel innovations. As startups rely heavily on partnerships with incumbent firms to bring their inventions to market, the small firms may avoid developing radical technologies that are not communicated well because of information friction. ODA is an ideal empirical context to test the variation in the novelty of entrepreneurial innovations across a group as a response to ODA. I find evidence that entrepreneurs are two times more likely to develop radical technologies when ODA eases startups generate convincing evidence of the prospect of novel drugs through small clinical trials designed for rare disease treatments. The magnitude of the impact is greater among a group of firms that suffer more from information friction *ex ante*, implying that the challenge of information transfer indeed keeps startups from promoting breakthrough innovation. The results also show that entrepreneurs hold their projects longer before contracting with partners as a result of ODA. The delay occurs since startups develop

more novel innovations, as they are enabled to provide convincing "proof of concepts" of those due to ODA. In the ODA-affected disease categories, finally, startups generate a greater and more sustainable stream of revenues from developing novel drugs by expanding the use of novel drugs to treat a greater number of disease indications.

To the best of my knowledge, the research is one of the first papers that study the qualitative aspect – novelty - of innovation transferred through the "market for ideas," thereby contributing to the growing literature on TCS. The findings suggest that, although small innovators are capable of breakthrough innovations, the firms in need of collaboration may be steered away from those and toward technologies that are easier to communicate. From the perspective, this research also provides an insight to the Schumpeterian question. We need to take the increasing trend of inter-firm collaboration between small entrant firms and large established firms into account to find a better answer for which firms (small or large) introduce novel innovations.

My findings are also related to the question regarding firm boundaries. This research shows how the type of technological innovation affects the division of labor among alliance partners. As a transaction of novel innovation requires more information, it may be efficient for a developing firm—a more informed party—to advance a technology for a long period enough develop a prototype product or to conduct a small market test. A public policy could facilitate the efficient allocation of resources between small innovators and large commercialization partners.

Finally, the evidence in this paper provides new insight into the ongoing controversy surrounding the exploitation of ODA. While some claim that firms are abusing the public resources to develop drugs that would have otherwise been developed, my research on the positive externality of ODA implies that it may increase welfare by facilitating the development of novel treatments for both rare diseases and common diseases that wouldn't have been brought to market because of huge information friction. It also implies that we might need more public interventions similar to ODA to help moderate the costly communication associated with breakthrough innovation.

This study encourages me to examine other aspects related to radical innovations developed by entrepreneurs. First, a firm promoting novel innovation obviously needs more funding to develop a prototype product before bringing it to a large financing partner. Private venture capitalists (VCs) and angels may fill this financing gap. In addition, mechanisms underlying the impact of VC investments may vary based on the types of innovation. One of the subsequent chapters of my dissertation studies the response of professional investors to ODA.

Second, it is important to understand the welfare effect of novel drugs brought by ODA. The development and the expansion of ODA-driven novel drugs benefit both patients who suffer from rare diseases and those from common diseases. However, in this situation, patients with common diseases must wait until novel therapies are brought first to treat rare diseases to use the ODA incentives. If the loss of welfare created by the delay

is considerable, then we may need to have interventions similar to ODA to ensure the timely delivery of novel drugs to both patients with rare diseases and those with common diseases (Budish, Roin et al. 2013, Howell 2015).

Finally, what types of entrepreneurs bring radical technologies to market? Technological startups have diverse origins, including corporation spin-offs and academic entrepreneurs. Accelerators and angel investors, private and corporate VCs, and public grant provision programs such as the National Institutes of Health (NIH) and the Small Business Innovation Research Program (SBIR) provide a variety of guidance and funding, that may influence the incentives and behaviors of financed startups in a different manner(Chatterji 2009). It would be interesting to observe how the impact of ODA varies over different types of entrepreneurs and different supporting mechanisms.

Tables

Table 1: Chapter 1. Descriptive Statistics

Descriptive Statistics

Statistic	N	Mean	St. Dev.	Min	Max
Entry year	72,972	2,002.894	7.393	1,983	2,014
Phase I trial year	16,005	2,004.431	6.441	1,989	2,014
Phase II trial year	17,234	2,004.298	6.668	1,989	2,014
Phase III trial year	9,310	2,003.664	6.987	1,989	2,014
Novelty score	72,972	70.061	174.427	1	1,344
Novel MOA (binary)	72,972	0.163	0.369	0	1
Molecular.Weight	34,527	466.767	282.251	0.000	3,736.210
logP	33,788	2.265	3.178	-28.460	20.680
H.Bond.Donors	34,207	2.489	3.617	0	53
H.Bond.Acceptors	34,207	5.594	4.738	0	66
Rotatable.Bonds	34,207	7.374	7.610	0	112
Small originators	87,523	0.574	0.495	0	1
Affected category	85,669	0.421	0.494	0	1
Licensed	87,523	0.166	0.372	0	1
Times from entry to licensing	13,060	1,473.975	1,422.639	0	10,655
Rare diseases	87,523	0.125	0.330	0	1
Entry after ODA	72,972	0.692	0.462	0	1
Patented	87,523	0.222	0.416	0	1
EUfirm	87,523	0.328	0.469	0	1
USfirm	87,523	0.429	0.495	0	1
Number of unique molecules	49,890				
Number of unique diseases	1,188				
Number of unique categories	15				
Number of unique MOAs	2,481				

Table 2: DiD Estimates: Impact of ODA on the Novelty of Entrepreneurial Innovation

	Dependent variable:				
	Novelty of MOA used in drugs				
	(1)	(2)	(3)	(4)	(5)
AffectedCategory	-0.634**	-0.669**	-0.045***	-0.230***	-0.508**
	(0.250)	(0.272)	(0.015)	(0.070)	(0.221)
AfterODA	-0.981***	-1.839***	-0.996***	-1.693***	-0.801***
	(0.067)	(0.170)	(0.073)	(0.097)	(0.128)
AffectedCategory:AfterODA	0.142*	0.148	0.115	0.120	0.321**
	(0.072)	(0.097)	(0.075)	(0.087)	(0.134)
Constant	0.049				
	(0.131)				
Molecule Controls	No	No	No	No	Yes
Year Fixed Effect	No	Yes	No	Yes	Yes
Category Fixed Effect	No	No	Yes	No	Yes

Note: Molecule-level observation. All estimates are from binomial logit regressions. Samples are biotech firm-originated molecules only.
*p<0.10; **p<0.05; ***p<0.01.

Table 3: DiD Estimates: Impact of ODA on the Novelty of Drugs Entering Phase I Trials

	Dependent variable: Novelty of drugs advanced to Phase 1 clinical trials				
	(1)	(2)	(3)	(4)	(5)
AffectedCategory	-2.440***	-2.580***	1.582***	-2.087***	-2.209***
	(0.401)	(0.432)	(0.059)	(0.335)	(0.483)
Ph1_afterODA	-2.548***	0.368	-2.545***	0.461**	-2.080***
	(0.299)	(0.254)	(0.304)	(0.192)	(0.425)
AffectedCategory:Ph1_afterODA	1.640***	1.710***	1.598***	1.675***	1.556***
	(0.300)	(0.356)	(0.310)	(0.362)	(0.433)
Constant	3.509***				
	(0.359)				
Molecule Controls	No	No	No	No	Yes
Year Fixed Effect	No	Yes	No	Yes	Yes
Category Fixed Effect	No	No	Yes	No	Yes

Note: Molecule-level observations. All estimates are from binomial logit regressions. Samples in Column (1) to (5) include all therapeutic molecules entered to the Phase I clinical trials.
*p<0.10; **p<0.05; ***p<0.01.

Table 4: Triple DiD Estimates: Heterogeneous Impact of ODA on the Innovation of US Biotech Firms and EU Biotech Firms

	Dependent variable:						
	Novelty of Innovation						
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
AffectedCategory	-0.723***	-0.777**	0.103	-0.446***	0.703**	-1.160***	-0.377
	(0.262)	(0.305)	(0.065)	(0.131)	(0.307)	(0.280)	(0.269)
AfterODA	-0.978***	-1.465***	-1.016***	-1.305***	-2.826*	-1.330***	-0.721***
	(0.092)	(0.149)	(0.109)	(0.120)	(1.468)	(0.118)	(0.258)
USfirm	0.388***	0.490***	0.337**	0.437***	0.886***		
	(0.137)	(0.149)	(0.151)	(0.164)	(0.127)		
AffectedCategory:AfterODA	0.014	0.061	-0.013	0.038	0.048	1.013***	0.116
	(0.139)	(0.145)	(0.148)	(0.138)	(0.342)	(0.153)	(0.226)
AfterODA:USfirm	-0.265**	-0.388***	-0.212	-0.335**	-0.556**		
	(0.123)	(0.139)	(0.140)	(0.159)	(0.232)		
AffectedCategory:USfirm	-0.203	-0.195	-0.175	-0.161	-0.383		
	(0.161)	(0.177)	(0.161)	(0.179)	(0.271)		
AffectedCategory:AfterODA:USfirm	0.459***	0.402**	0.441**	0.378**	0.919**		
	(0.169)	(0.177)	(0.173)	(0.181)	(0.364)		
Constant	0.348***						
	(0.115)						
Molecule Controls	No	No	No	No	Yes	Yes	Yes
Year Fixed Effect	No	Yes	No	Yes	Yes	Yes	Yes
Category Fixed Effect	No	No	Yes	No	Yes	Yes	Yes

Note: Molecule-level observations. All estimates are from binomial logit regressions. Samples in Columns (1) to (5) include all therapeutic molecules developed by small biotech firms. Columns (6) and (7) are DiD estimates with the molecules originating from American biotech firms and from European biotech firms, respectively.
*p<0.10; **p<0.05; ***p<0.01.

Table 5: Survival Analysis Estimates: Impact of ODA on Licensing Probability and Timing of Deals

	Dependent variable: log(hazard ratio of being licensed)				
	Survival Analysis: Likelihood of Contracting a Licensing Agreement				
	(1)	(2)	(3)	(4)	(5)
AffectedCategory	-0.179***	-0.165***	0.296	0.180	-0.031
	(0.038)	(0.040)	(0.205)	(0.207)	(0.056)
AfterODA	0.334***	2.381***	0.329***	0.510	0.074
	(0.034)	(0.583)	(0.034)	(0.583)	(0.053)
AffectedCategory:AfterODA	0.081*	0.099**	0.094*	0.110**	0.133*
	(0.048)	(0.049)	(0.048)	(0.049)	(0.071)
Molecule Controls	No	No	No	No	Yes
Category Fixed Effect	No	No	Yes	No	Yes
Year Fixed Effect	No	Yes	No	Yes	Yes
Observations	7,676	7,676	7,676	7,676	3,452
R^2	0.033	0.139	0.040	0.143	0.120
Max. Possible R^2	1.000	1.000	1.000	1.000	1.000
Log Likelihood	-60,869.150	-60,425.380	-60,841.250	-60,404.640	-24,455.220
Wald Test	246.390*** (df = 3)	1,300.770*** (df = 31)	303.600*** (df = 15)	1,334.830*** (df = 43)	489.960*** (df = 23)
LR Test	257.240*** (df = 3)	1,144.779*** (df = 31)	313.034*** (df = 15)	1,186.250*** (df = 43)	440.433*** (df = 23)
Score (Logrank) Test	249.475*** (df = 3)	1,524.387*** (df = 31)	307.086*** (df = 15)	1,568.237*** (df = 43)	521.423*** (df = 23)

Note: Molecule-level observations. All estimates are from Cox proportional hazard models.
*p<0.10; **p<0.05; ***p<0.01.

Table 6: DiD Estimates: Impact of ODA on the Subsequent Commercialization of Novel Drugs

	Dependent variable:					
	Drug Label Expansion (Re-purposing)					
	(1)	(2)	(3)	(4)	(5)	(6)
AffectedCategory	-0.024	-0.026	0.010	0.047	0.047	0.033
	(0.024)	(0.024)	(0.041)	(0.035)	(0.036)	(0.058)
ODA	-0.021	0.074***	-0.298	0.056**	0.104	-0.549
	(0.019)	(0.029)	(0.254)	(0.027)	(0.070)	(0.569)
AffectedCategory:ODA	-0.005	0.00003	0.131**	0.017	0.030	0.245***
	(0.027)	(0.028)	(0.052)	(0.043)	(0.043)	(0.079)
Constant	0.243***			0.321***		
	(0.016)			(0.022)		
Molecule Controls	No	No	Yes	No	No	Yes
Year Fixed Effect	No	Yes	Yes	No	Yes	Yes
Observations	24,140	24,140	4,880	7,106	7,106	1,710
Log Likelihood	-29,999.790	-29,882.590	-6,676.685	-10,323.580	-10,234.080	-2,674.318
Akaike Inf. Crit.	60,007.580	59,831.190	13,459.370	20,655.170	20,534.170	5,454.637

Note: Molecule-level observations. All estimates are from Poisson regressions. Samples in Columns (1) to (3) include all therapeutic molecules. Samples in (4) to (6) only include novel therapeutic molecules.
*p<0.10; **p<0.05; ***p<0.01.

Figures

Figure 1: Drug Approval Process in the US

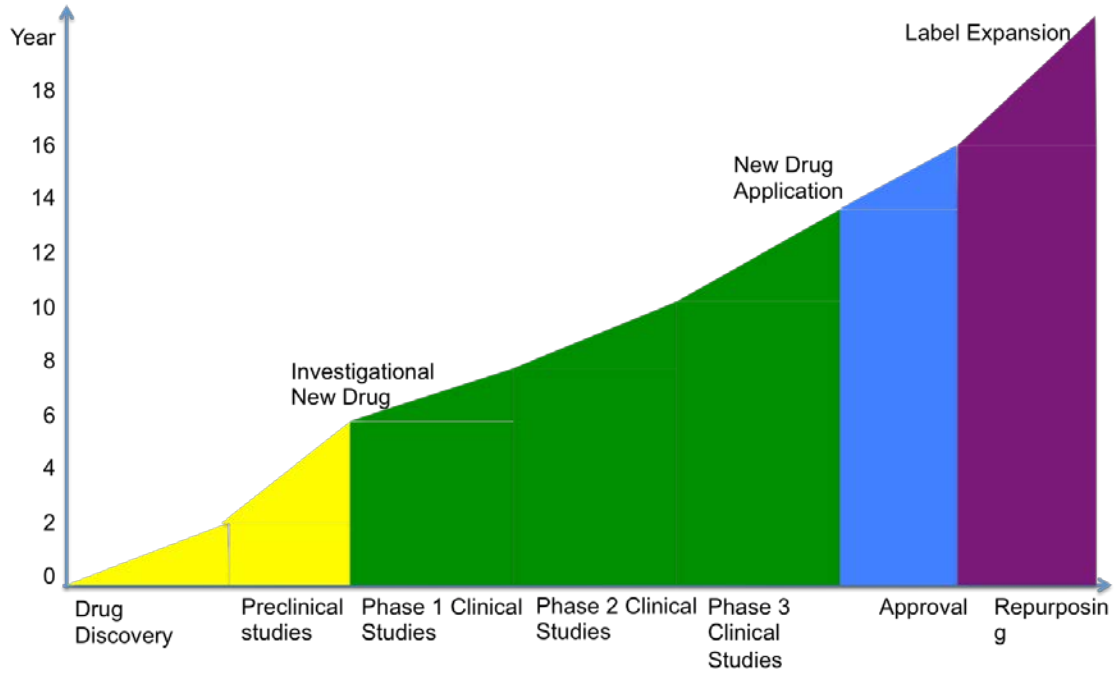


Figure 2: Mechanisms Behind the Impact of ODA

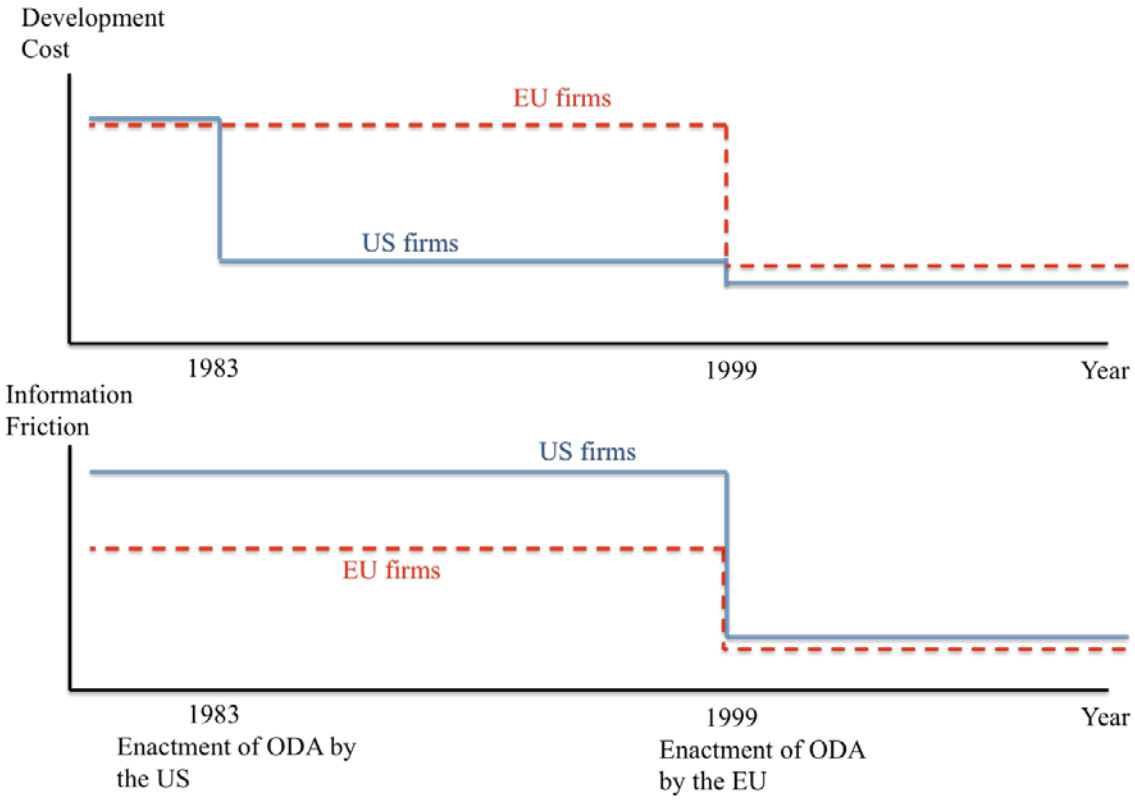


Figure 3: Category Classification of Common Diseases and Rare Diseases

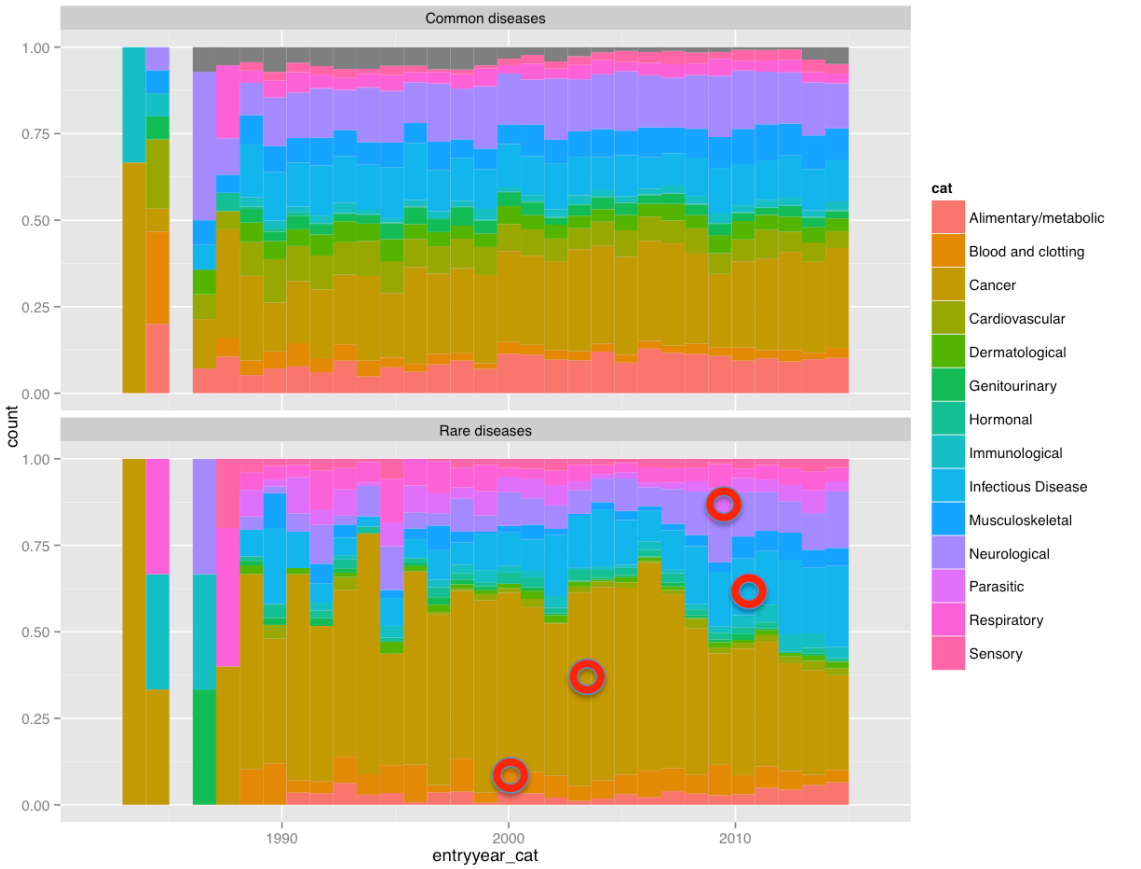


Figure 4: Novelty of Entrepreneurial Innovation over Time

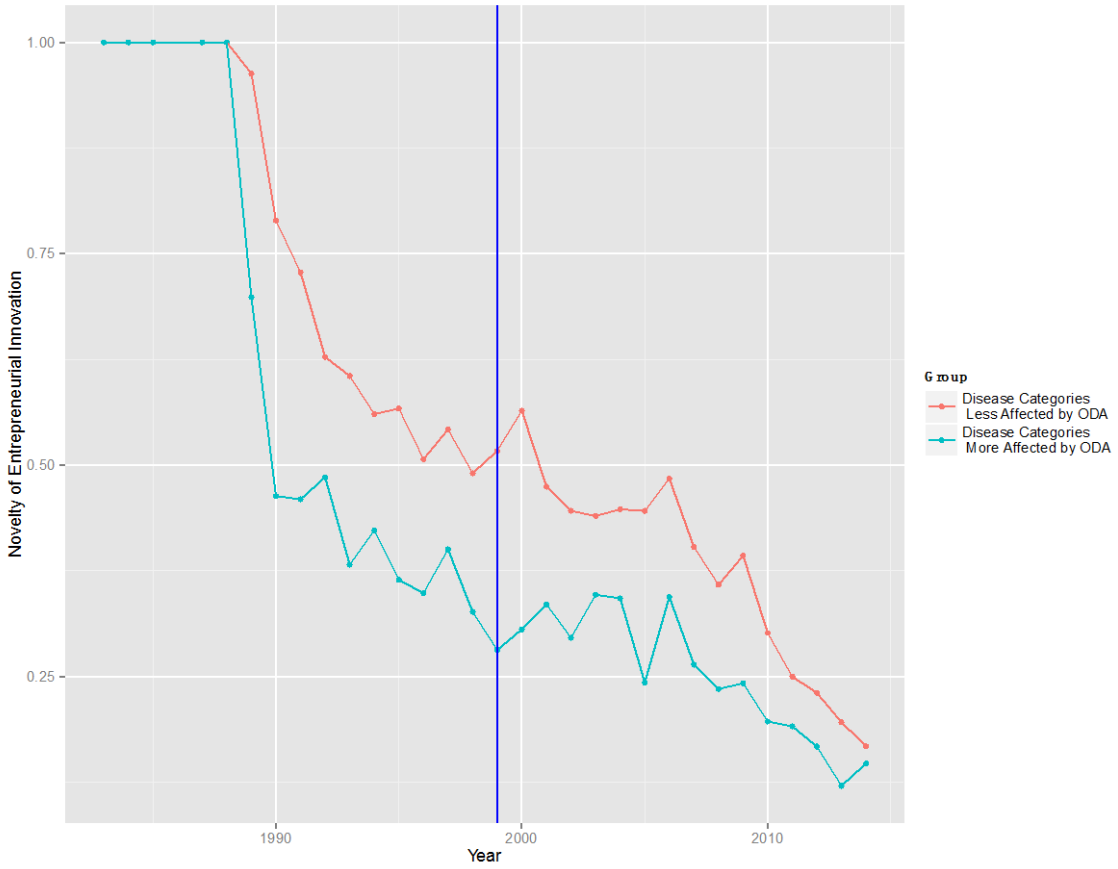


Figure 5: Changes in the Novelty of Innovation by Firm Region and Disease Groups

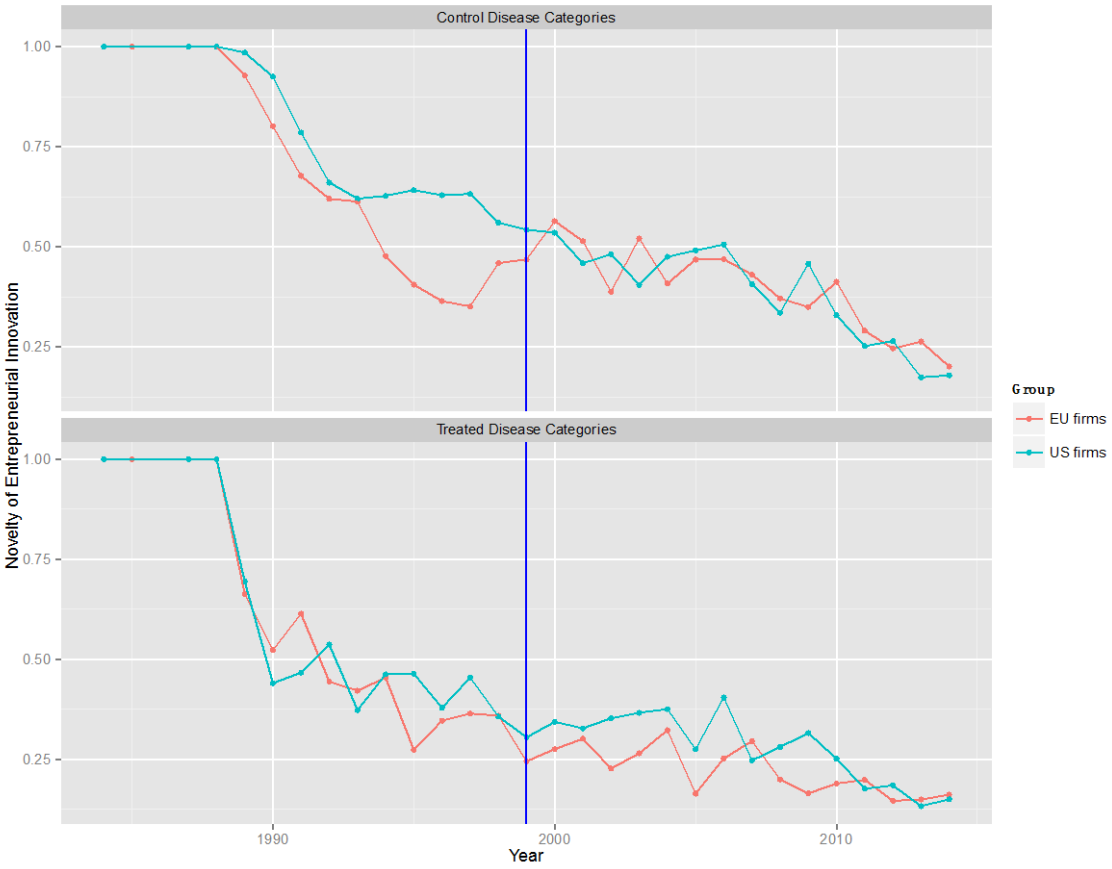
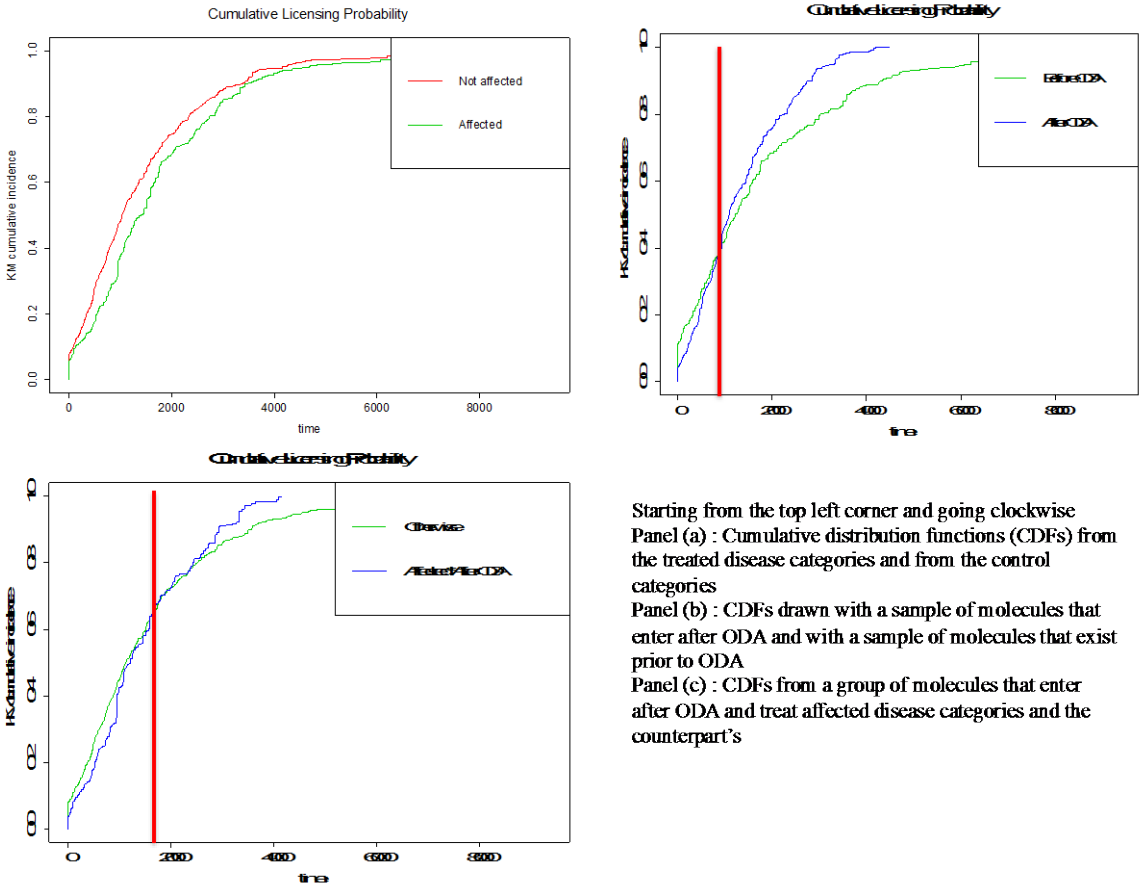
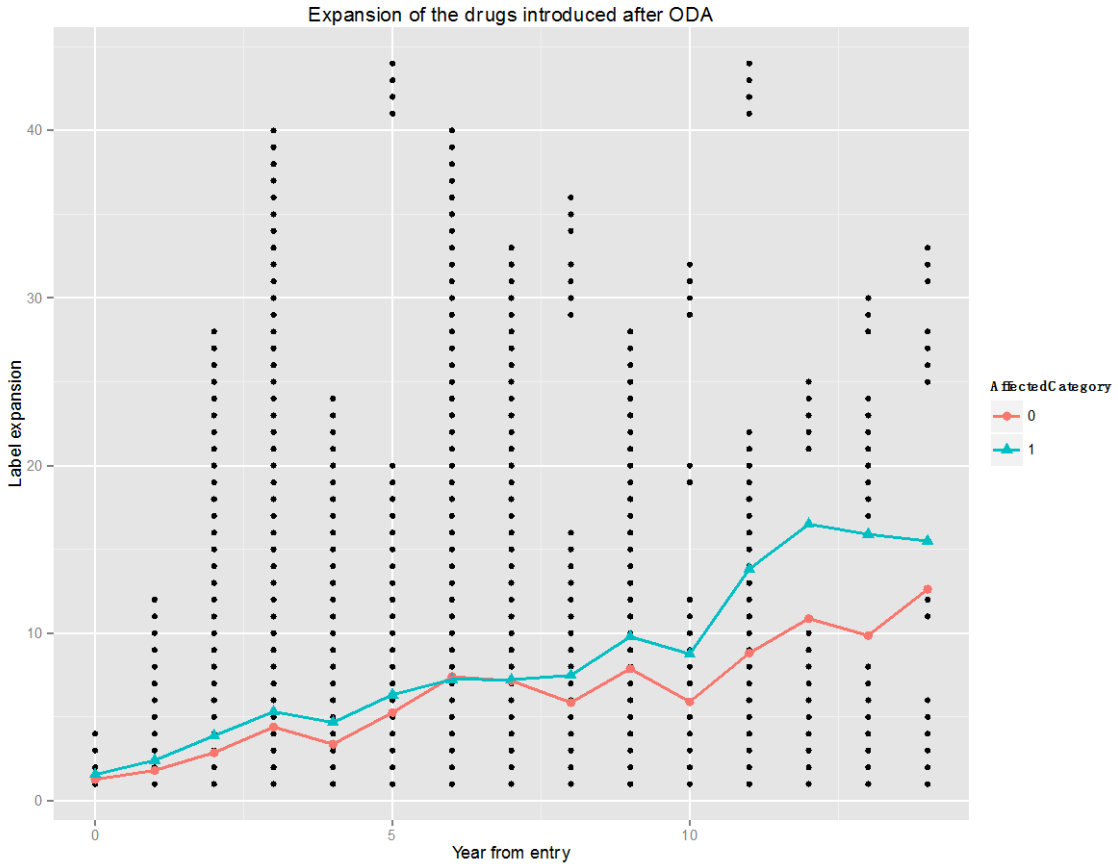


Figure 6: Cumulative Survival Functions of Licensing Probability



Starting from the top left corner and going clockwise
Panel (a) : Cumulative distribution functions (CDFs) from the treated disease categories and from the control categories
Panel (b) : CDFs drawn with a sample of molecules that enter after ODA and with a sample of molecules that exist prior to ODA
Panel (c) : CDFs from a group of molecules that enter after ODA and treat affected disease categories and the counterpart's

Figure 7: Label Expansion of Novel Drugs



Note: The sample includes novel drugs introduced after the ODA.

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