Who are generic manufacturers?
Evidence from paragraph IV generic entries in 1998-2013

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**Abstract:** The pharmaceutical industry has seen a dramatic increase in early patent challenges under paragraph IV by generic manufacturers, as encouraged by the Hatch-Waxman 1984 and the MMA 2003. However, the characteristics of generic manufacturers that engage in PIV challenges have not previously been studied.

Using fixed-effect Poisson regressions to analyze data on generic drug approvals under paragraph IV in 1998 - 2013, I examine whether heterogeneity among generic manufacturers is in correlation with their activeness in PIV challenges.

The findings suggest that a firm's absorptive capacity, namely, its previous experience in obtaining FDA approvals and manufacturing drugs has a positive relationship with the amount of PIV certificates that the firm gains. Experience reduces the cost of preparing generic drug applications and increases the probability to obtain FDA approvals. A firm's size is also in a positive relationship with the amount of PIV certificates that it gains.

These findings provide an understanding about the characteristics of generic manufacturers in the PIV contexts and the changes in these characteristics over time.

**Keywords:** generic, pharmacy, imitation, absorptive capacity, paragraph IV, PIV challenges
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Chapter 1

Introduction

In recent years, pharmaceutical industry has seen a surge of early entries from generic man-
ufacturers. Traditionally, the patent system has been considered to provide an adequate
scope to protect innovation from temporary competition. However, in recent decades vari-
ous regulations and legal changes were enacted to promote more affordable healthcare and
encourage early generic entries. Among them, Medicare Prescription Drug, Improvement,
and Modernization Act in 2003, in particular, has strengthened the provision of exclusivity
for generic firms. As a result, the industry has seen a dramatic increase in early patent
challenges through paragraph IV, also known as PIV challenges. The trend started in
1998 and increased substantially from 2006 onwards. In fact, generic manufacturers have
won many challenges. A number of branded pharmaceutical companies have lost patent
coverage on their most lucrative drugs. For example, in November 2011 Pfizer lost its
patent to Ranbaxy on the blockbuster drug Lipitor, formerly known as the best-selling
prescription drug in history. It resulted in a 19% profit decline in 2012.

Although many studies have examined the impact of these policies on pharmaceutical
innovation and generic sectors, there is still very little knowledge about PIV applicants
- the primary force that drives the transformation of the market’s competition. The
understanding of PIV applicants can bring insights about the consequences of policies and
about the main players that benefit from it.

The goal of this study is to examine the characteristic patterns of generic PIV applic-
ants and their correlation with PIV activities. Moreover, I will study how these charac-
teristics evolved when the institutional environment changed. To be specific, I attempt to
answer three questions:

- Is firms’ innovation intensity in negative correlation with its activeness in PIV challenges? Do firms become less innovative when they are active in PIV challenges?

- Are firms with prior experience and high absorptive capacity more likely to file PIV challenges?

- Is firms’ size in correlation with the amount of PIV challenges they engage in?

I exploit Poisson Regression to draw the correlation between PIV activities and applicants’ main characteristics: innovation levels, absorptive capacity and companies’ size. Fixed-Effects are used to take into account time effects and to eliminate autocorrelation in the panel data.

My analysis exploits the data from the Orange Book, i.e., the data on approved drugs by the FDA, and data on the approved PIV certificates from Drugs@FDA and FOIA. By linking the approved PIV certificates with the Orange Book, I can build a list of successful PIV certificates with their application details and determine the main PIV applicants and their activeness in PIV challenges. In other words, it builds the information about the dependent variable. Then I collect the applicants’ main characteristics information: the financial data from Datastream and the drug’s portfolio from the National Drug Code Directory. These data allow me to study the relationship between applicants’ key features and their imitation activities.

After the introduction on the institutional background, literature reviews, and imitation theory, the analysis proceeds with an overview on PIV applicants’ background. This part will discuss the largest PIV holders, applicants’ size, geographical origin and firms’ age. The aforementioned is followed by a section on the methodology of the study and empirics models. Finally, the study concludes with the result and the summary sections.
Chapter 2

Institutional Background

The pharmaceutical industry relies on the patent system to incentivize research and innovation activities. In the last two decades, some major adjustments in the US patent regulations have dramatically changed the face of the industry. In 1984, the Congress enacted the Hatch-Waxman with the purpose of promoting new drug inventions. It compensates for the delay in the review period by extending the patent length accordingly. The second goal is to make new drugs more affordable for patients in a shorter time. By those means, generic firms are allowed to challenge the patent early before its expiration dates under the Paragraph IV Patent Certification. It can state that "the patent is invalid, unenforceable, and/or not infringed on by the new drug for which the application is submitted." In return, they can enter the market if winning and the first PIV filer gets a 180-day exclusivity. Although their original purpose is to seek balance between promoting R&D and maintaining the competition, the Hatch-Waxman is considered to favour generic firms. In this session, I will go through some institutional backgrounds regarding ANDA applications’ procedures and paragraph IV challenges.

2.1 Changes in Abbreviated New Drug Application Procedure: Cheaper and Simpler Applications

There are four pathways through which generic companies can gain FDA approvals of their generic version of brand name drugs. They can file the Abbreviated New Drug

\[1\text{CFR 314.94(a)(12)(i)(A)(4)}\]
Application (ANDA) under one of these following paragraphs: “(1) the patent information has not been filed with the FDA, (2) the patent has expired, (3) the generic will not enter the market prior to the date on which the patent expires, or (4) the patent is invalid, unenforceable, and/or not infringed on by the new drug for which the application is submitted”\(^2\). Paragraph IV is the new way that was added in the Hatch-Waxman 1984. It created a dynamic mechanism for generic manufacturers to challenge weak patents and to accommodate for the purpose of providing affordable health care for patients. The following section explains about Paragraph IV in more detail.

The requirements for generic applications, ANDA, have been loosened. It makes the application process faster and cheaper. In the pre-Hatch-Waxman period, ANDA filers had to demonstrate that their generic version satisfies the safety and efficacy requirements with preclinical and clinical trials. The House of Committee on Energy and Commerce issued a report in 1984 noting that the submission of a full NDA for generic applicants creates an inefficient use of resources\(^3\). The report stated that “FDA considers such retesting to be unnecessary and wasteful because the drug has already been determined to be safe and effective. Moreover, such retesting is unethical because it requires that some sick patients take placebos and be denied treatment known to be effective.”\(^4\) As a result, in post-Hatch-Waxman, with generic drug applications one does not need to go through preclinical and clinical trials to provide safe and efficacy evidence of the drug products. Instead, one only need to establish that their products are “bioequivalent\(^5\)” of the brand name drugs.

2.2 Paragraph IV in detail

2.2.1 How to challenge a patent under paragraph IV?

Hatch Waxman Act 1984 introduced a data exclusivity period for each new approved branded product. The data exclusivity period is limited to a maximum of 7 years (3-year, 21 U.S.C §355(j)(2)(A)(i)-(iv).


\(^3\)Id. at 16

\(^4\)Id. at 16

5-year, 7-year data exclusivity is granted depending on the type of exclusivity\footnote{21 C.F.R. 314.108.}. During this data exclusivity period, no generic entry can occur. After the data exclusivity only patents protect branded products. In other words, after the conclusion of data exclusivity if patents are proven to be invalid or the new generic version of branded products are proven not to infringe the patent through Para-IV challenge, generic drugs can enter the market.

After the conclusion of data exclusivity and before the expiration of the patents protecting the innovating drug, generic manufacturers can enter the market and compete with the incumbent by filing an ANDA under paragraph IV. The applicant has to prove that (i) the generic drug is bioequivalent to its branded drugs and that (ii) the generic drug does not infringe on innovators’ patents or the patents are invalid.

When a generic manufacturer files a generic application under paragraph IV, it must notify the innovator. Within 45 days, the innovator has two options (1) do nothing and FDA can approve the generic version of the branded product or (2) sue the generic manufacturer for patent infringement. If the innovator files a suit, it triggers a 30-month stay on FDA action. During this stay, FDA cannot take any action on the application unless there is a court ruling. If the court ruling favors the generic manufacturer, FDA may approve the ANDA. The successful first-filer is granted a 180-day exclusivity. It is the sole generic provider in the market and FDA will not approve consecutive ANDAs for the same innovating drug during that time. After this 180-day exclusivity, any generic producers can enter the market.

There are a variety of mechanisms to satisfy these two conditions at the same time. Here is one illustration (Tang, 2013). A innovator developed a new formulation of drug X, containing active ingredients A, B and an inert carrier C which is known to enhance the drug’s effectiveness. A generic manufacturer files a PIV challenge stating that its generic version of branded drug X does not infringe the innovator’s patent. The active ingredients A and B are important in that they contribute to the product’s bioequivalence and cannot be easily replaced. But there are many alternatives that are bioequivalent for the carrier C. Generic manufactures can find out these ingredients from the description of working mechanism of C in the patent. The generic applicant can create a generic version with
active ingredients A, B and a substitute carrier C1. X is a new formulation drug, not a
new chemical entity drug so active ingredients A and B are not covered by the patent.
Neither is C1 stated in the patent. Thus the generic drug comprised of A, B and C1
does not infringe the patents and generic manufacturers only need to prove its product’s
bioequivalence to the branded drug, which can be considered to be easy.

2.2.2 Why does Hatch-Waxman 1984 provide a favourable environment
for generic manufacturers to flourish?

Prior to 1984, safety and effectiveness data of drugs were considered to be trade secrets.
Generic manufacturers previously might not have been able to gain FDA approval because
it is difficult for them to obtain safety and efficacy (Tang, 2013). The public information,
therefore, plays a crucial role to accommodate generic manufacturers to invent around the
new non-infringed process and file Para-IV application.

In addition, generic manufacturers can file the application for PIV challenges before
the conclusion of the data exclusivity period, aiming to get an immediate approval at
the end of the data exclusivity time. Therefore, for a non-New Chemical Entity Drug
(non-NCE) with a 3-year data exclusivity from the approval time, generic companies can
seek an FDA approval for the generic version right after the exclusivity expires by filing
an ANDA early. In that case, the generic version of a non-NCE can enter the market as
early as 3 years after the brand name drug was launched in the market.

The Hatch-Waxman Act also introduced an ANDA mechanism that accommodates
resolution for patent disputes between innovators and generic producers. An ANDA ap-
plicant must file a certification for its generic version of each patent that is listed in
Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as
the “Orange Book”. However, the ambiguous language of the Act caused some controver-
sies for innovators and generic companies. Branded drug holders took advantage of this
and successfully delayed generic entry by extending the dispute and delaying court time.
Reacting to it, The House and the Senate passed the “Medicare Modernization Act of
2003”, also called as the MMA 2003 to limit the time to solve a patent dispute. According
to it, the maximum amount of time to solve a patent lawsuit for a PIV challenge is 30
months. Since then, generic challenges written under paragraph IV have been increasing
The 180-day exclusivity for the first successful PIV challenger provides a strong financial incentive for generic entry. The observed drug price in the U.S. from 1999 to 2004 in Figure 2.1 shows that the first generic competitors enjoy almost a full price compared to the pioneer drug. As a consequence, the average revenue by a successful PIV challenge is estimated to be $60 million (Higgins and Graham, 2009). In addition to duopoly power, the ANDA procedure is adjusted to be substantially cheaper compared to a full NDA. The Federal Trade Commission estimated that the average cost of a PIV challenge is about $5 million (Higgins and Graham, 2009) while the cost for developing an innovative new drug is $800 million (A CBO Study: Research and Development in the Pharmaceutical Industry, 2006).

Figure 2.1: Generic competition and Drug Price (1999-2004)
Chapter 3

Literature Review

This paper draws upon literature on the imitation theory. Cohen and Levinthal (1990) first coined the term “absorptive capacity”, describing the endogenous abilities of firms to imitate. Abernathy and Utterback (1978) mentioned the idea before that the absorptive capacity is achieved by R&D in manufacturing operations. In other words, firms are more capable to imitate when they have experience in recent-to-the-time technology and invest in R&D. Morton (1999) used the theory to predict the endogenous decision of generic entries. She found that firms’ experience in certain forms of family drugs can increase their likelihood to make a generic entry in similar family drugs.

Valdani and Arbore (2013) categorized three types of imitators: newcomers who are attracted by profits and the potential opportunities in the market, incumbents who imitate to maintain their relative market shares and retailers. The paper also discusses the imitation timing and the market potential for late entrants. Finally, Lieberman and Asaba (2006) answered the last question about why firms imitate each other under various business setups. He suggested that firms’ motivations to imitate generally fall into two categories: (1) firms follow the others who are assumed to have superior information or (2) firms imitate their rivals in order to match their portfolio and maintain their comparative market share.

Regarding the pharmaceutical industry, there has been a significant amount of works studying generic manufacturers. Some works focused on the increase of the generic competition in the US over the last decade. Berndt and Aitken (2011) provided a thorough overview on the generic entry trend and its effect on drug prices and market penetrations.
from 1984 to 2009. Grabowski (1996) showed that the generic competition had intensified after Hatch Waxman. Saha et al. (2006) analyzed the sample of 40 brand-name drugs that were first challenged in 1992-1998 to study the interaction among the generic entries, prices and the market share.

However, studies about paragraph IV challenges are still limited in number. Grabowski (2004) pointed out that many leading drugs under the patent protection are being challenged early in their market life. Recently, Olson (2013) from the FCT took advantage of the 180-day exclusivity to study the effect of additional generic entrants on the competition and drug prices.

In regard to its impact on welfare, Bokhari and Fournier (2013) found that the first entry of a generic drug can have a large welfare gain due to the elastic demand of the ADHD drug markets. However, Branstetter et al. (2016) found that the generic entry overall provides a modest gain in total welfare. The welfare is just transferred from producers to consumers and the total consumption does not increase significantly after generic entries.

The likelihood a drug is challenged under the paragraph IV is not only affected by its sales and revenue (Grabowski and Kyle, 2007) but also its patent portfolio (Hemphill and Sampat, 2011). Grabowski and Kyle (2007) found that while there has been an increase in PIV challenges for drugs with modest annual sales, drugs with larger sales attract the most early generic challenges. They also have shorter market exclusivity periods than smaller drugs. Blockbusters with annual sales over $1 billion, on the other hand, have faced less challenges in recent years. Hemphill and Sampat (2011) studied the likelihood of early generic challenges taking into account the characteristics of drugs’ patent portfolio. They found that PIV challenges are attracted to weak patents, which expire later than the basic patents.

**My contribution to the literature**

Prior pharmaceutical research focused mainly on the impact of the generic entry on the market, the competition and welfare. However, it provides little information about generic manufacturers and changes to these firms under a more favourable environment. Research about imitation provides a thorough overview on imitation activities. Yet there is not any work that specifically focuses on the pharmaceutical industry. Therefore, this
study attempts to fill the gap in the literature to examine the heterogeneity of generic firms that engage in PIV challenges. In addition, I study the difference in behaviors of generic firms based on their characteristics. These behaviors include the dynamic changes in imitation activities, innovation level and their absorptive capacity.

The closest paper to my topic is that of Scott Morton (1999) which predicted the generic entry decisions based on firms’ characteristics. Morton found that generic firms specialize in entering the market that they have experience with in terms of scientific as well as marketing dimensions. Specifically, firms’ portfolio characteristic, namely its previous experience with a drug or a therapy, reduces the cost of ANDA and increase the chance of a generic entry. Firms are also more likely to enter markets that are similar to those already in their portfolios.

Morton’s findings provide a foundation for my paper on firms’ absorptive capacity, which explains firms’ ability to imitate and file PIV challenges. However, while Morton tried to explain the decision making of generic companies with every single entry based on firms’ characteristics, I use firms’ characteristics to explain the overall activeness in PIV challenges. My approach can capture the changes in firms’ characteristics and their imitation activities over time. In particular, it points out the changes brought by the MMA 2003 that changed the institutional environment of PIV challenges.
Chapter 4

Imitation Theory

4.1 How can firms imitate? - Absorptive Ability

Imitation is a common practice in the pharmaceutical industry and the generic sector has experienced an explosive growth in the past 25 years. Its contribution increased from 20% of total prescription then to 70% today (Frank (2007) and Engelberg et al. (2009)). The lucrative profits from imitation attract rent seekers, but not everyone has the ability to imitate. Cohen and Levinthal (1990) introduced the idea of the absorptive capacity, explaining the endogenous abilities of companies to recognize and exploit the external knowledge for their operations. In order to build that imitative capacity, it requires not only basic skills but also the knowledge of the most recent technology development. Abernathy and Utterback (1978) and Rosenberg (1982) suggest that the absorptive capacity can be improved through byproduct R&D in manufacturing operations. Thus, a firm is better able to replicate drugs if the company already has experience in manufacturing drugs with similar forms, similar ingredients or the therapeutic class of the drug that they want imitate. Morton (1999) has confirmed the idea. She showed that generic firms prefer to enter the markets that are similar to their prior portfolios or the markets in which they have revenue or sales to hospitals.

Experience with a family drug not only enables imitators to replicate the drug but also makes the entry cheaper and more profitable. The pharmaceutical industry is characterized by high fixed costs (invention costs and application costs) and low manufacturing costs. Although Hatch-Waxman 1984 brought the expenses for generic applications -
ANDA - significant lower than applications for innovating drugs - NDA, the fierce generic competitions under the uncertain market conditions make the entry costs a large expense in a generic drug project. When a firm specializes in familiar markets, it lowers the entry cost and increases the chance to get the FDA’s approval. In the PIV challenge context, each drug form and their route into the body requires different types of machinery to manufacture. They have certain characteristics and cleanliness standards. Therefore, if a firm’s portfolio has a similar drug form and route, it does not need to buy the new equipment and it can reuse the machinery. It also has a experienced staff that is acquainted with the equipment, production procedures and the preparation for FDA approvals. Moreover, experience with certain ingredients or with a certain therapeutic class can make the preparation for FDA approvals cheaper because firms already have FDA-certified suppliers. It can also create economies of scale to produce another drug with the same drug family.

4.2 Who are the imitators?

Valdani and Arbore (2013) pointed out that in the imitation game, in general, imitators can fall into many categories. They can be newcomers who have not been in the industry before but sense the opportunity brought by an innovation. The profits or future profits of the product attract their entries. They usually aim at market segments that have not been exploited yet. For example, Lino’s coffee, a newcomer in the Italian breakfast market, copied Starbucks’ operation when Starbucks had not yet entered. Newcomers can also introduce innovative imitation products to capture the niche markets. For example, Samsung entered the digital camera market to diversify its product portfolio. In pharmaceutical contexts, specialization becomes the core competitive advantage for small firms and newcomers. The consolidation among big generic manufacturers have put pressure on smaller firms. Large manufacturers usually take up a large market share. They also have financial resources to pursue an aggressive price competition. Therefore, specialization becomes essential for small generic companies and newcomers to compete in the generic sectors. They can focus on niche therapeutic areas whose products are difficult to manufacture and have high entry barriers such as injectable drugs. These markets are usually not attractive to the big players because of their low profit margin. Moreover, companies
that offer only injectable drugs, rather than a full range of medicines, can still negotiate
good prices with hospitals (Reuters, n.d.). These are the strategies that Generamedix,
Claris Life Science, Stride Shasun and World Fine Chemicals used to enter the generic
markets.

The second potential imitators are the innovation incumbents in the industry. They
could be direct rivals of the innovators and feel threatened by the innovating products
in the market. There are two strategies that incumbents can pursue in their imitation
activities. They can either imitate immediately to match the rival portfolio in order to
maintain their market share. Or they could until the success of the innovation is certain
to make the decision of entering the imitation market. Pfize’s acquisition of Hospira is
an example of this case. While Pfizer is a traditional innovator, Hospira was the leading
manufacturer in generic injectable drugs. Pfizer added Hospira’s portfolio to its generic
portfolio to upscale its generic size. More importantly, Hospira had a strong position in
biosimilars. Biosimilar drugs are complex biological medicines that are hard to replicate.
Thus, some blockbuster biological drugs such as Roche’s Herceptin to treat breast cancer
have been able to maintain their monopoly and high prices even after their patent has
expired. The knowledge and experience in biosimilar drugs of Hospira can help Pfizer
enter these potential markets that it would not otherwise enter and level the playing field
with other innovators.

Imitators can also be imitator incumbents. They are big players in the imitation
industry and have a lot experience with ANDAs. The profit from their imitation activities
is attractive enough for them to still be in the game. In my sample, most of the largest
PIV holders are in this category. For example, Teva, Mylan, Sun Pharm are among the
top 5 PIV holders and they are also the leading generic manufacturers in the world.

The last type of imitators is retailers. They take advantage of their own tangible and
intangible resources to imitate the best-selling branded product. In my sample, Belcher
Pharmaceuticals is in this category. It has a full-circle operation from manufacturing,
packaging and distributing products. However, this type of players only make a small
contribution in PIV challenges.
Table 4.1: Estimate of average research and development costs, (DiMasi et al., 2003)

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<tr>
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<td>Preclinical</td>
</tr>
<tr>
<td>New Drug Application (NDA)</td>
<td>$335m(4.3 years)</td>
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<tr>
<td>Abbreviated New Drug Application (ANDA)</td>
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4.3 Why do firms choose imitation over innovation? – Imi-
tation advantage

When a firm decides to invest in R&D, they face a choice of whether to invest in innovation or in imitation. So which factors make imitation more attractive?

Firstly, imitation investment requires a lower capital endowment, and it is suitable for small and medium companies. Table 4.1 shows that the estimated cost to develop a new entity drug is about $802 million with an average time of 11.8 years. The cost is 160 times more expensive than to develop a generic drug and get a FDA approval. Therefore, an investment in innovation requires a large capital capacity that must be sustained for a long time, which is impossible for small companies and newcomers. The generic sector naturally becomes attractive for these companies, especially when the post Hatch-Waxman environment becomes friendlier towards generic manufacturers.

Moreover, innovation is a risky investment. It not only requires large financial resources but also comes with uncertainty. Figure 4.1 shows that a research project usually lasts more than a decade with many stages of preclinical and clinical trials. However, a large investment does not guarantee that the product will make it into the market. The failure rate of new entity molecule research is very high with only 21.5% of projects receiving FDA approvals (Figure 4.1). The further a project goes on, the heavier the financial burdens are if the project fails. One recent example is Eli Lilly’s failure with the experimental drug to treat Alzheimer in its final stage. Bloomberg (2016) reported that Lilly had spent about $3 billion over three decades developing the treatment for Alzheimer’s disease. The experiment failed to make statistical improvements on the patients’ condition with their Alzheimer in its third stage. The market reacted strongly to the news and Eli Lilly’s stock
fell 15% during the same day that the news were published (Google Finance). However, the financial payoff for a successful project is massive. In Eli Lilly’s example, the success of a medicine, which can effectively ease the progression of the disease, slow down the erosion of mental ability and shorten the patients’ stay in nursing home, can generate approximately $3 billion annually (Bloomberg, 2016). On the other hand, what is unknown for generic companies is how many manufacturers exist in the market. The number of manufacturers in a specific drug market affects the expected profits of each manufacturer. Even in unfavourable market conditions, the cost to enter the generic market is approximately $5 million so the stakes are not as high as with innovation drugs (Higgins and Graham, 2009).

![Figure 4.1: The probability of new drug development entering each phase of clinical trials, (DiMasi et al., 2003)](image)

Lastly, Lieberman and Asaba (2006) suggests that firms decide to imitate in an effort to maintain their relative positions and market shares with their rivals. It is more common among firms with similar market shares and resource endowments. Once one firm succeeds with a new launch, the others will try to imitate to maintain their relative market share.

### 4.4 When do firms make generic entries?

The timing of generic entry is a strategic decision that depends on the uncertainty of the environment. In Valdani and Arbore (2013), there are three main factors that affect the timing of imitation maneuvers. The first factor is the uncertainty of the demand. The point of imitators’ delay of entry is to wait until the realized demand and for the
maturity of growth and revenue. Thus, in that case, waiting does not mean to lose out on opportunities but it is a strategic step to take advantage of the innovator’s effort of having marketed and educated customers about the products. It also reduces the uncertainty of the new technologies and allows the innovator to try and make the first errors. In pharmaceutical settings, this factor is not the main concern because the earliest time that generic drugs under paragraph IV can enter the market is 3 years after the introduction of the branded drug. Therefore, the market demand is already realized at the time the entry decision is made and the marketing and market’s penetration is mature. Thus, generic entries do not have to face the uncertainty of the demand. It is an advantage of imitation over innovation in the pharmaceutical industry.

The second concern in timing is the costs. An early entrant faces a higher entry cost because they endure more constraints from innovators and intellectual protection. They have to try out new technology when it has not yet reached its mature production stage and the product is not produced at optimal cost. The first generic entrant under paragraph IV faces not only application costs, but also the costs of defending the patent infringement in court. Late entrants can avoid the latter costs, but they can not enjoy the 180-day-exclusivity to be the sole generic provider in the market.

The last issue correlates with how fast firms are able to imitate. As mentioned in the earlier section, the ability to imitate depends on the absorptive capacity of each company, so the required time to imitate varies from company to company, causing late entries.

4.5 Model for endogenous PIV challenges

In this section, building on endogenous imitation theory (see Kanniainen and Stenbacka (2000)) and generic entry (see Morton (1999)), I present strategic behaviours of generic firms in PIV challenge activities.

Assume that $0 \leq \alpha_i \leq 1$ stands for the success probability of PIV entry. $\alpha_i$ is assumed to be the firms’ decision.

Assume that the cost for a generic entry is $\alpha_i^2 \frac{bc}{2}$, in which $b \in [0, \infty)$ denotes the patent breadth. In the context of PIV challenges, for the sake of brevity I assume that patents last forever and the patent breadth $b = 0$ after the expiration of the 180-day exclusivity.
and any generic producer can enter the market. Morton (1999) suggested that firms are heterogeneous in their resources, such as, application expenses, machinery, connections with hospitals, etc. Thus they face different investment costs to make a generic entry. In the above formula $c_i$ denotes the cost.

The game consists of a zero period and the first and the second period. In the zero period, the branded drug is protected under the data exclusivity period and no generic entry is allowed during this time. The first period starts after data exclusivity period. Firms then make the decision whether or not to enter the market by reducing their fixed cost. The first successful applicant can enter the market and enjoy duopoly profit $\pi_d$ for 180 days.

The second period starts after the 180-day exclusivity and other followers can freely enter the market as long as they can prove that their products are bioequivalent to the branded drug and their process does not infringe on the patents, which can be considered to be easy. The patent breadth $b = 0$ so entry costs are zero. In the pharmaceutical industry, although the product is very homogeneous and it should follow Bertrand competition, Caves et al. (1991), Frank and Salkever (1997), Wiggins and Maness (2004) and Olson (2013) showed that it follows Cournot competition and the price drops after subsequent generic entries. Thus each generic player in the market earns Cournot profits $\pi_c$.

Firms then choose $\alpha_i$ to maximize their profits

$$\max_{\alpha_i} \pi_i = \alpha_i \int_0^T e^{-rt} \pi_d dt + \alpha_i \int_T^\infty e^{-rt} \pi_c dt + (1 - \alpha_i) \int_T^\infty e^{-rt} \pi_c dt + \alpha_i^2 \frac{bc_i}{2}$$

The first integral and second integral in Equation 4.1 captures the generic drug makers’ profits within and after the 180-day exclusivity time respectively if, with a probability $\alpha_i$, the firm successfully challenges the branded drugs the earliest and obtains the exclusivity. The third integral captures the profits, with a complement probability $1 - \alpha_i$, in the situation that generic manufacturers fail to obtain the exclusivity and they have to wait until the conclusion of the exclusivity to enter the market. The last term is the cost of the generic firm’s investment.
The optimization for 4.1 is equivalent to:

$$\max_{\alpha_i} \pi_i = \int_0^T \alpha_i e^{-rt} \pi dt + \int_T^\infty e^{-rt} \pi dt - \alpha_i^2 bc_i$$

Firms will choose

$$\alpha_i(T) = \frac{\gamma(T) \pi d}{bc_i}$$  \hspace{1cm} (4.2)

where $T = 180$, denoting the 180-day exclusivity period and $\gamma(T) = (1 - e^{-Tr})/r > 0$.

From Equation 4.2, the decision to challenge patents early depends on the duopoly profit that an applicant gets during the 180-day exclusivity period $\pi d$ and on the patent breadth $b$ as has been confirmed by Grabowski and Kyle (2007) and Hemphill and Sampat (2011). Grabowski and Kyle (2007) found that market size can indeed predict the likelihood that a branded drug will be challenged under paragraph IV. The larger the branded drug’s market size, the larger duopoly profits an applicant gets during 180-day exclusivity and the more attractive it is for generic manufacturers to challenge its patents. Moreover, Hemphill and Sampat (2011) showed that the entry decision depends on patent breadth. Generic makers are more likely to aim at weak patents, i.e. those with narrow breadth. The last determinant is the investment cost which heavily depends on firms’ experience with similar drugs (Morton, 1999).
Chapter 5

Data

5.1 Data and Sample Construction

Successful PIV Applications - I use the data on approved drugs, listed in the 2001-2013 edition of the Approved Drug Products with Therapeutic Equivalence Evaluations database, also widely known as the Orange Book. This data contains information about approved ANDA drugs under the names of those generic companies that sponsored those applications.

Hatch-Waxman has allowed generic companies to apply for commercial marketing before a patent’s expiration through Paragraph IV Patent Certification. In order to distinguish ANDA under paragraph (i) - (iii) from paragraph (iv), I obtained the data of successful PIV certifications from Izhak et al. (2016). The data is collected from listed patents for successful PIV challenges from ANDA approval letters and patent litigation court dockets. The letters are received from two sources: Drugs@FDA database and FOIA requests in monthly basis. Then I linked these PIV certifications to approved ANDA Drugs in Orange Book by application number. This data provides detailed information of each successful PIV application.

ANDA and NDA drug portfolio - To collect information about the drug portfolio of each PIV applicant, I use drug approval databases from the National Drug Code Directory (NDC directory). The NDC database provides an up-to-date directory of all drug approvals through the FDA via electronic applications. I match the names of PIV applicants with the names of the drug sponsors in NDC data. This process is carried out
through coding. After obtaining the data, I manually check the matching results and remove some incorrect matches. This dataset is used to build a firm’s absorptive capacity and its innovation tendency.

There is one potential confounding factor in this process. The matching process was performed to match the standardized names of the PIV applicants with the names of drug holders. So if the matching results had more than one drugs’ holders with the same name in NDC, the result could not distinguish which one is the PIV applicant. For example, one PIV applicant was Orchid Healthcare. First, I input the standardized name of it, which is "Orchid". Then my code would search through the names of drug holders in NDC and pull out all observations in NDC that contained the word "Orchid" in their names. The result returned four drug holder names: Orchid Pharma, Orchid Healthcare, Orchid Hlthcare and Orchid Healthcare Inc. Orchid Healthcare, Orchid Hlthcare and Orchid Healthcare Inc. are one entity and it is the PIV applicant in concern. However, Orchid Pharma is a different entity. I manually crosschecked the matching results against those in the company’s main website to determine whether Orchid Healthcare and Orchid Pharma were the same entity. It turned out that Orchid Healthcare, and Orchid Pharma were not the same entity, I determined which one was the PIV applicant in concern. After determining that Orchid Pharma was not the PIV applicant, I remove all observations with Orchid Pharma as the drug holder. However, there were some situations in which different drug holders had exactly the same name. In this kind of situations, mismatches are possible.

**Financial data and general characteristics** - Financial data is collected from Datasstream in the period of 1998 - 2013 and from companies’ main website if the data was not available in Datasstream. However, the dataset exits some missing observations, contributing to 9.4 percent of the total PIV challenges. The majority of missing points is from private companies whose financial data is not available or from public companies before they went public. Missing observations does not correlate to any fundamental characteristics.

General characteristics of PIV applicants were manually gathered from various sources: firm’s main website, Wikipedia, Bloomberg, Glassdoor and Linkedin. They contained basic information about the companies, such as headquarters location, the number of employees,
estimated sales/revenue and the foundation year. The collection method for firms’ basic
information is more flexible, so the data has no missing observation, but its quantitative
data contains only estimated values instead of the exact number. However, for the purpose
of building descriptive statistics, these estimated numbers provide a rough idea of firms’
size and firms’ general characteristics.

*Update Applicant’s Name* - Pharmaceutical firms are characterized by a considerable
degree of merger activities. One firm can have many subsidiaries. Some subsidiaries are
specialized in generic while others engage in Research and Development and have a large
patent portfolio. To deal with mergers and conglomerates, I treat all subsidiaries as one
entity under the name of their parent company. The entity structure is gathered from
FactSet fundamentals to determine who is the ultimate parent of the applicants. If more
than one company had the same name as the applicant, I visited the main website of each
company. If I could determine that that company operated in the generic field and its
drug portfolio contained the drug name that was listed in successful PIV certifications
under the same applicant name, I would assign that company to a sample. After this step,
I obtained the information of the applicants and their parent companies (if applicable). I
then used that information to update the applicant names.

*Constructing the panel data* - The time span in my data is 1998-2013 where 1998 is
the time that the first successful PIV challenge is approved and 2013 is the last year that
the data is available. In a perfect situation, I would have liked to run a regression where
the number of PIV challenges of firm i on year t is explained by its financial data at year
t. However, the financial data is missing during some years, leading to a large decrease
in sample size. Therefore, I chose to utilize the method from Lerner (2002) to divide the

The cutoff point is chosen based on two reasons. First, MMA 2003 has changed the
nature of PIV challenges environment and its impact is observed after 2006. As mentioned
in the Institutional Background section, MMA 2003 accommodates PIV filing by removing
controversies that prevent generic manufacturers from filing PIV challenges. The changing
environment provides a favourable condition for PIV applicants to file patent challenges
and obtain the certificates in shorter time. It took approximately three years from the
time MMA was introduced until the increase in PIV’s record is observed due to FDA
approval time. As the result, there is a dramatic increase in the number of successful PIV certificates in 2006 (Figure 5.1).

Second, there is a significant difference between applicants that started to challenge patents before 2006 and late applicants. The profile of PIV applicants that entered PIV challenging in 1998 - 2006 is made of large pharmaceutical companies. Among them are familiar names in the industry, such as Allergan, Reddys Lab, Endo, Mylan, etc. These applicants that entered the sample between 1998 - 2006 contributed to 73% total PIV challenges and 90% total exclusivities. They can be considered to be the main driver in PIV challenges. The Hatch-Waxman introduced the mechanism for PIV challenges in 1984. However, the activities are not active until 2006 (Figure 5.1) because branded companies took advantage of the ambiguous language of the Act to delay generic entries. The early entrants engaged in some important court cases that opened a gateway for later PIV practices and can be considered to be the pioneers in challenging patents. On the other hand, about 70% PIV applicants obtained their first PIV certificates after 2006. The majority of late applicants are small Indian and American firms. The late entrants are mostly not entitled to exclusivity. They hold only 10% of exclusivities.

The panel data is unbalanced. There are firms that were established after 2006 so there is no record of these firms in the first period 1998 - 2005. The number of PIV challenges of firm i in period t is calculated as the sum of PIV count during period t and the financial data of firm i is the average value in that period.

5.2 My contribution to the data

The data about PIV challenges is available through Izhak et al. (2016). However, information about PIV applicants’ names exists typing errors and inconsistent entity structures. For example, one applicant can have many similar names, or subsidiaries of the same parent company are reported under different names. Therefore, a significant work is made to correct the spelling errors and to update the applicants’ names based on their entity structures. The result of this work is that each PIV applicant’s name is treated in a consistent manner in the dataset and all duplicate records are removed from the dataset.

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1 Companies’ size is defined by the North American Industry Classification System (NAICS)
In addition, information about applicants’ portfolio is collected through National Drug Code Directory - NDC databases. Although the matching process to obtain the drug portfolio of each PIV applicant is done by coding, the results are needed to be rechecked to make sure that the drug holders in NDC database are PIV applicants. As the result, it requires a lot of effort to extract the right drug portfolio.

In general, information about PIV challenges, PIV applicants’ company structure, their drug portfolio and their financial data are widely available, but they are from different sources with different formats. Therefore, gathering all available information into a single data file in a systematic way is an important process for further analysis. As the result, the integrated data contains all the important characteristics of PIV applicants and their activities in PIV challenges and support the later analysis.

5.3 Sample Descriptive Statistics

5.3.1 PIV challenges

Figure 5.1: The number of PIV certificates 1998 - 2013

Figure 5.1 shows that the number of successful PIVs has steadily surged from 2006. Prior to 2006, there were less than 40 approved applications. Three years after MMA
Table 5.1: Sample Descriptive Statistics

<table>
<thead>
<tr>
<th></th>
<th>Obs</th>
<th>Mean</th>
<th>Std.</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIV Count</td>
<td>108</td>
<td>9.32</td>
<td>21</td>
<td>0</td>
<td>108</td>
</tr>
<tr>
<td>Exclusivity Count</td>
<td>108</td>
<td>1.8</td>
<td>4.8</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>Assets (100 millions US $)</td>
<td>94</td>
<td>52.8</td>
<td>162.4</td>
<td>0.04</td>
<td>1196</td>
</tr>
<tr>
<td>The count of branded drugs - NDA and BLA</td>
<td>108</td>
<td>4.19</td>
<td>9.6</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>The count of generic drugs</td>
<td>108</td>
<td>21</td>
<td>38.8</td>
<td>0</td>
<td>195</td>
</tr>
<tr>
<td>R&amp;D/Assets</td>
<td>108</td>
<td>0.05</td>
<td>0.09</td>
<td>0</td>
<td>0.8</td>
</tr>
<tr>
<td>NDAs/Assets</td>
<td>108</td>
<td>0.28</td>
<td>0.87</td>
<td>0</td>
<td>6.4</td>
</tr>
</tbody>
</table>

The summary statistics is made per firm per period

came into effect in 2006, the number of approvals climbed to 208, reached 417 in 2007 and 566 in 2012. A PIV application usually takes approximately three years to get approved. Thus the uptrend from 2006 reflects a surge of PIV filings in 2003. The figure also depicts a decrease in 2013 because of the lag in receiving information about PIV challenges from Drugs@FDA database and FOIA.

The first successful PIV challenges for a certain drug is entitled to 180-day market exclusivity. In Figure 5.1, the number of exclusivities also increases from less than 20 prior 2003 to 43 in 2006, 56 in 2011. However, the number of exclusivity does not increase as substantially as PIV count. Given that there is only one exclusivity (or two in rare circumstances) granted for one drug, the slowly upward trend shows that there are more generic entries per drug after 2006 than in the earlier period. The reason for that patterns will be discussed further.

5.3.2 Cross-section Summary

Table 5.1 presents the summary statistics of the sample. The sample consists of 108 observations of 54 generic manufacturers. I create a panel of 54 PIV applicants and examine the count of successful PIV challenges approved in 1998 - 2013 in two eight-year periods. 2013 is the last year in the analysis because as mentioned above, information about successful PIV challenges is received on a monthly basis, and I only have a relative full PIV record until 2013.

The key variable of interest in the analysis is the number of successful PIV challenges at a firm level in four periods. It is, on average, 9.32 with a substantial variation across
firms and time. The exclusivity is also a good indication of the activeness in PIV challenges because the applicants who are entitled to 180-day exclusivity play a more active role in PIV challenges than the others. The average exclusivity count for eight years is 1.8, 5 times smaller than the PIV count. It infers that for every 5 PIV entries, there is only one that is entitled to market exclusivity.

Firms’ average assets per period have the mean of 0.53 billion. Its standard deviation is 3 times larger than the mean. Thus there is a big difference in firms’ size among applicants. The latter section explains about firms’ size in more detail. Similarly, R&D investment also has a big variation among firms. The average R&Ds/Assets is 0.05, meaning that PIV applicants, on average, spend 5% of their total Assets on R&D investment. Given that the average R&D intensity by the innovation pharmaceutical industry in Japan is up to 13.3%, in the US to 17.1% and in EU to 13.3% (Commission, 2015), the R&D intensity in the sample is substantially lower, reflecting the nature of a low investment in the generic sector.

The difference between the count of branded drugs and the count of generic drugs are substantial. The average count of generic drugs is 10 times more than the count of branded drugs. It shows that PIV applicants, on average, holds more generic stocks than innovative products.

5.3.3 Panel Summary

In the end, the dataset has 54 applicants with two time periods. Table 5.2 shows the summary of within and between variations in the sample. For demographic variables such as Assets, Portfolio Count, R&D/Assets, between-variation, i.e., variation across applicants, is larger than within-variation, i.e., variation over time. It suggested that the applicants are of different characteristics with deviated sizes and innovation levels.

Between variation for PIV count is of similar magnitude with within variation, reflecting that there are changes of PIV count within each applicant over time and each applicant also differs from each other. To provide more detail on the variation of the PIV count over time, it is useful to look at the transition probabilities, after first aggregating all non-zero PIV count into a single category in Table 5.3.

There is considerable persistence. 67% of the applicant with a zero PIV count in one
Table 5.2: Panel summary of variables

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Std.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIV Count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall</td>
<td>9.3</td>
<td>21</td>
</tr>
<tr>
<td>between</td>
<td>15.4</td>
<td></td>
</tr>
<tr>
<td>within</td>
<td>14.4</td>
<td></td>
</tr>
<tr>
<td>Exclusivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall</td>
<td>1.8</td>
<td>4.8</td>
</tr>
<tr>
<td>between</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>within</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Assets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall</td>
<td>52.8</td>
<td>162</td>
</tr>
<tr>
<td>between</td>
<td>143</td>
<td></td>
</tr>
<tr>
<td>within</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Portfolio Count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall</td>
<td>46</td>
<td>87</td>
</tr>
<tr>
<td>between</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>within</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>R&amp;D/Assets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall</td>
<td>0.05</td>
<td>0.089</td>
</tr>
<tr>
<td>between</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>within</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>NDAs/Assets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall</td>
<td>0.28</td>
<td>0.87</td>
</tr>
<tr>
<td>between</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>within</td>
<td>0.6</td>
<td></td>
</tr>
</tbody>
</table>

There are 94 observations with 54 groups.

Table 5.3: Transition probabilities of the PIV count

<table>
<thead>
<tr>
<th>PIV count</th>
<th>0</th>
<th>&gt;= 1</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>66.67</td>
<td>33.33</td>
<td>100</td>
</tr>
<tr>
<td>&gt;=1</td>
<td>14.29</td>
<td>85.71</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>16.95</td>
<td>83.05</td>
<td>100</td>
</tr>
</tbody>
</table>

period also have zero PIV certificates next period, and 83% of applicants who gain at least one PIV certificate in one period get PIV approvals next period.

5.4 Descriptive Characteristics Analysis

5.4.1 Applicants

The most active PIV applicants are presented in Table 5.4. Most of them are the early PIV applicants who started to be active in PIV challenges in the first period. They are also among the biggest pharmaceutical conglomerates worldwide with a long history operating in generic medicines, Over-the-counter drugs (OTC) and Active Pharmaceutical Ingredients (API). Teva, Mylan, Sun Pharm and Novartis’ generic division - Sandoz - are
now the leading generic pharmaceutical companies by revenue. Besides, some applicants, such as Allergan, Novartis, and Endo also engaged in the development of branded drugs. It thus seems that traditional generic manufacturers are the most active applicant to file PIV challenges.

<table>
<thead>
<tr>
<th>Applicant</th>
<th>Country</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Teva</td>
<td>Israel</td>
<td>130</td>
<td>11 %</td>
</tr>
<tr>
<td>2. Allergan</td>
<td>Ireland</td>
<td>115</td>
<td>10 %</td>
</tr>
<tr>
<td>3. Mylan</td>
<td>US</td>
<td>111</td>
<td>10 %</td>
</tr>
<tr>
<td>4. Sun Pharm</td>
<td>India</td>
<td>78</td>
<td>7 %</td>
</tr>
<tr>
<td>5. Novartis</td>
<td>Swiss</td>
<td>74</td>
<td>6 %</td>
</tr>
<tr>
<td>6. Apotex</td>
<td>Canada</td>
<td>61</td>
<td>5 %</td>
</tr>
<tr>
<td>7. Reddys Lab</td>
<td>India</td>
<td>58</td>
<td>5 %</td>
</tr>
<tr>
<td>8. Endo Pharm</td>
<td>Ireland</td>
<td>46</td>
<td>4 %</td>
</tr>
<tr>
<td>9. Aurobindo</td>
<td>India</td>
<td>42</td>
<td>4 %</td>
</tr>
<tr>
<td>10. Hikma</td>
<td>US</td>
<td>37</td>
<td>3 %</td>
</tr>
<tr>
<td>Others</td>
<td>-</td>
<td>397</td>
<td>35%</td>
</tr>
</tbody>
</table>

5.4.2 Companies’ size

There are many ways to define companies’ size. I select the definition of U.S. Small Business Administration (SBA) because it provides the classification of small business for each industry based on the North American Industry Classification System (NAICS). Other definitions give a common standard to classify business into a small, medium and large enterprise. However, given a bigger size in the pharmacy than in other industries, a common definition of firms’ size for all industries may not be suitable. I use the SBA definition with NAICS Codes 325412 - Pharmaceutical Preparation Manufacturing. According to SBA, pharmaceutical firms with employees less than 1,250 are qualified to be a small enterprise.

Figure 5.2 presents the distribution of firms’ revenue across firms’ size. Firms with annual revenue less than US$ 100 million fall into the small category. Noticeably small firms are mainly from U.S.(74%) and India(14%). the FDA and American government established a supportive environment for small U.S. enterprises. They can access to the SBA loan and grant program. In addition, they can do contracting with the U.S. government in a fair term with big pharmaceutical corporations. Furthermore, the FDA has
been organizing annual conferences and Generic Drug Forum to assist small pharmaceutical companies to learn about the development, testing, reviewing, and approval of generic drugs. These favorable supports nourished the development of small American generic firms.

### 5.4.3 Geographical origin and Companies’ Age

#### Table 5.5: Top countries hold the most PIV challenges

<table>
<thead>
<tr>
<th>Country</th>
<th>No.</th>
<th>%</th>
<th>PIVs per firm</th>
<th>Size</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td>India</td>
<td>368</td>
<td>32%</td>
<td>13.6</td>
<td>0.78</td>
<td>0.22</td>
</tr>
<tr>
<td>US</td>
<td>243</td>
<td>21%</td>
<td>6.1</td>
<td>0.23</td>
<td>0.78</td>
</tr>
<tr>
<td>Ireland</td>
<td>188</td>
<td>16%</td>
<td>62.7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Israel</td>
<td>130</td>
<td>11%</td>
<td>130</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Switzerland</td>
<td>75</td>
<td>7%</td>
<td>37.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Canada</td>
<td>71</td>
<td>6%</td>
<td>17.8</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Japan</td>
<td>22</td>
<td>2%</td>
<td>5.5</td>
<td>0.75</td>
<td>0.25</td>
</tr>
<tr>
<td>Germany</td>
<td>11</td>
<td>1%</td>
<td>11</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Australia</td>
<td>9</td>
<td>1%</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Netherlands</td>
<td>7</td>
<td>1%</td>
<td>3.5</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

I investigate the top countries that hold the most PIV certificates and the distribution of firms’ sizes in each country. I report countries of origin and the number of PIV
certificates from which their holders originate.

Not surprisingly, India is the most active countries, contributing to a third of total PIVs. However, the average certificates per each applicant is smaller than other countries in top 6 except the US. In the 1970s after independence, the Indian government carried out the weak patent law and drug price control in order to encourage domestic companies to produce bulk drugs and to be independent of drug imports. Reverse engineering was the main activities of Indian manufacturers at that time and the competition among domestic firms was intense. This trend created a large number of domestic manufacturers with the capacity to develop a cheap process in a short time. "By the end of the 80s, Indian firms were manufacturing practically every new molecule which was commercially viable without access to process details from the innovator company" (Kale and Little, 2007). The experience in reverse engineering, its cost competitiveness and high-quality cheap labor force made a vital role for Indian manufacturers to enter the global market. However, Indian generic companies only started to kick off drug exports to other developing countries and to advanced countries when they invest in R&D after the liberalization of the pharmaceutical market. They adopted innovative imitation by creating a non-infringe process, challenging existing patent and obtaining ANDAs as a ticket to enter American and European markets. Indian companies only started to take off since the middle of 1990 so they are quite young with an average age of 37.4 years.

America is the second biggest contributors to PIV challenges. American firms, however, are small young firms and they are comprised of 45% small and medium enterprises. On the other hand, Israel and Ireland have just a few applicants but they are giant pharmaceutical corporates in the generic pharmacy. They have established 112 and 68 years ago respectively.
Figure 5.3: Firm age by country
Chapter 6

Empiric and Methodology

6.1 Methodology

6.1.1 Modeling Count Data

Data Summary

Number of PIVs is a countable variable with discrete, non-negative values. The basic distribution of count data is Poisson distribution. However, our sample violates the Poisson assumption that the variation of dependent variable, PIV count, is larger than its mean. Sample mean of PIV count is 9.32 and sample variance is $21^2 = 441$. So there is a great overdispersion.

The distribution has a long right tail. Almost half of total observations is less than 3 and the maximum is 108. The proportion of zeros is 12.28%. This is relatively low for count data so excess zero-count would not be a problem in our sample.

Modeling Strategies

Cameron and Trivedi (2010) suggested Poisson maximum likelihood estimator (MLE) approach for overdispersed data. MLE estimator is consistent as long as the conditional mean assumption $E(y|x) = \exp(x'\beta)$ is satisfied. Then one can relax the equivariance assumption to obtain a robust estimate of the variance-covariance matrix of the estimator (VCE).
Figure 6.1: Histogram of PIV count

**Poisson Model**

Poisson MLE, denoted by $\hat{\beta}_p$, is the solution to the ML first-order conditions:

$$\sum_{i=1}^N y_i - \exp(x_i^\prime \beta) x_i = 0$$

If the Poisson model is correctly specified, the estimator $\hat{\beta}_p$ is consistent for $\beta$ even when the count is not actually Poisson distribution. With overdispersion, Poisson MLE can be used to obtain consistent estimator but variance-covariance matrix of the estimator needs to be corrected with robust VCE. Robust VCE for overdispersion will be larger than normal variance-covariance estimate obtained from Poisson MLE.

### 6.1.2 Modeling Panel Count-Data

Panel regressions can capture variations over individual units and variations over time. Each additional time period of data is not independent of previous periods, thus the standard errors need to be corrected.

There are some common features that panel count data inherits from cross-section count data. First, panel estimators have the same robustness properties as cross-section estimators. The estimators are consistent, provided that the conditional mean is correctly
specified. Second, similar with heteroskedasticity-robust standard errors in cross-section data, panel-robust standard errors need to be used in overdispersed data.

Panel model tries to capture individual effects. It specifies

$$y_{it} = \alpha_i + x_{it}'\beta + \varepsilon_{it}$$

where $x_{it}$ are regressors, $\alpha_i$ are random individual-specific effects, and $\varepsilon_{it}$ is an idiosyncratic error. The individual-effects are modeled in Pooled, Random-effects and Fixed-effects models. These methods were drawn from Cameron and Trivedi (2010).

**Pooled model**

A natural starting point is a Pooled Poisson model for PIV count, using data of all applicants in all periods. Pooled estimator is consistent when $E(y_{it}|x_{it}) = \exp(x_{it}'\beta)$. For panel data, it is essential to use robust clustered standard error. Robust standard errors will correct the overdispersion. Clustering for applicants can solve error correlations that commonly exist in panel data. It can also take individual effects into its estimate. Normal standard errors assume that the regression errors are independent and identically distributed. However, in the panel data, if the dependent variable is overpredicted in one year for a given applicant, then it is likely to be overpredicted next periods. Failure to control for this correlation leads to underestimating the standard errors.

**Random-effects model**

Random effect model estimates the individual effects $\alpha_i$ with the assumption that individual effect $\alpha_i$ is random and uncorrelated with $x_{it}$, or $\text{Cov}(x_{it}, \alpha_i) = 0$. The random effect estimator is more efficient than Pooled estimator or Fixed-effect estimator. It tries to capture the pattern of the whole sample data rather than estimates only the changes over time of individuals in fixed-effects model. Although it requires stricter assumptions on homogeneity for an unbiased estimator, it is a more efficient method to estimate the panel data.
**Fixed-effects model**

Fixed-effects model estimates the individual effects $\alpha_i$ for each unit in the sample. Unlike the strict assumption in RE models, the fixed-effect estimator is unbiased and it can mostly reduce the effect of omitted variables in the estimation. It allows the correlation between $\alpha_i$ and $x_{it}$ in any periods. As a result, any independent variable that is constant over time cannot be included in a fixed-effect model. One big advantage of fixed-effects model is that it can reduce the chance that a relationship is driven by omitted variables. Robust FE estimator is consistent in most cases. However, it only concerns changes within a cluster over time and ignores a lot of signals in the cross sample.

**Random-effects or Fixed-effects model?**

There is an essential distinction between FE and RE. If the effects are fixed, then pooled model and RE model is inconsistent and within estimator/FE estimator needs to be used. However, when an individual effect is uncorrelated with the regressors, FE is unfavorable because it only captures within variation, leading to an inefficient estimation and it is unable to estimate coefficients of time-invariant regressors. Therefore, ones have to face the trade-off between high variance and high bias.

FE estimator is inefficient and creates a high variance. FE estimator can produce estimates that are highly dependent on the sample. It means that inference of the FE estimator on overall population is limited. In addition, FE model causes a significant decrease in the number of observations. Applicants with only one record are removed from FE model, leading to a 15% drop in the observation number. Besides, FE model estimates individual effect for each applicant, so the degree of freedoms also decrease by the number of applicants. These characteristics will increase the standard error substantially. On the other hand, RE would suffer from bias problems. My data is drawn from the entire population of PIV challenges, so biasness from partial pooling is not the problem. However, the correlation between explanatory variables $x$ and individual effect $\alpha_i$ needs to be tested.

The Hausman test can be used to compare the consistency of FE estimator and RE estimator. It tests the null hypothesis whether the difference between the consistent
estimator (FE estimator) and the efficient estimator (RE estimator) are systematic. The alternative hypothesis is that there is a significant difference between two coefficients and that the efficient RE estimator is not consistent. This is because RE estimator makes exogenous assumption while FE estimator does not. If this assumption is wrong, this will be reflected in the difference between two coefficients.

6.2 Empirical Framework

6.2.1 Choice of variables

**PIV challenges** - I employ two measures to represent the activeness of a particular applicant in PIV challenges. The first measure is the count of successful PIV challenges, regardless the applicant’s eligibility for 180-day-exclusivity. It represents the activeness in PIV challenges of one firm in one period. Second, I create a weighted PIV count, which puts more weight on PIV entries with 180-day exclusivity. Discrimination of PIV challenges with exclusivities against the rest is due to the fact that successful PIV with exclusivity brings larger financial gain than subsequent PIV entries. In addition, the first-to-file PIV application for a certain drug is more costly due to patent infringement lawsuits that only the first applicant engages in. It also requires the ability to replicate the drug in a short time, which can only achieve if a firm is able to apply the most recent technology. According to Olson (2013), the drug price during the exclusivity period, on average, is 70% higher than the price outside the exclusivity period. When more generic entrants enter the market, the price drops with an additional entrant. Assumed that a molecule’s market size is stable because the brand has expanded the market size as much as it can, the profits also decline with an additional entrant. For simplification, I assume that the financial gain from a generic entry is proportional to the drug price. Therefore, a successful PIV entry with exclusivity will bring 70% more payoffs than a PIV entry outside exclusivity. Thus, the weighted PIV count is calculated as PIV Count + 0.7 * Exclusivity Count.

**Innovation propensity** - I used two measures as a proxy for firms’ innovation intensity. First is the count of NDA divided by total assets. This variable is the innovation stocks of a certain firm (the count of NDA - branded drugs), adjusted to firm size. It reflects how
intensive a firm is in innovation.

The second measure is the R&D expenditure adjusted to assets. It is a standard variable to represent the innovation intensity in the literature. By accounting standards, R&D expenditure includes both the investment for innovation and the investment for imitation. For an innovator that focuses all of its operations on developing branded drugs, R&D per Assets is a measure of its innovation intensity. On the other hand, for an imitator that only operates in the generic pharmacy, R&D reflects its investment in imitative activities and R&D per Assets becomes the indicator of its imitation intensity. For those who are active in both imitation and innovation, this measure can be used to describe investment spending in relation to the intensity of PIV challenges.

Absorptive Capacity - Firms’ ability to replicate a drug and to prepare the generic applications for FDA approvals depends on its previous experience in the industry. I use the portfolio count as a measure of firms’ absorptive capacity. A firm with a wide range of experience in branded drugs and generic drugs would have more knowledge and resources to invent a new non-infringe process to challenge a patent. In addition, previous experience in manufacturing drugs can minimize the cost of the application process and machinery.

6.2.2 Measuring the correlation of PIV challenges, innovation and absorptive capacity

When first introducing the Hatch-Waxman 1984 FDA aimed to encourage innovation and early entry of generic drugs. However, whether an increase in PIV challenges hinders innovation is an interesting problem for policymakers. In this paper, I try to examine the correlation between firms’ innovation, absorptive capacity and its activeness in filing PIVs. The empirical model for the count of PIV challenges of a given applicant i, in period t

\[
P_{IVit} = \beta_1 * Innovation_{it} + \beta_2 * Portfolio_{it} + \beta_3 Assets_{it} \\
+ \tau_{it} 0613 + \lambda_1 Portfolio_{it} \times y_{0613} + \lambda_2 Assets_{it} \times y_{0613} + \alpha_i + \varepsilon_{it} .
\]  

(6.1)

The variables in 6.1 are as follows:

- \( P_{IVit} \) is the count of PIV/weighted PIV that firm i holds in period t.
• *Innovation* \(_{it}\) is the innovation propensity of firm \(i\) in period \(t\). I use two measures representing the innovation propensity. The first measure is NDA count divided by assets, i.e., the number of branded drugs that firm \(i\) holds in period \(t\) adjusted to its asset. The second measure is R&D expenses divided by assets.

• *Portfolio* \(_{it}\) is the measure of firm \(i\)’s absorptive capacity in period \(t\). It is calculated as the total number of branded drugs and generic drugs in firm \(i\)’s portfolio from the establishment date until period \(t\). The count of drugs in firm \(i\)’s portfolio describes firm \(i\)’s experience in the industry. It is an advantage for firms to reduce the generic entry costs.

• *Assets* \(_{it}\) is the total assets of firm \(i\) in period \(t\) (expressed in billions of 1998).

• \(y_{0613}\) is the time dummy variable for period 2006 - 2013.

• \(\alpha_i\) is the individual effect of firm \(i\).

• \(\varepsilon_{it}\) is the error term which includes other unobserved factors.

There are two measures of the innovation propensity. The first measure NDAs/Assets reflects the activeness of firms’ operations in branded drugs. It is expected to have a negative relationship with PIV challenges (Figure 6.2). Because of the unbiasedness of NDAs/Assets, this model provides a reliable result about the relationship between PIV challenges and the innovation intensity.

The second measure \(R&D/Assets\) brings a different perspective. As mentioned in the earlier part, R&D per Assets reflects either the innovation intensity or the imitation intensity, depending on whether R&D is used on innovation projects or on imitation projects.

Absorptive Capacity, represented by *Portfolio* \(_{it}\) variable, is added to take into account the role of firms’ previous experience in PIV challenges. As mentioned in the earlier part, a firm’s absorptive capacity plays an important role in its decision to imitate (Morton, 1999). A firm with previous experience in imitating drugs or creating drugs has a good base knowledge and cost advantage to replicate new drugs and challenge patents early. Especially in PIV challenge context, it is optimal to replicate the branded drug as early as possible to gain 180-day exclusivity (only the first successful applicant is entitled to this
exclusivity). In order to replicate the branded drug in a limited time, a generic firm needs to be in the technological frontier to apply new techniques. Therefore, the absorptive capacity is expected to have a strong correlation with successful PIV certificates. This correlation is observed in our sample with the correlation coefficient of PIV count and Portfolio count of $0.75$ (Figure 6.3).

Time dummy variables are added into the model in order to separate time effects from the main effects. PIV activities have been on an upward trend since 2003 (Figure 5.1), thus a control variable to take into account the time trend is necessary. The time period in the model is divided into two periods because of the difference in the institutional nature before 2006 and after 2006 and the difference between early applicants that started to be active in PIV challenges before 2006 and after 2006.

Before 2006, PIV activities contained a lot of uncertainty. PIV applicants that were active in the first period engaged in some important courts that opened the gateway for later PIV practices. The first mover action contains risks and requires a large absorptive capacity. The MMA 2003 came into effect and makes PIV entry more accessible by preventing an evergreening practice that branded companies used to delay generic entry. It also provides instructions and guidelines to support PIV challenges. It reduces the uncertainty that existed in the earlier period. Due to these reasons, I include the interaction

Figure 6.2: The scatter plot of PIV count and NDAs/Assets
of time dummy with Absorptive Capacity $Portfolio_{it}$ and control variable $Assets_{it}$ to quantify this difference.

After controlling for firm size with $Assets_{it}$ and time effects, the model attempts to capture the main correlation of innovation level and PIV activities and the correlation between absorptive capacity and PIV activities.
Chapter 7

Results and Analysis

The regression results in Table 7.1 are the estimators from Poisson Regressions. Firstly, I ran Pooled models without taking into account time effects. Cluster robust standard errors were used to eliminate autocorrelations over time.

Secondly, I took into account individual effects in the regression. After initial regressions, I ran Hausman tests in order to determine whether random effects could be used. The Hausman tests failed to reject the null hypothesis that RE estimators are not exogenous. So RE could be considered in the analysis.

However, RE regressions produced similar coefficients with FE models in all variables except NDAs/Assets and R&D/Assets. Yet the coefficients of NDAs/Assets and R&D/Assets were statistically insignificant in both the FE models and the RE models. They brought little meaning to my interpretation.

Given that the RE regressions and the FE regressions produced similar coefficients of statistically significant variables and the FE estimates are always consistent, I will only report the result of the FE models. Robust standard errors were used in the results.

Innovation

Innovation variables NDAs/Assets and R&D/Assets are positively correlated with the PIV count but they are not statistically significant. I also experimented to make them interact with time dummies, but the results are statistically insignificant.

Absorptive Capacity

The absorptive capacity, represented by the count of drugs in the firms’ portfolio $Portfolio_{it}$, have a positive coefficient with a high confidence. In Pooled models in (1)
and (2), the coefficient of Absorptive Capacity and the interaction term \((\text{Absorptive Capacity})^*y_{0613}\) are 0.02 and \(-0.01\) respectively. In 1998 - 2005, for a PIV applicant with an average portfolio count of 46.69, their expected PIV count will be \(\exp(0.02 * 46.69) - \exp(0.02 * 0) \approx 2.5\) times more than that of a PIV applicant without any experience, i.e., portfolio count = 0.

In 2006 - 2013, the correlation between the portfolio count and PIV challenges decreases by half. It reflects the difference in the nature of the institutional environment. Under a favorable institutional environment, 70% of all PIV applicants in the sample become active in 2006 - 2013. The majority of late entrants are small firms from India or America. Their average portfolio count in 2006 - 2013 is 5 times smaller than that of early applicants during the same period.

As mentioned earlier in 5.4.3, the participation of Indian firms in PIV challenges after 2003 is not accidental but an inevitable outcome. The MMA 2003 came into effect at the right time after Indian firms shifted the focus from domestic market to export and set up the operations in the U.S. market. More importantly, the biggest strength of Indian generic firms is reverse engineering\(^1\), which is the most critical task in preparation for PIV challenges. Entering American pharmaceutical markets at the right time with the right advantage, Indian firms started to make subsequent PIV entries in 2006 - 2013 as reflected in this model. Although the scope of this study is only until 2013, it is noteworthy that in the later years, the expansion of Indian companies has driven the generic competition and drugs’ price war in America (Altstedter et al., 2017).

With a low absorptive capacity and less experience in pharmaceutical industry, late applicants make most of their entries on drugs that are already challenged by other applicants. These entries are easier to obtain and require fewer resources to pursue. As a result, there were, on average, 6.4 generic entries per drug in 2006 - 2013 compared to 1.4 entries per drug in 1998 - 2005. Subsequent generic entries are less risky, less costly, and require a lower absorptive capacity than the first one. Therefore, the coefficient of \((\text{Absorptive Capacity})^*y_{0613}\) is negative, showing that experience plays a smaller role in PIV entries in 2006 - 2013 than in 1998 - 2005.

When taking into account fixed effects in (3) and (4), the results suggest a similar

\(^1\)reverse engineering is a process to reformulate a product with similar bio-equivalence.
pattern. Absorptive Capacity is positively correlated with the activeness in PIV challenges. Although the correlation decreases in 2006 - 2013, the overall correlation still suggests a statistically significant positive relationship between the two variables.

When putting more weight in PIVs with a 180-day exclusivity, the correlation slightly increases, showing that previous experience in the industry supports firms in achieving 180-day exclusivities.

The findings together with Morton (1999) confirm that firms’ absorptive capacity accommodates their generic entry. The more experience and research investment a firm has, the more likely it gains PIV certificates.

**Assets**

Assets in 1998 - 2005 are negatively correlated with PIV challenges but not statistically significant. The applicants that have been active in PIV challenges since 1998 are traditional generic manufacturers, for example, Teva, Mylan, etc. At that time, generic entries mostly occurred after the patent expired and the engagement in PIV challenges depended on manufacturers’ willingness to take risks rather than their sizes. Therefore, the relationship between Assets and PIV challenges is not statistically significant.

In 2006 - 2013, Assets and PIV challenges are positively correlated with a high statistical confidence. Firms with bigger size are more likely to be active in PIV challenges.
Table 7.1: Regression Analysis

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<th>Pooled FE</th>
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<td></td>
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<td>(2)</td>
<td>(3)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>Absorptive Capacity</td>
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<td>***0.026 [0.01]</td>
<td>***0.024 [0.01]</td>
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<td></td>
<td>***-0.01 [0.002]</td>
<td>***-0.015 [0.006]</td>
<td>***-0.0140 [0.006]</td>
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<td>*0.002 [0.001]</td>
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</table>

Robust standard errors in parentheses
* = Significant at the 10% confidence level; ** = significant at the 5% confidence level; *** = significant at the 1% confidence level
Chapter 8

Summary and Conclusion

8.1 Summary and Implication

The characteristics of a generic pharmaceutical firm’s portfolio strongly determine its activeness in PIV challenges. A PIV applicant with a large portfolio is more likely to gain PIV certificates. Absorptive capacity also increases a firm’s likelihood to obtain the first generic entry and gain the duopoly power with 180-day market exclusivity. This confirms the prediction of the basic model mentioned in section 4.5. The model argued that previous experience lowers the investment cost to make a generic entry and motivates PIV filings. The lower entry costs could be interpreted as equipment resources and knowledge capacity. For example, a firm’s machinery can be reused to manufacture new drugs with similar forms. Moreover, a firm’s knowledge in reverse engineering can increase its capacity to invent around patented drugs and create a non-infringed process.

The relationship between PIV challenges and absorptive capacity decreases by half in 2006 - 2013, which shows the fundamental difference in the characteristics of early PIV applicants who started to be active in PIV challenges since 1998 and late applicants who entered after MMA 2003. The late entrants with a lower absorptive capacity make most of their entries on drugs that are already challenged by other applicants. Due to the participation of late applicants, the average generic entries for one drug in the second period 2006 - 2013 are 4.5 times more than in the earlier period.

The results complement Morton (1999)’s findings. Morton utilizes the characteristics of firms’ portfolio to predict the likelihood of a generic entry for a particular market. Her
finding explains the strategic behaviour of a firm’s decision making on a drug level. My analysis, on the other hand, is made on an aggregate level. I utilize the characteristics of a firm portfolio to predict the intensity of their imitation. Instead of focusing on a particular entry decision, I study the overall activeness of their activities to find similar patterns among PIV applicants before and after the MMA 2003. Morton (1999) paper creates an insight into firms’ decision making and I use it as a mechanism, explaining how the characteristics of a portfolio have a positive relationship with imitation activities. In general, absorptive capacity is confirmed, either on a drug level or on an aggregate level, to be a good determinant when it comes to a generic firm’s imitation activities.

Finally, firm size has a positive relationship with PIV challenges. Before MMA 2003, the institutional background for PIV challenges was uncertain. Thus the engagement in PIV activities in 1998 - 2005 depended on firms’ willingness to take risks and firm size did not have a statistically significant role in PIV challenges. After MMA 2003, under a more favourable environment, firms with bigger size have been more active in PIV challenges. Large firms, by default, have more financial resources to prepare applications for FDA approval and make generic entries.

8.2 Direction for further research

My studies focus on PIV activities during 1998 - 2013 due to the lack of more recent data. However, Altstedter et al. (2017) reports a generic price erosion, leading to a big loss of large generic pharmaceutical companies, such as Mylan, Teva and Sun Pharm. The main reason is due to the global expansion of small Indian firms. PIV activities of these companies are captured in the analysis, but their presence was minimal before 2013.

Recently the presence of family-owned drug makers from India in the American generic market is growing. It has changed the competition in the American generic drug market. They use aggressive pricing strategies, which sometimes can lead to a 90% price reduction in prices. In particular, the FDA, encouraged by the Trump administration, promotes downward pressure on drug prices. They speed up the generic approvals and grant more drug approvals than before (Chen and Paton, 2017). As a result, India drug makers gain the most from this action.
Indian generic drug makers play a crucial role in American generic competition, yet there are no studies that focus on these companies. As a result, further research can attempt to examine the behaviour of Indian generic manufacturers and the impact from the generic entries of Indian firms on the competition.
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