Too Costly To Convince: How Do Entrepreneurs Market Breakthrough Innovation Through Partnership?

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Abstract

This research examines the strategic conditions that drive entrepreneurial innovators to pursue novel innovation, rather than innovation that is closer to existing technologies. Since radical breakthrough innovation is harder to communicate than incremental counterpart, entrepreneurial innovators may be steered away from breakthrough innovation where the cost of developing credible information of breakthrough idea is exceedingly high. In the context of Orphan Drug Act (ODA), this study uses a difference-in-difference approach to measure whether entrepreneurs are more likely to bring novel innovation when the policy change unexpectedly lowers the cost of developing convincing information through a small market test. Using a new measure of novelty of innovation and a detailed panel dataset of therapeutic molecules, the empirical study finds that biotech startups bring more breakthrough drugs in the markets affected by ODA. This research also finds that, in the ODA-affected areas, entrepreneurs hold novel projects longer before contracting with large partners and to generate more revenue streams from pursuing novel innovation. Taken together, this study suggests that the cost of convincing hinders entrepreneurs to market novel innovation and that a public policy can moderate the inefficiency in "market for ideas" by decreasing communication cost.

KEY WORDS –technology commercialization strategy (TCS), innovation, entrepreneurship, inter-firm alliance, information asymmetry, biotechnology, the pharmaceutical industry

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"Investors tend to be herded into the drugs that depend on proven mechanisms. Once a novel pathway survives clinical studies, they crave projects targeting the same mechanism, leaving other pioneering but worthwhile projects overlooked," manager at a bay area biotech company

Introduction

What types of innovation do startups bring to market through partnership? To increasing extent, entrepreneurs have commercialized their inventions in a cooperative setup. They license technological intermediates to large incumbent firms, to access partners' well-established commercialization assets (Teece 1986, Pisano 1991, Gans and Stern 2003, Arora, Fosfuri et al. 2004). Market transaction of an immature technology, however, requires 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 harder to communicate than incremental counterpart, due to 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). Where it is hardly possible to convey credible information about the prospect of novel innovation, startups may avoid pursuing radically novel projects that they are capable of. My research aims to understand what constraints entrepreneurs seeking to commercialize novel innovation face and how they overcome the pitfalls using policy incentives.

I use a difference-in-difference approach to measure whether entrepreneurs are more likely to bring novel innovation when a policy change unexpectedly lowers the cost of developing credible information. The empirical context analyzed in this paper is Orphan Drug Act (ODA). The act originally aims to facilitate the development of treatments for rare diseases. Interestingly, small drug developers have found that the policy incentives ease them to develop "proof-of-concept" products of novel drugs with which to persuade partners (Howell 2015). Using a new measure of novelty of innovation and a panel dataset of therapeutic molecules, the empirical study examines whether biotech startups are more likely to market breakthrough drugs in the areas affected by ODA. This research also finds that, in the ODA-affected areas, entrepreneurs hold novel projects longer before contracting with large partners and to generate more revenue

streams from pursuing novel innovation. I address that the goal of this paper is not to evaluate the direct impact of ODA on orphan drug development. Rather, this research sheds a new light on a positive externality of ODA: the act reduces information asymmetry between entrepreneurial innovators and large incumbent firms seeking to collaborate for novel innovation.

To fix ideas, 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 treat a series of autoimmune diseases. But, neither the company could afford to run costly clinical studies independently nor it could find a financing partner without having precedent evidence. Alternatively, it developed Infliximab as a treatment for Chron's disease, a rare inflammatory disorder. By doing so, it took advantage of the incentives provided by ODA. Moreover, because the rare disease affected only a small number of patients, the company didn't have to recruit many patients for clinical studies, which saved considerable costs. 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. Since two years later, as an independent subsidiary of Johnson & Johnson, Centorcor, Inc has 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, considered as one of the most successful orphan drugs. The example of Remicade demonstrates how a biotech startup convinces a large partner of the value of a radical drug, showcasing it in a small market using the ODA incentives.

Why should we care about 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 deliver radical innovation 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 mechanism to deliver their innovation to market, failure in "market for ideas" may distort the incentives of entrepreneurial innovators. Prior research studying the market inefficiency has mainly focused on the danger of unwanted spillovers (Arrow 1962, Gans, Hsu et al. 2008, Katila, Rosenberger et al. 2008). This study suggests that the huge cost of transferring information to a partner can also be a source of market inefficiency. The empirical findings provide practical implications to startups and policy makers upon how to moderate value translation problem associated with radical breakthrough innovation. Moreover, this research traces a whole stream of revenues generated from novel technologies beyond the initial commercialization success, shedding a new light on the long-term effect of pursuing novel innovation on the growth of an individual firm.

In addition, this study makes methodological and therapeutic implications. With a few exceptions (Chatterji and Fabrizio 2014, Teodoridis 2014), the direction of entrepreneurial innovation has been overlooked due to measurement challenges. It is even harder to investigate types of commercialized innovations, because one cannot use a patent data: filing a patent does not necessarily mean that a patent holder commercializes the technology. This empirical study brings a new measure of novelty of marketed technologies using the originality of scientific mechanisms behind a drug.

More importantly, less attention has been paid to the types of innovations because prior research analyzes commercialization choices of entrepreneurs in the lens of sequential decision-making process: a startup innovates, and then decides whether to market its technology and, if so, how. In reality, however, entrepreneurs consider external factors affecting profit generation from the beginning, to decide which projects to advance and finally bring to market. In this sense, 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 (TCS). In particular, a handful of recent literature focuses on the dynamics of TCS where entrepreneurs alternate commercialization modes to acquire complementary assets (Wakeman 2010, Hsu and Wakeman 2013, Marx and Hsu 2013) or to develop

information necessary for partnership (Marx, Gans et al. 2014). My research aims to add new causal evidence on the dynamic TCS research, connecting the TCS studies to the literature on radical breakthrough innovation.

The paper proceeds as follows. Section 1 discusses related literature and derives testable hypotheses. Section 2 describes the empirical context as well as a brief scientific background. Section 3 introduces data and Section 4 explains methodology. Empirical results follow in Section 5. Section 6 concludes.

Theory and Hypotheses

A sheer volume of studies on economics and innovation report that market outcomes depend on the quality of available information (Greenwald, Stiglitz et al. 1984, Myers and Majluf 1984, Tadelis and Zettelmeyer 2011), and that breakthrough innovation is more vulnerable to communication challenge, compared to innovation closer to existing knowledge base (Alvarez-Garrido 2015). It suggests that entrepreneurs promoting novel innovations may have extra burden in using market mechanism for commercialization. Then, changes in environmental factors affecting the cost of convincing may impact the types of innovations transferred in "market for ideas."

This section first discusses why it is harder for startups pursuing novel innovation to find incumbent partners, compared to counterparts developing technologies depending on existing scientific base. Then, I review the TCS literature to discuss dynamic strategies that startups use to overcome the constraints. I derive a series of testable hypotheses drawing upon the previous research.

Challenges against partnership for novel innovation

Novel breakthrough innovation is vulnerable to information asymmetry problem. A developer knows the value of a novel technology better than anybody else, but often fails to convey the information to a potential partner. Why does the value translation problem occur?

First, large incumbent firms often lack scientific understanding to evaluate radically novel technologies. Many technologies outsourced from entrepreneurial innovators are at the scientific frontier, which could disrupt the way 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 1980s and 1990s, many pharmaceutical companies, most of which had developed drugs based on small-sized chemical molecules, struggled to evaluate the potential of biotechnology-based drugs (Pisano 2006, Hughes 2011, Werth 2013). Even now biotech firms are considered to have better understanding of the new technology than large partners, which accounts for increasing inter-firm collaboration. When a partner has not enough knowledge to understand a technology subject to partnership, it is hard to distinguish true information from cheap talk and, thus, vulnerable to a "lemons problem (Akerlof 1970, Pisano 1997, Mirowski and Van Horn 2005)." In this case, it is critical to have previous evidence on performance to convince less-informed party of the prospect of a technology. By its nature, however, a radically breakthrough innovation lacks precedent performance record. It makes most communication efforts of startups unverifiable.

Second, incumbent firms don't have 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 Pixar's case. Since its foundation, Pixar annually visited Disney in pursuit of 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," Frank Thomas, a filmmaking giant at Disney, wrote, "and old-fashioned animation has more control and more freedom, and also offers a greater range of expression." It was evident to Disney that Pixar's three dimensional (3D) computer animation technologies couldn't match Disney's capabilities, specifically in the aspects that Disney thought consumers of animation valued (Price 2009).

In addition to asymmetric information, high costs involved in novel innovation also make partnership challenging. Development of radical technologies incorporates high uncertainty, and thus, greater failure rates, because of the unique and unprecedented

nature. The low probability of success doesn't rationalize costly investment required for commercialization of new technology.

Not only that, incumbent firms internally have greater cost of integrating radical technologies, due to the fear of cannibalization of existing competences. A firm pursuing radical innovation needs to adopt new knowledge as well as new organization process (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 that are competence-destroying (requiring new organizational skills to successfully commercialize) and competence-enhancing (those that build upon the existing knowhow) (Marx, Gans et al. 2014). It documents that new entrants have greater incentive to pursue competence-destroying innovations, while established incumbent firms tend to support innovations that sustain or reinforce their existing portfolio (Levinthal and March 1993, Christensen and Bower 1996). When smartphone market was emerging, for example, LG electronics decided not to enter into the smartphone market, stating "feature phone forever" as its informal slogan. The decision wasn't reversed until the ultimate parent firm of LG replaced most executive board members of the mobile phone division as well as ended a long-term partnership with a consulting partner.

Although both information asymmetry and high cost explain the difficulty of commercializing novel innovation through partnership, the latter doesn't necessarily distort incentives of players in "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 for novel innovation.

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

Technology commercialization strategies and types of technological innovation

Inspired by the seminal work of Teece (1986), the TCS literature studies the determinants of commercialization choices of entrepreneurial innovators, between independent market entry and collaboration with incumbent partners. While partnership with incumbent firms allows entrepreneurs to tap into well-established complementary assets in a timely and cost effective manner, transfer of technologies at early stage also causes the danger of unwanted knowledge spillover (Arrow 1962, Caves, Crookell et al. 1983, Katila, Rosenberger et al. 2008). A stream of TCS research finds that, the more significant incumbent firms' complementary assets are for commercialization and the stronger protection intellectual property regime provides, the more attractive cooperative commercialization choices become to entrepreneurial innovators (Gans and Stern 2003, Arora, Fosfuri et al. 2004, Gans, Hsu et al. 2008).

A handful of recent literature points out that prior research doesn't reflect dynamic aspect of TCS. Commercialization of a technology is not a static game. Rather, startups "switchback" between independent market entry and cooperation with incumbents to either acquire essential assets and skills or to 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) finds that, when entrepreneurial innovation involves a disruptive technology, startups initially pursue market entry before switching to a cooperative commercialization strategy to reduce high integration cost of incumbent firms.

The example of Pixar and Disney demonstrates the use of initial market entry in pursuit of future partnership. When Pixar had constantly failed to attract attentions from Disney, Lucasfilm suggested Pixar a partnership to generate the famous scene of Startrek where the Enterprise spaceship crewmembers practice battles using a virtual simulation machine. The Startrek 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. A few years later, Disney finally partnered with Pixar to use the disruptive technology to produce animation (Price 2009).

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

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

Hypothesis 1-1. The Orphan Drug Act leads entrepreneurs to develop radical breakthrough innovation.

One challenge of using ODA for this study is that the act affects incentives of drug developers through multiple channels. Specifically, it is challenging to tease out the impact led by decrease in information asymmetry from the impact caused by cost reduction. Two mechanisms may impact entrepreneurs' behaviors in different ways. If information friction problem is the main reason that firms seek for orphan designation, we should observe that molecules developed by the applicants are more novel, and thus, are harder to communicate. In contrast, cost reduction leads firms to develop "marginal" drugs that would have not been developed otherwise because of too high uncertainty or mediocre economic value. Those marginal drugs don't necessarily be novel. Moreover, if

the cost reduction channel is the main driver, there should be no difference in the magnitude of impact between distinct groups experiencing different level of information asymmetry problem.

To clarify the impacts caused by different channels, I compare the behaviors of the US-based biotech firms and the EU-based biotech firms. I argue that ODA affects two groups through different mechanisms: the former through the information asymmetry mechanism and the latter through the cost reduction mechanism, relatively.

The difference in timing of the ODA enactment across two regions and regional variation justifies the argument. ODA have existed since 1983 in the US, allowing the US firms to benefit from cost reduction led by ODA. If an US firm wanted to take advantage of the cost benefits to advance marginal drugs, it could apply for orphan status in the EU without waiting for the adoption of ODA by the EU. While the extra cost reduction may still impact US firms' incentives, the cost reduction impact is relatively marginal compared to the impact on the EU firms. By contrast, because the act was first introduced in 1999 in the EU, the EU-based firms observed relatively dramatic drop of drug development costs. To summarize, the cost reduction channel has more significant impact on the EU firms than the US firms.

On the other hand, the information friction channel affects the US firms in a greater magnitude. While both the US and the EU biotech firms can reduce value translation problem using the ODA incentives, it is a group of the US firms that *ex ante* suffers more from information asymmetry problem in the EU market. Compared to the EU firms, the US firms have relatively fewer networks with the European Medicine Agency (EMA) and with the European pharmaceutical companies. Network, reputation, geographic distance, language and culture barriers all disproportionately hamper the US firms over the EU firms. The EU version of ODA can help the foreign firms to moderate information friction in the EU market.

Figure 2 visualizes the differential impact of ODA on the US firms and the EU firms. I predict that a group of firms that had had greater communication challenge is more likely to develop novel drugs after ODA. An assumption behind the next hypothesis is that the EU version of ODA affects the US firms mainly through the information channel and that the cost reduction channel affects the EU firms more than the US firms.

Hypothesis 1-2. The impact of the Orphan Drug Act on novelty of innovation is greater for the US-based biotech firms.

Meanwhile, the decreased market testing cost led by ODA also affects the way startups and incumbent partners collaborate as well as market outcomes. In many cases, startups transfer technological intermediates at early development stage to finance the projects. It doesn't cause a problem when startups and incumbent partners can correctly estimate the value of technologies at early stage. For example, when two firms collaborate for technologies closer to existing scientific evidence, both parties have enough information available for valuation. When it comes to the transfer of radical technologies, however, the transaction at early development stage worsens information asymmetry problem, and, thus, negatively affects market outcomes led by lack of information. When it becomes available to showcase a prototype product in a small market, startups developing novel innovation may want to advance the project up to the extent that the firms can credibly persuade partners about the prospect of radical technologies. John Lewicki, the head of research and development at OncoMed Pharmaceuticals addresses this point clearly.[2] The novel drug company wants to "hold onto the (novel) drugs for 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," said Lewicki.

Hypothesis 2-1. ODA leads entrepreneurs to hold their drug development projects longer before contracting with partners.

Understanding the change in partnership practice helps us to answer the following question: who should conduct market test of radical technologies? From a startup's perspective, doing initial market test by itself is beneficial, because the market test outcomes reduce information friction and, thus, put the firm on superior bargaining

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

position during negotiation. The circumstance helps a large partner either, because the partner can use more information at the timing of deal. Moreover, from the social welfare perspective, allowing startup innovators to play active roles in developing radical technologies may lead to efficient resource allocation among alliance partners (Grossman and Hart 1986, Aghion and Tirole 1995), causing superior market outcomes. The next hypothesis investigates the impact of ODA on the performance of "market for ideas."

Hypothesis 2-2. ODA increases the probability that an entrepreneurial innovator contracts a partnership agreement.

Lastly, I examine how the ODA affects the long-term commercialization performances of pursuing novel innovation. A firm's expected returns from investing in a particular knowledge arise from not only its current product building on this knowledge but also the whole stream of potential products in the future exploiting this knowledge (Toh and Polidoro 2013). Do startups promoting radical innovation make more profitable and sustainable revenue streams? How does external condition moderate the compensation? The third hypothesis seeks answers for these questions.

Hypothesis 3. The Orphan Drug Act helps startups generate grater and sustainable revenue streams from pursuing radical innovation.

A strength of this research lies in that the empirical study traces a whole stream of revenues generated from breakthrough innovation beyond the initial commercialization success. It deepens our understanding on the process through which a startup expands an initially marketed technology to multiple markets to recoups R&D costs occurred in early stage. Thus, it sheds a light on the long-term performances of developing breakthrough innovation.

Empirical Context

Drug approval process

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

Figure 1 visualizes the drug approval process in the US. A drug developer first identifies a therapeutic molecule or a target that possibly treats one or multiple disorders. It takes 2 – 8 years to optimize a lead molecule. Then, with the lead molecule, a company conducts preclinical studies including animal studies to test the basic safety and the efficacy of the molecule approximately for 5 years. When the drug candidate survives all required preclinical studies, the developer submits an Investigational New Drug (IND) application to FDA, to conduct clinical studies.

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

In many cases, a developer seeks label expansion of an approved drug beyond the initially targeted disease indication (Shineman, Alam et al. 2014). The “re-purposing” of existing drugs requires another sets of clinical studies, but the risk and the cost related to label expansion are much lower than developing a brand-new molecule because the safety and the efficacy of a drug are previously proven.

Orphan drug act (ODA)

ODA was first enacted by the United States (US) in 1983 to facilitate the development of treatments for rare diseases. In the US, rare disease is defined as one that

affects fewer than 200,000 people a year. Rare diseases had remained "orphan" because too small market sizes didn't justify the costly development of medications. To intervene in the market failure problem, the policy provides orphan drug developers a variety of incentives including tax benefits associated with clinical trial costs, regular guidance meeting with FDA and market exclusivity. The considerable success of the act encouraged the European Union (EU) and other countries to adopt the similar legislation (Lichtenberg and Waldfogel 2003, Cheung, Cohen et al. 2004, Yin 2008). The EU's adoption of ODA in 1999 marked the biggest 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 make use of the incentives provided by ODA, a drug developer has to file an application that states 1) which molecule to use, 2) which disease indication to target, and 3) why the molecule is the best therapy for the specified disease. An applicant should prove why the target disease satisfies the rare disease criteria. When a regulatory agency approves the application and grants an orphan designation to the molecule, the developer can enjoy the ODA incentives to develop a designated molecule as an orphan drug (Grabowski 2005).

Currently, there are 7,000 rare diseases worldwide affecting approximately 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 were marketed and 2,500 compounds have been granted orphan designations. Marketed orphan drugs include the well-known drugs including 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 in other types of cancer and rheumatoid arthritis, it had sales of $5.24 billion in 2010, marked as the world's second most profitable drug (EvaluatePharma 2013).

Recently, there has been an interesting controversy surrounding the expansion of orphan drugs for multiple indications. 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 and, thus, would have been

developed without ODA (Wellman-Labadie and Zhou 2010, Stephens and Blazynski 2014). The FDA recently admitted the gamesmanship, by stating that

> [...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 benefits both patients that suffer from rare diseases and those from common diseases.

Data

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

The study mainly draws upon the Pharmaproject database to collect the list of pharmacological research projects and associated characteristics. I collect unique drug id, drug name, originator, licensees, target disease indications, related patent numbers, and the dates of main events including entry, patent application, licensing agreement, approval, and expansion to new disease indication. Also, the dataset includes detailed molecule specific characteristics including Mechanism of Action (MOA), 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 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 and orphan designation data. The clinical trial data are collected from clincialtrial.gov. The US orphan designation data are obtained from the website of FDA and the EU data are from the EMA. The final version of dataset includes a detailed history of each drug candidate, including both successful drugs and discontinued ones, 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 entered between 1983 and 2014. The drugs are based on 2,481 unique MOAs. There exist 1,189 disease indications and 12% of these are rare diseases. The diseases are categorized into 15 disease categories, including Alimentary/Metabolic, Blood & Clotting, Cancer, Cardiovascular, Dermatological, Genitourinary, Hormonal, Immunological, Infectious Disease, Musculoskeletal, Neurological, Parasitic, Respiratory and Sensory disorders. 42% of total molecules fall in the disease categories mostly affected by ODA. Small biotech firms develop 57% of therapeutic molecules in the dataset. I exclude established biotech companies such as Amgen and Genentech from a list of small biotech firms. The giant first-generation biotech firms possess as equivalent level of complementary resources, experience and reputation as large pharmaceutical companies do.

Empirical Study Design

Methodology

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

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

Where Y_{ijt} represents the outcome variable (novelty of innovation, indicator of whether to be licensed or not, timing between entry and the first licensing deal, and market expansion), i indexes individual therapeutic molecule ($i \in \{1, \ldots, N\}$), j indexes disease categories ($j \in \{1, \ldots, J\}$) and t indexes year ($t \in \{1, \ldots, T\}$). *AfterODA* is a binary variable equals to 1 if a molecule enters within a disease category after 1999 and 0 otherwise.

Affected is a binary variable equals to 1 to a group of molecules that belong to the disease categories disproportionately affected by ODA and 0 otherwise. I use the nature of rare diseases to decide the treatment group and the control group. Appeared in Figure 3, most rare diseases are either genetic disorders or abandoned disorders for economic reasons, generally falling in the blood & clotting disorders, cancers, infectious diseases and parasitic diseases categories. The four categories more affected by ODA are my treatment group, while 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 the effect caused by the shocks specific to the treated disease categories and by the shocks that concurrently take place with ODA, respectively. I include disease category fixed effect and year fixed effect. X_i is a vector of control variables. Errors are clustered at 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 less known group and the more known group in the treated disease categories to the evolution of the gap between the less known group and the more known group in the control disease group. The estimated formula is as follows:

$$Y_{ijkt} = \alpha_j \sum I_j + \gamma_t \sum K_t + \mu_i \mathrm{X}_i + \beta_0 Affected_{ij} + \beta_1 AfterODA_{it} + \beta_2 LessInfo_{ik} + \beta_3 Affected_{ij} * AfterODA_{it} + \beta_4 Affected_{ij} * LessInfo_{ik} + \beta_5 AfterODA_{it} * LessInfo_{ik} + \beta_6 Affected_{ij} * AfterODA_{it} * LessInfo_{ik} + \varepsilon_{ijkt}$$

Where $LessInfo_{ik}$ is an indicator variable equals to 1 if a molecule is originated by a group of less known firms (*H1-2*) - the US firms. Molecule specific controls are included.

To test the second hypothesis on the probability of making a partnership and the timing of the first licensing contract, I run 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 takes place 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 molecule and the date of the first licensing contract. The estimated regression formula is the same as that for *H1-1*.

I use the same DiD formula to test the third hypothesis. *H3* examines the trajectories of label expansions for other 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, while I use binomial logit regression for *H1* where dependent variable is a binary variable.

Variables

Dependent variables

Novelty of innovation (H1) I measure novelty of drugs using the originality of mechanisms used by the drugs. A drug intervenes in 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. mAb-based cancer drugs deliver toxins directly to the problematic cells. A majority of allerge medications blocks the histamine receptors to reduce the level of histamine absorbed into a body. These mechanisms are called Mechanism of Actions (MOA). 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 drug as appeared 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 Developemnt 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. Then I sort molecules by disease category and entry dates, to generate a sequence number. If the number is 1, it means that the molecule introduces a brand-new mechanism for the first time. 2 indicates that the drug is the second drug that adopts a novel mechanism. From the sense, the sequence number is a "novelty score."[3] Then, I construct a binary variable that assigns 1 to the first five drugs that use a novel mechanism and 0 otherwise. The reported regression results use the binary variable as the dependent variable. I run robustness checks by adjusting the window and also using the novelty score as a dependent variable. The empirical results are robust to the modifications.

Propensity and timing of licensing partnerships (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 that informs if an event of interest - a licensing deal, in this case - takes place or not. I construct a binary variable that gives 1 if a molecule is subject to at least one licensing agreement and 0 otherwise. The other 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 a new therapeutic

[3] Note that MOA is not a subject of patent. While patents offer strong protection for pharmaceutical inventions, patents do not award exclusionary rights over the scientific principles underlying drugs.

molecule. I use as the entry date the date that each molecule first appears in the database. Then, I sort all licensing agreements associated with a therapeutic molecule by dates and select the earliest deal. Finally, I calculate the time difference between the entry date and the date of the first alliance.

Market expansion (H3) As appeared in Figure 1, a drug developer generates a subsequent stream of revenues by re-purposing a previously approved drug. Firms pursuing label expansion have to specify which additional diseases to target and run a required set of clinical trials. The Pharmaproject database identifies each attempt of label expansion with the name of new target disease and the date of statement. I construct a count variable that numbers the market expansion events of drugs.

Independent variables

Affected It is a binary variable equals to 1 if a molecule is developed to treat a disease belong to the Blood & Clotting category, the Cancer category, the Infectious Disease category and the Parasitic category and 0 otherwise.

AfterODA It is a binary variable equals to 1 if a molecule is entered after 1999 and 0 otherwise.

LessInfo To clarify what channels through which ODA impacts the novelty of entrepreneurial innovation, *H1-2* compares the size of the impact between the group more vulnerable to information friction and the less concerned group. I restricted samples to a group of biotech firms and construct a firm-level group dummy variable that assigns 1 to the US firms and 0 otherwise. Because the US biotech firms have less information available to players in the EU including EMA and European pharmaceutical companies than the EU counterparts, the EU version of ODA affects the US firms largely through the information asymmetry channel.

Control variables

Molecule-specific characteristics I control for whether a molecule is patented or whether it is a New Chemical Entity (NCE). Also, I control route, origin, drug diffusion rate (logP), weight and structure (H.Bond doners, H.Bond acceptors and rotatable bonds) of each therapeutic molecule.

Results

Novelty of innovation (*H1*)

Figure 4 presents the trend of the novelty of entrepreneurial innovation over time. It is not surprising that the novelty of innovation decreases over time, because firms repeatedly use pre-existing MOAs. In the treated disease categories, the decreasing pattern is greater. However, after the ODA, the novelty of drugs in the treated categories springs back, while the novelty keeps decreasing in the control categories.

Table 2 shows the DiD estimates of the novelty of drugs developed by biotech startups. In the base line logit regression in Column (1), the coefficient of the ODA dummy is – 0.981, which gives the odd ratio exp (-0.981) = 0.37. Firms are 37% less likely to develop drugs based on novel mechanism after ODA. Switch from the control disease categories to the treated disease categories yields a change in log odds of (-0.981 + 0.142) = -0.839. The ratio of these two odds ratios is the coefficient of my interest. The coefficient of the interaction term is 0.142, which indicates that firms within the treated categories are 15% more likely to adopt new mechanisms to develop drugs. The magnitude becomes greater and more significant when I control year fixed effect, firm fixed effect, and molecule specific control variables. The coefficient of the interaction in Column (5) is 0.321, showing that firms in the treated categories are 37% more likely to develop novel 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 progressed otherwise. On the other hand, firms developing novel MOAs decide to target the disease categories more affected by ODA. To separate these two mechanisms, I replicate the estimation in Table 2 using the Phase I clinical trial starting dates instead of the dates of molecule entries. As shown in Figure 1, it takes approximately 6 to 8 years for a newly studied molecule to enter into clinical studies. Moreover, for a firm to sponsor Phase I clinical trial, FDA or EMA should approve an IND application, which takes significant times and efforts. Thus, if novelty of drugs entering into Phase I clinical

trials increases after ODA, it indicates that 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 compared to Table 2. The ratio of the odds ratios in Table 3 ranges from 4.74 to 5.16, informing that firms in the treated categories are five times more likely to advance novel drugs to the Phase I clinical trials, compared to those in the control categories.

Next, I test *H1-2* to investigate the heterogeneous impact of the EU ODA over region. ODA simultaneously reduce information asymmetry and drug development cost. I compare the behaviors of the US firms and the EU firms, using that the act affects the US firms mainly through information asymmetry channel and the EU firms through cost reduction. The trend of novelty by firm region in Figure 5 supports my prediction. In the control disease categories, novelty of drugs developed by both the EU firms and the US firms steadily decreases and there seems to be no difference between two groups. In the treated categories, however, the US firms bring more novel drugs than the EU firms do.

Table 4 shows the outcomes of triple DiD estimations. The coefficient of interest is one of $Affected_{ij} * AfterODA_{it} * LessInfo_{ik}$. The coefficient accounts for the evolution of the gap between the US firms and the EU firms. The ratio is approximately 2 and significant across all columns. It indicates that the US firms are two times more likely to introduce novel drugs as a result of the ODA by the EU. Alternatively, I restrict my samples to the molecules developed by the US firms and those by the EU firms, to run DiD regressions with the restricted samples. Column (6) and Column (7) also suggest that the US developers adopt radical technologies more than the EU firms do.

Collaboration practice (*H2*)

I turn to the survival analysis to examine the collaboration practice and the probability of finding a partner. Figure 6 presents the cumulative density functions of survival functions. In the empirical context, "survival" means that at least one licensing agreement is made upon a subject molecule. Panel (c) in Figure 6 shows that, in the ODA affected group, firms have higher probability of licensing deals at the end. However, the density of the affected group continually lags behind the counterpart

density within 1,800 days from entry. It suggests that developers in the affected group postpone the first licensing deal until they can create as much information as possible before going to a negotiation table. To check the difference in the timing of licensing deals, I run a two-sample Kolmogorov-Smirnoff test. The test gives D = 0.0555 and p-value = 0.00006637, rejecting the null hypothesis.

Table 5 echoes the prediction. The coefficient of the interaction terms indicates that the ratio of odd ratios is exp(0.133) = 1.14. After ODA, molecules in the treated disease categories have 10% higher probability of getting licensed.

Market expansion (*H3*)

Finally, Table 6 shows the DiD estimates of label expansion, i.e., re-purposing of drugs. With label expansion of approved drugs, developers are allowed to sell the drugs in other disease markets beyond the initially targeted disease. Thus, re-purposing becomes an important and sustainable means to generate revenue from investing in a technology. The Poisson regression yields a significant and positive coefficient of interaction term. Exp(0.245) = 1.28 indicates that, given the other predictor variables are held constant, molecules in the affected group are expanded for 0.28 more disease indications.

The samples include many molecules that are never expanded for other disease indications. To take this into account, I run negative binomial regressions and check that the size and the significance of the coefficients are similar. Figure 6 visualizes that, among the novel drugs entered after ODA, molecules in the treated disease categories are expanded to approximately three more disease indications than those in the control categories.

Discussion and Conclusion

Breakthrough innovation improves social welfare as well as the growth of an individual firm in a significant manner, yet relatively little is known about what leads entrepreneurial firms to commercialize novel innovation. Where startups heavily depend on partnerships with incumbent firms to bring their inventions to market, firms are not

able to advance radical technologies that are not to be well communicated because of information friction. ODA provides an useful empirical context, generating variation in novelty of entrepreneurial innovation across a group of *ex-ante* similar disease categories. I find evidence that entrepreneurs are 15% more likely to develop radical technologies where the availability of a small market test led by ODA drops the cost of generating credible information. The magnitude of the impact is greater among a group of firms with less previous information, implying that information asymmetry mainly accounts for the lack of investment in breakthrough innovation. The results also show that entrepreneurs hold their projects longer before contracting with partners. Lastly, in the ODA-affected disease categories, startups generate a greater and more sustainable stream of revenues from developing novel drugs, by expanding the novel drugs for a greater number of disease indications.

To the best of my knowledge, the research is one of the first papers studying the qualitative aspect of innovation transferred through "market for ideas," speaking to the growing literature on technology commercialization strategies (TCS). The findings suggest that, while small innovators are prone to introduce breakthrough innovation, the firms in needs for collaboration may be steered toward technologies that are easier to communicate. From this perspective, this research seeks an answer to the Schumpeterian question on which firms introduce novel innovation, between small firms and large firms and the main attributes, in the context of collaborative technology commercialization.

My findings are also related to the boundary of firm question. This research shows how technological innovation type affects the division of labor among alliance partners. As transaction of novel innovation needs more information, it is efficient for a developing firm – more informed party - to hold a technology long enough to develop a prototype product or run a small market test. A public policy could lead to efficient allocation of resources among partnering firms, by financing an informed party when its technology incorporates high uncertainty.

Lastly, the evidence in this paper sheds a new light on the ongoing controversy surrounding exploitation of ODA. While proponents claim that firms are abusing the public resources to develop drugs that would have been anyway developed, the research on the positive externality of ODA demonstrates that developers of novel drugs face as

much barriers as orphan drug developers do, mainly due to information asymmetry. Then don't we need more public interventions such as ODA to help reduce the information asymmetry associated with breakthrough innovation?

This study promotes me to study a related stream of research. First of all, a firm promoting novel innovation needs additional funding to develop a prototype product before bringing it to a large financing partner. Private venture capitals (VCs) and angels may close the financing gap. Mechanisms of the impact of VC investment may vary over types of innovation. The subsequent chapter of my dissertation studies the changes in the composition of investors.

Second, it is interesting to understand the welfare effect of the ODA-driven novel drugs. The development and the expansion of ODA-driven novel drugs benefit both groups of patients that suffer from rare diseases and common diseases. However, because novel drug developers should develop treatments for rare diseases first to benefit from the ODA incentives, patients of common diseases have to endure delayed arrival of novel treatments. If welfare loss created by the delay is considerable, we may need more interventions like ODA to ensure the timely delivery of novel drugs to both the patients of rare diseases and those of common diseases (Budish, Roin et al. 2013, Howell 2015).

Figures and Tables

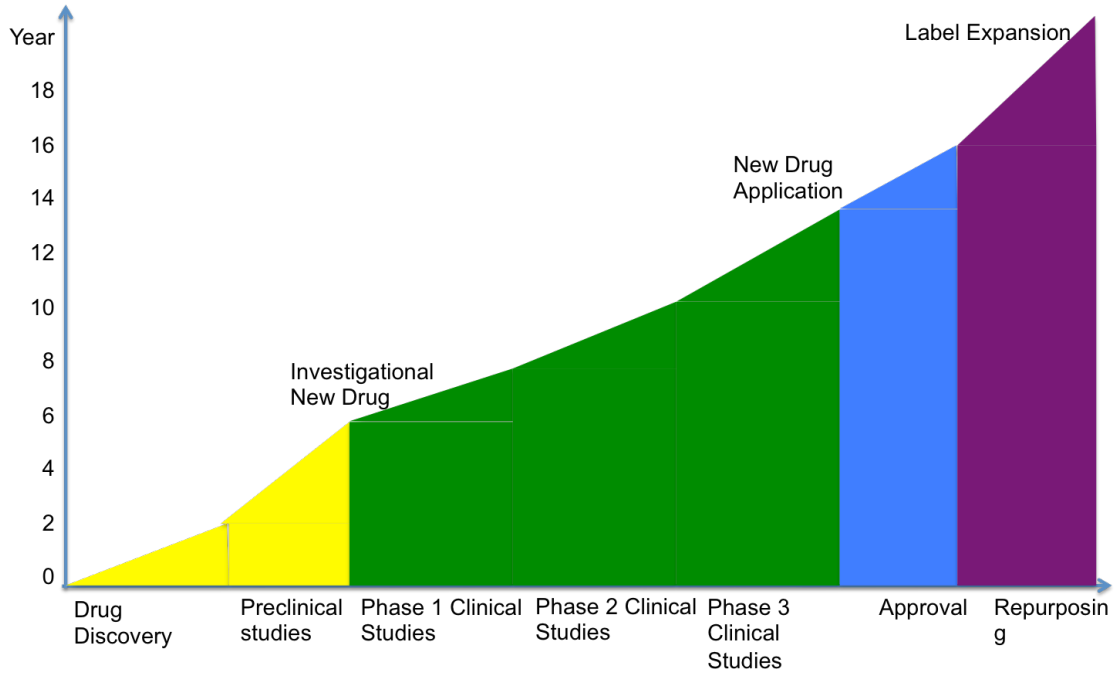


Figure 1. Drug Approval Process in the US

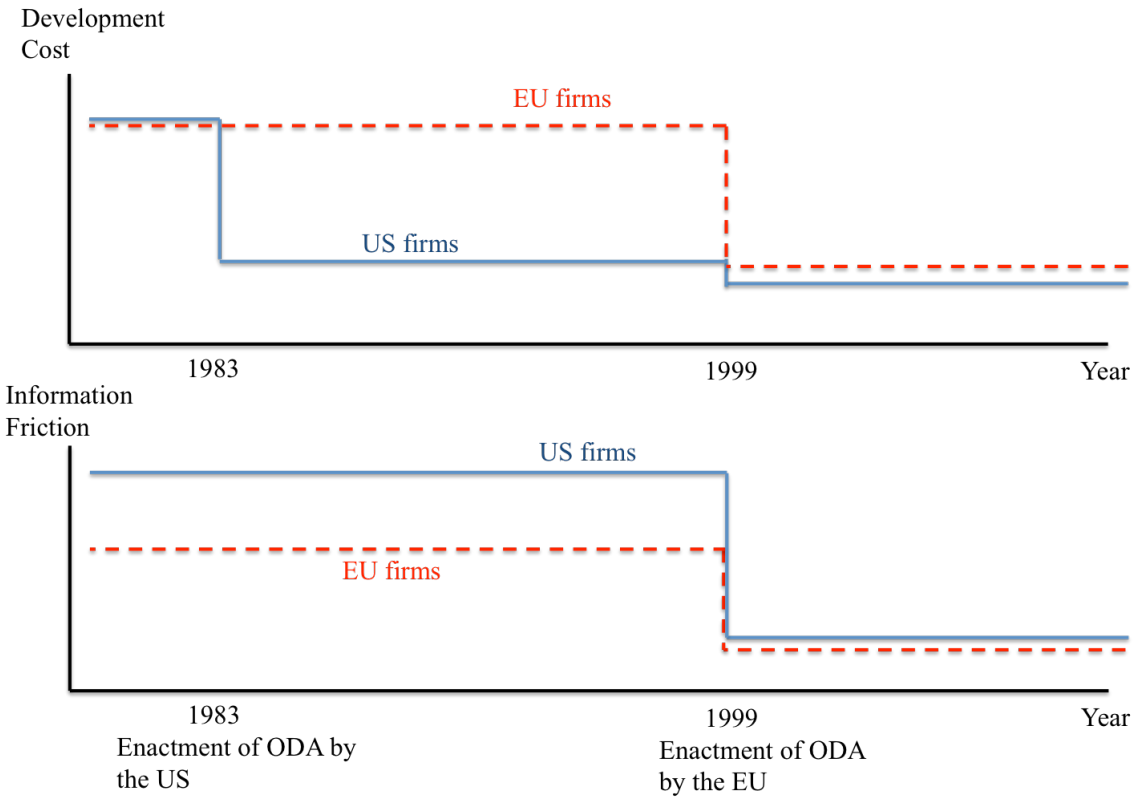


Figure 2. Mechanisms Behind the Impact of ODA

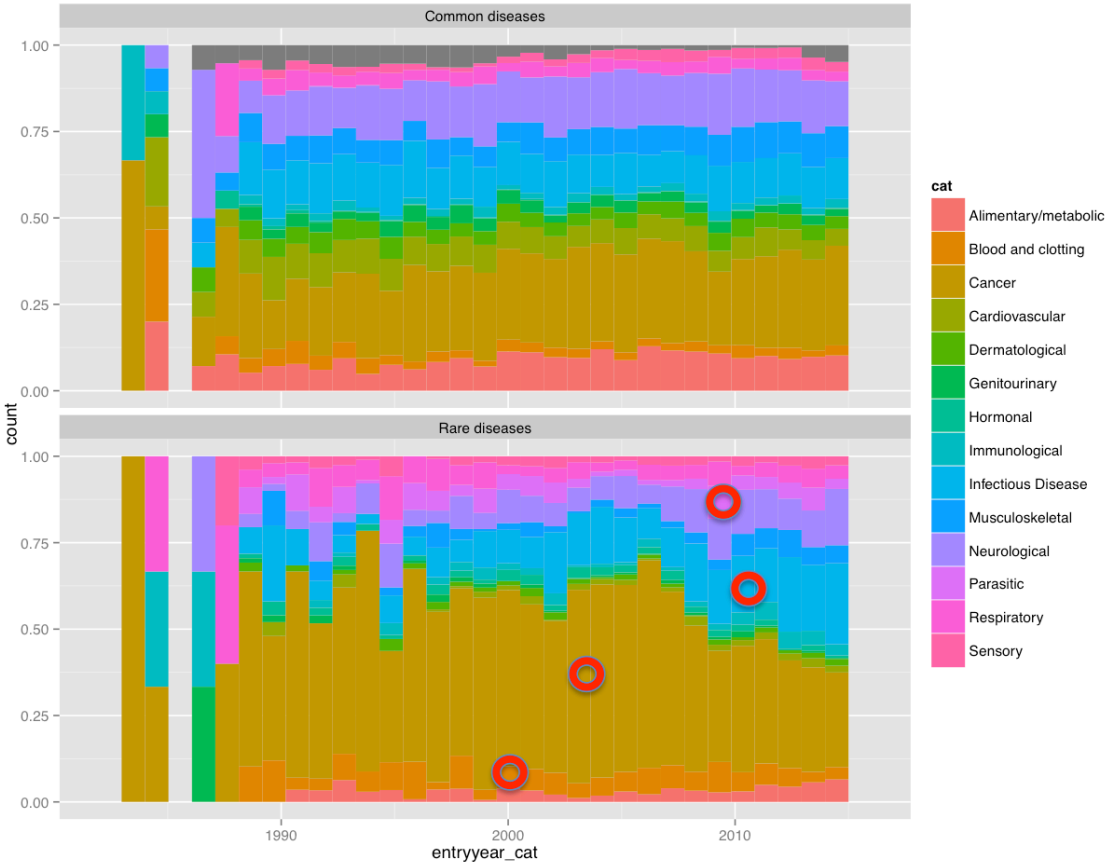


Figure 3. Category Classification of Common Diseases and Rare Diseases

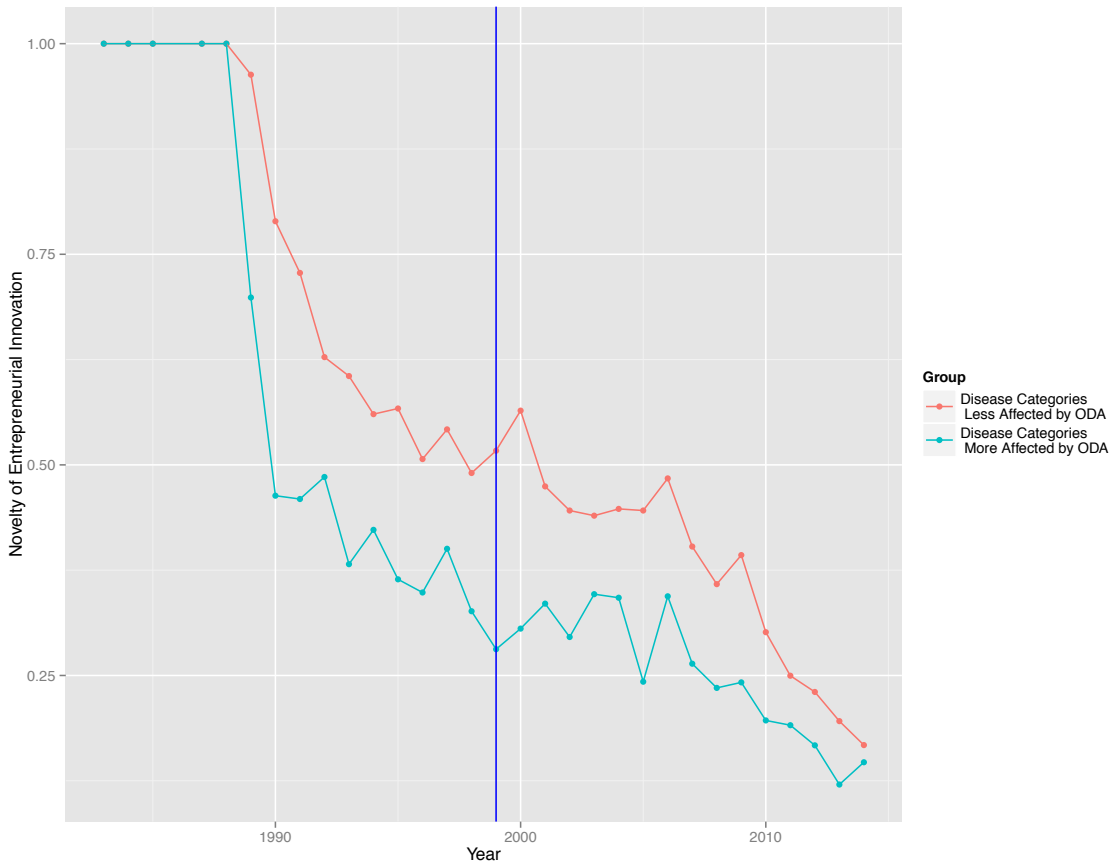


Figure 4. Novelty of Entrepreneurial Innovation over Time
Note: y variable is 1 if a drug adopts a brand-new mechanism of action and 0 otherwise.

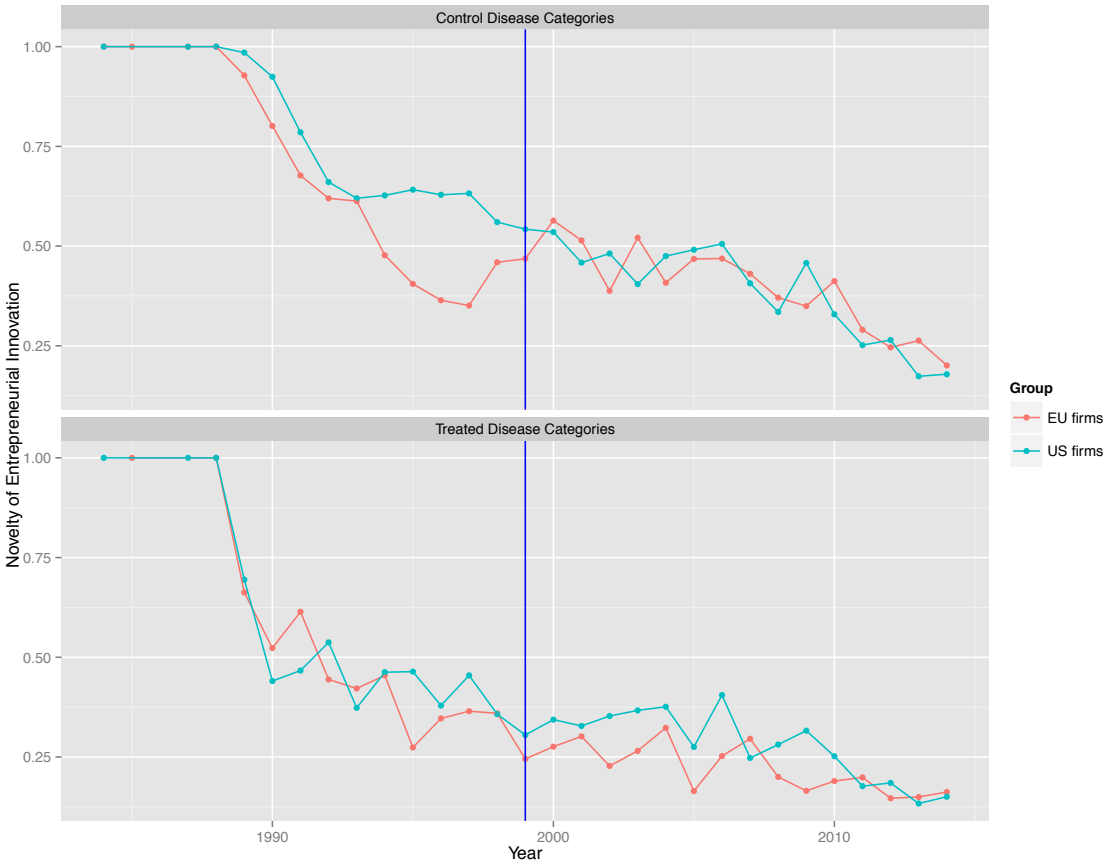
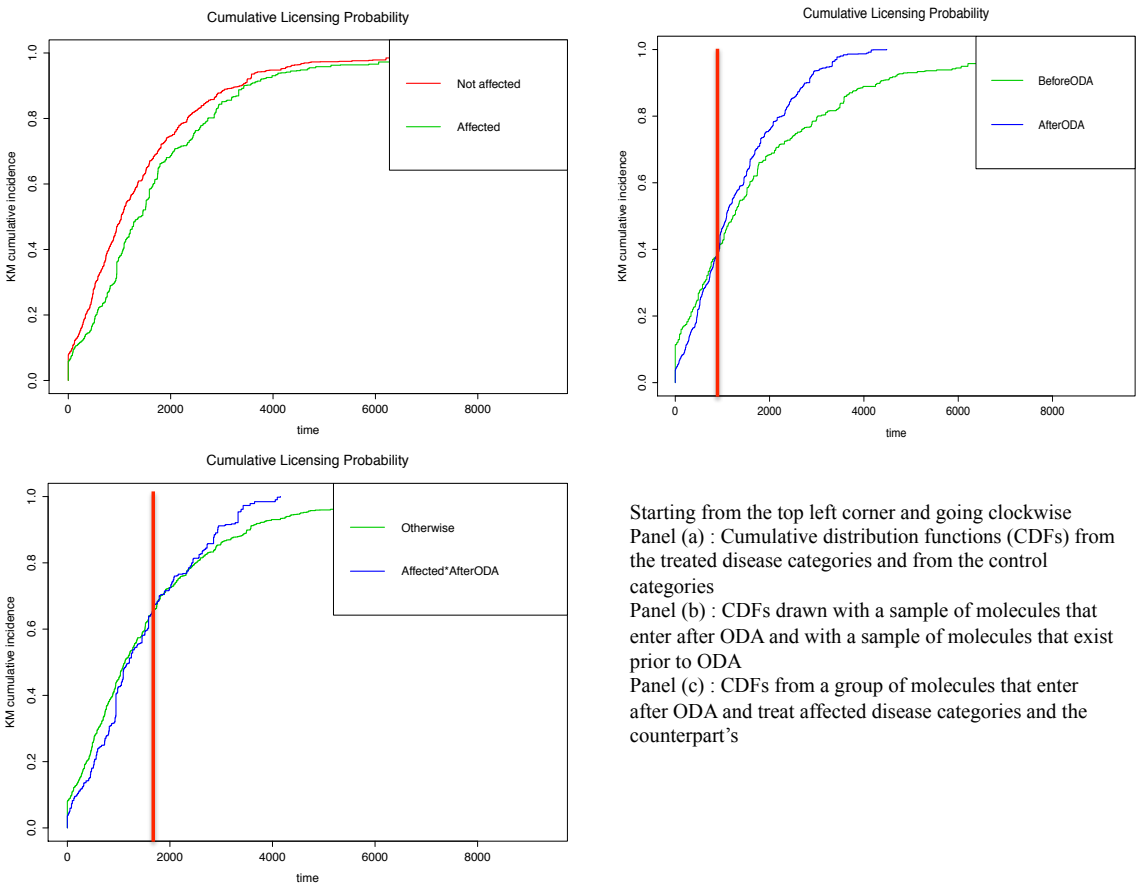
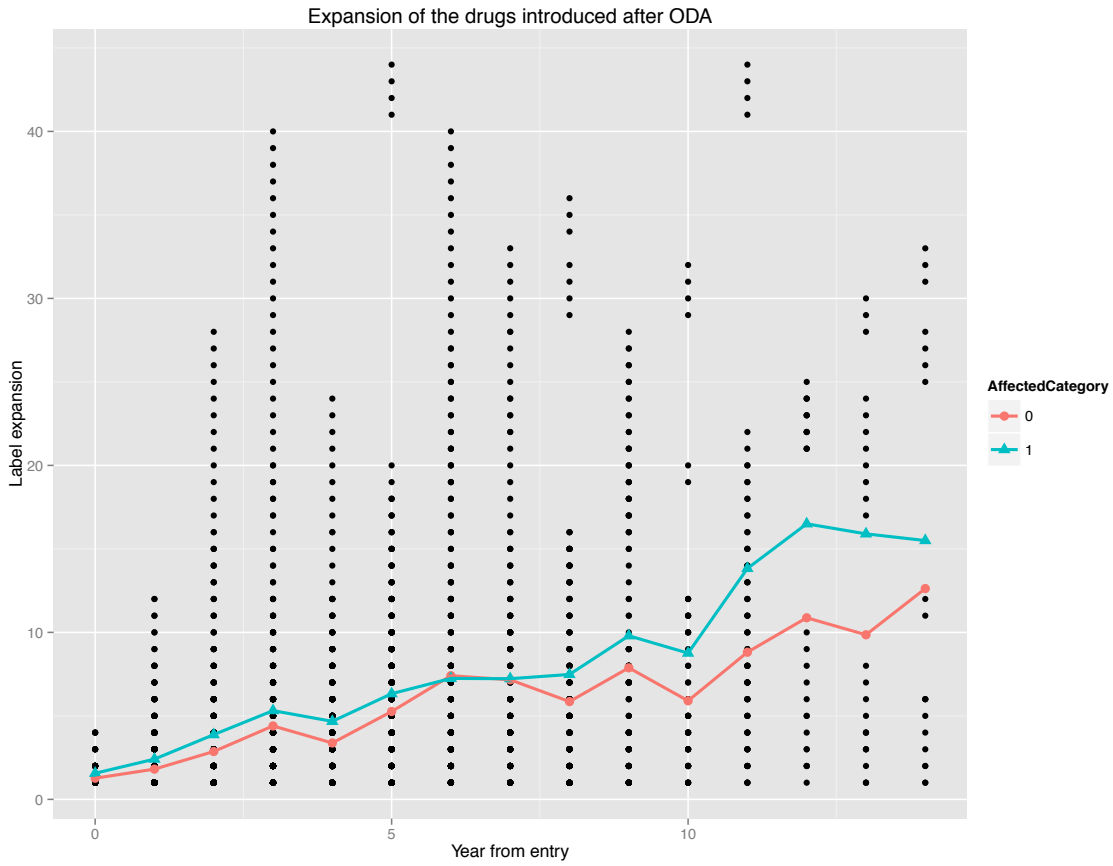


Figure 5. Changes in Novelty of Innovation By Firm Region and Disease Groups



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 6. Cumulative Survival Functions of Licensing Probability



Note: The sample includes novel drugs entered after ODA.

Figure 6. Label Expansion of Novel Drugs

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 1. Descriptive Statistics

	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 2. DiD Estimates: Impact of ODA on Novelty of Entrepreneurial Innovation

	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 3. DiD Estimates: Impact of ODA on Novelty of Drugs Entered into Phase I Trials

	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 Column (1) to (5) include all therapeutic molecules developed by small biotech firms.
Column (6) and (7) are DiD estimates with the molecules originated by American biotech firms and by the European biotech firms respectively.
*p<0.10; **p<0.05; ***p<0.01.

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

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

	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 Column (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.

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

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