L.H. PATTIKAWA

Innovation in the Pharmaceutical Industry

Evidence from Drug Introductions in the U.S.

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Innovatie in de farmaceutische industrie

Aanwijzingen van productintroducties in de V.S.

Proefschrift

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Lenny Pattikawa

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1. INTRODUCTION

And it is in America that drug companies are facing the loudest and fiercest criticism. They (Big Pharmaceutical companies) stand accused of focusing on me-too drugs which confer little clinical benefit over existing medicines; rushing these to market through cunning clinical trials designed to make them look better than they are; and suppressing data to the contrary. The industry is also lambasted for expensive, aggressive and misleading direct-to-consumer advertising, which sometimes create conditions to fit the drugs, rather than the other way around. Hobnobbing with doctors means giving them food, flattery, friendship at best, and outright bribery at worst. … Indeed, critics argue that society is largely on the losing end of its dealing with the industry. The Economist, March 17th 2005

1.1 BACKGROUND OF THE THESIS

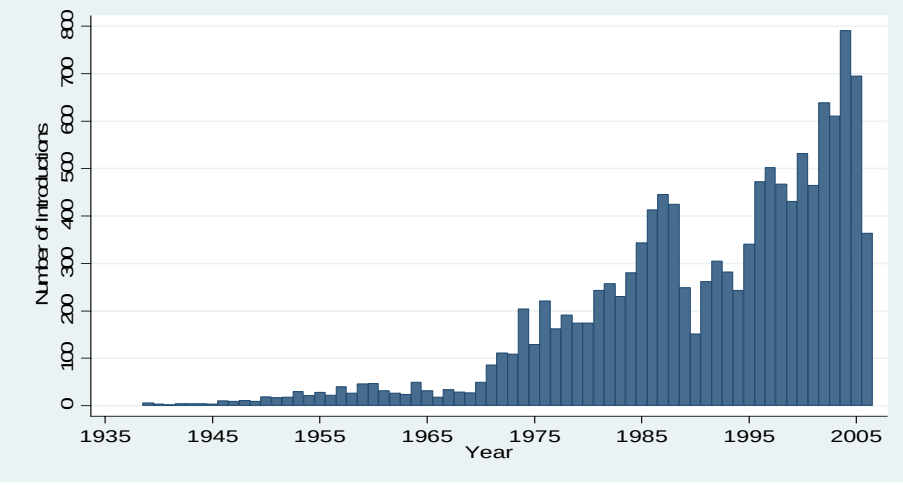
The 20st century witnessed some of the most revolutionary innovations in the history of modern medicine. The effective polio vaccine, for example, that was first announced in the 1950s has defeated one of the most dreadful epidemic diseases in history. The introduction of the contraceptive pill in the 1960s has been claimed to accelerate sexual revolution in the Western world. Another not less important list of products contains the introductions of antibiotics, AIDS medications, diabetes medications, and anti-depressants, just to name a few. The advance of science has spurred a steady stream of new drugs that have no doubt improved human conditions all over the world. In terms of numbers, the U.S. drug market has been flooded by the introduction of new drug products in the last decades. Figure 1.1 shows that the number of drug introductions is growing faster and faster. While the average number of drug introductions in the 1950s and 1960s was under 100 drugs each year, this number is more than five times as high in the 1990s.

In spite of the growing number of drug introductions and the introduction of revolutionary new drugs, the pharmaceutical industry has increasingly been criticized for its lack of innovativeness. A recent report by the National Institute for Health Care Management (NIHCM) and the U.S.

Government Accountability Office (GAO) claims that in the 1990s the majority of drug introductions in the U.S. are based on incremental innovations that provide no significant clinical improvement over existing drugs. Highly innovative new drugs, namely drugs that contain new *active ingredients*[1] and that also provide significant clinical improvement, are limited (NIHCM 2002; GAO_2, 2006).

Some go even further by claiming pharmaceutical companies to be responsible for the upsurge of U.S. health care cost. A recent CMS (Centers for Medicare and Medicaids Services) report expects that by 2015 health care spending in the U.S. will reach $4.0 trillion and 20% of GDP (CMS, 2005). Relman and Angell (2002) argue that drugs are unnecessarily expensive because drug companies spend a much larger amount of profit on marketing and administration instead of putting them back into R&D. The critics are often referring to the high profit earned by the pharmaceutical industry, which is above the average of the U.S. economy.

Figure 1.1 Annual Number of Drug Introductions in the U.S.



Source: see appendix B

1 Appendix A provides more detail on several terms that are specific to the (U.S.) pharmaceutical industry . These terms can be recognized by their italic shape when they are first mentioned in this book.

1.2 WHAT IS THIS THESIS ABOUT?

The above illustration has led to the writing of this dissertation. We aim to answer the following questions. (1) What is the performance of the pharmaceutical industry in terms of innovativeness and profitability? (2) What is the role of advertising and product differentiation for pharmaceutical firms' profitability over time? (3) What are the drivers behind pharmaceutical companies' motivation to introduce drug extensions?

We choose the U.S. pharmaceutical industry as a setting for our studies for two important reasons. First, this market comprises 70% of the total drug market in the world making it more or less representative. The U.S. market is also the biggest market in the world in terms of revenue. In 2000, the revenue of U.S. pharmaceutical industry was $97 billion. As a comparison, the five largest European markets accounted for $51 billion of revenue in the same year (Kyle, 2005). Second, getting drug approvals in the U.S. is considered an important step in new drug marketing. Known for its demanding requirements, the U.S. drugs authority has become an international benchmark. Once a drug receives approval from the U.S. authority it has a bigger chance to be approved in other countries.

The structure of this dissertation is presented in figure 1.2. Table 1.1 provides a more detailed overview of the empirical chapters.

As an introduction to the industry analysis in chapter 3, we describe in chapter 2 three basic features of the modern U.S pharmaceutical industry. First, we present several basic conditions for competition in the industry that include market definition, types of firms and types of drug products. We also describe a typical product life cycle in the industry. Second, we discuss the Hatch-Waxman Act, a regulatory framework aimed to balance incentives for continued innovation among brand-name pharmaceutical firms with opportunities for market entry by generic firms. The Act was aimed to create a balance between keeping the drug prices down on the one hand and on the other hand giving incentives for innovation research. Finally, we take a look at several prominent criticisms addressed toward the industry and we also present their counterarguments.

Chapter 3 answers the first research question of this thesis by providing an

industry analysis of the U.S. drug sector. Before we discuss the industry's performance, we first present several basic analyses on issues such as (1) the demand and supply conditions of the industry; (2) the forces that affect pharmaceutical firm's profitability; (3) pharmaceutical firms' strategies to cope with existing regulations in order to sustain profitability, which include, for example, the strategies that exploit the loopholes of the Hatch-Waxman Act. Thereafter, we discuss several indications on innovativeness and profitability of major U.S. pharmaceutical firms over time by using new evidence and a measure that is different from previous empirical research.

One of the main findings in chapter 3 is that the market valuation of the pharmaceutical industry has increased substantially in the past decades, leaving the average of U.S. economy far behind. In chapter 4, we investigate the role of advertising and product differentiation on the stock market valuation of pharmaceutical firms. Despite the vast increase of advertising expenditure, as well as the high degree of product differentiation, few empirical studies examine their relationship with the profitability of pharmaceutical firms. Instead, the focus has been on the R&D role on pharmaceutical firms' profitability. Additionally, our study provides an opportunity to test the popular claim that pharmaceutical firms put more emphasis on advertising instead of R&D.

Chapter 5 aims to answer the final question of this dissertation regarding the prevalent behavior of pharmaceutical companies in product differentiation strategies. We use a real option framework that assumes that a line extension is a firm's response to uncertainty both within and outside the firm. Using a repeated events duration model, we identify some determinants that affect firm's decisions to extend or modify an existing drug product. These include uncertainty regarding firm's stock volatility, financial constraints, competitive pressure and advertising growth. Our results show an important role for advertising and stock price volatility.

In chapter 6, we summarize the key findings of this dissertation, discuss their implications on firms' strategies, give recommendations on public policies, draw our study limitations, and mention several directions for future research.

In appendix F, we present a study on new product performance. Although this topic does not relate directly to the main theme of the dissertation, we included it because it is our first research activity that eventually led us to study innovation more deeply. In this study we use a meta-analysis technique that summarizes research findings on factors that are associated with new product performance.

Figure 1.2 Structure of the Thesis

Chapter 1: Introduction

What are the motivations behind this thesis?

Chapter 2: The U.S Pharmaceutical Industry: An Introduction

What are the important features of the industry?

Chapter 3: The U.S. Pharmaceutical Industry: An In-depth Analysis

What is the industry's performance in terms of innovativeness and profitability?

Chapter 4: The Effects of of Advertising and Product on the Performance of U.S. Pharmaceutical Firms

What are the impacts of advertising and product differentiation on the U.S. pharmaceutical firms' stock market performance?

Chapter 5: Product Differentiation Strategy: What Drives Line Extensions

What are the determinants of product line extensions?

Chapter 6: Discussion and Implications

What are the main findings and their implications?

Table 1.1 Outline of the Book

Chapter 1	Introduction to the motivation of the thesis and the formulation of research questions				
	Research Objective	*Dependent Variable*	*Theoretical Perspective*	*Methodology*	*Observations used*
Chapter 2	To provide three basic features of the modern U.S. pharmaceutical industry	n.a.	n.a.	Descriptive analysis	
Chapter 3	To perform an industry analysis	n.a.	Industrial Organization	Descriptive analysis	Various sources; 12.699 introductions drug products; period: 1939-2005
Chapter 4	To investigate the role of advertising and product differentiation in the stock market value of pharmaceutical firms	Market Value	Tobin's q	Panel data	538 firm-year observations; 27 companies; period: 1971-2005
Chapter 5	To model pharmaceutical firms behavior in product differentiation.	Rate of drug extensions	Real option	Survival analysis	1142 to 8772 observations, 335 new chemical entities drugs; 27 companies; period 1950-2005
Chapter 6	Conclusions: summary of the main findings; academic contributions; implications for firm strategies and public policy, research limitations; suggestions for future research.				

2. THE U.S. PHARMACEUTICAL INDUSTRY: AN INTRODUCTION

ABSTRACT

This chapter provides an introduction to the industry analysis of the U.S. pharmaceutical presented in the next chapter. In this chapter, we concentrate on three issues that have a pronounced impact on the current settings within which the pharmaceutical firms operate. First, we describe several basic conditions for competition in the drug market that include market definition, types of firms and types of drug products. The second part of this chapter is devoted to the Hatch-Waxman Act, a set of regulations that that have laid the foundation for the modern generic system in the industry. The third and last part highlights several criticisms that have been addressed toward the industry and their counterarguments.

2.1 INTRODUCTION

There are two important goals that pharmaceutical industry is aimed to fulfill for society. First, it is in the benefit of society to improve competitiveness in the market for drugs in order to keep drug prices at a relatively competitive level. A competitive drug market is considered to limit the upsurge of health care costs in the developed countries. Second, it is in the best interest of society if the industry's technology advances at a reasonably fast rate. Looking at the history of the pharmaceutical industry, these two goals have been frequently perceived to conflict each other (Craig and Malek, 1995; CBO, 2006).

Recently, the industry has been under severe criticism with claims that it fails to fulfill both goals. In terms of competitiveness, there is a growing perception that pharmaceutical companies are managed to sustain substantial profit by maintaining high prices for drug products (Relman and Angell, 2002). It has been widely recognized that the U.S. pharmaceutical industry is one of the most profitable industries in the U.S. (Public Citizen, 2002; CBO, 2006). However, studies on innovation in the industry show that the market is dominated by the development of incrementally modified drugs (CBO, 2006, NIHCM, 2002). Additionally, despite the continuing rise of the R&D spending, pharmaceutical companies have been less innovative compared to other high tech industries (CBO, 2006). In addition,

withdrawal of the high profile cardiovascular drugs Vioxx and Bextra, substantial spending on advertising, and intensive firm lobbies within the government have contributed to public skepticism (Public Citizen, 2001).

Against these criticisms, there exist several arguments on the other side of the fence. The discovery and development of new drugs are time consuming, complicated, and expensive. Therefore, many drug development projects are risky, despite their attractive return on R&D. Without some scheme of market exclusivity that enables to pay back the investment in drug development, drug firms will not have enough incentive to innovate. As a result, the introduction of important medicines is potentially delayed. Therefore, the assessment of industry performance should take into account a long term view on the industry's technological rate (Scherer, 1970; Scherer, 2001; Grabowski, Vernon and DiMasi, 2001). Furthermore, the fact that the market is dominated by modified drugs does represent social value as these drugs can offer significant benefit to the consumer (CBO, 2006). For example, a more convenient dosage form can stimulate patients to take their medication and therefore improve their health.

Against this background, we aim to perform an industry analysis of the U.S. pharmaceutical industry. This chapter provides an introduction to this analysis by describing three important settings in which the pharmaceutical firms operate. First, we present several basic conditions for competition in the industry that include market definition, type of firms and types of drug products. We also describe a typical product life cycle in the industry. Second, we discuss the Hatch-Waxman Act, one of the most influential Patent Act regulations in the U.S. We explain two important forms of market exclusivity for drug products that aim to stimulate innovation as well as competition, namely (1) patent protections and (2) *marketing exclusivity*. Finally, we take a look on several prominent criticisms addressed toward the industry and we also present their counterarguments.

We arranged this chapter as follows. Section 2.2 presents a market definition of the pharmaceutical industry and shows several basic conditions for competition that include type of firms and products. Section 2.3 gives an introduction to the Hatch-Waxman Act. In section 2.4, we present several criticisms and their counterarguments. Section 2.5 summarizes this chapter.

2.2 MARKET DEFINITION AND TERMINOLOGY

Pharmaceutical companies perform business activities in research, development, and the marketing of drugs that aim to improve the well-being of the patients. In a traditional sense, drugs are chemical based, meaning that one chemical is usually focused to treat a specific symptom or disease. Nowadays, there has been increasing attention on biotechnology that use proteins to treat the underlying mechanism of a disease and quite successful drugs based on this technology have reached the market. In this thesis, however, we focus on firms that specialize in the 'traditional' view of drugs.

Brand name companies versus Generic companies

Pharmaceutical companies can be classified into two major groups. The first group consists of the so called brand name companies. These firms undertake research to discover new drugs or to innovate existing drugs and bring them to the market. In the U.S., a brand name firm must have an approved *New Drug Application* (NDA) that fulfills the safety and efficacy requirements of the *Food and Drug and Administration* (FDA). The process of obtaining an NDA approval is costly and time consuming.

The second group of companies is formed by the so called generic companies that market the copy of the existing drugs by submitting an *Abbreviated New Drug Application* (ANDA). The ANDA procedure is much easier than that of the NDA, provided that ANDA applicants do not violate the existing drug's patent regulations. In the rest of the book, we use the terms pharmaceutical firms, innovative firms and brand name firms interchangeably to refer to the first category of firms.

Multiple-Source versus Single-Source Drugs

Drug products based on NDA's are called brand name drugs or branded drugs. They are generally patented based on their chemical formulation or on their manufacturing process. Patented brand-name drugs that have similar therapeutic working may exist, but they usually have a different chemical formulation. Meanwhile, drugs launched based on an ANDA are called generic drugs.

Brand-name drugs that are still under patent protection are also called

single-source drugs, because the rights to produce these drugs belong to the firm that holds the patent of that drug product. When these patents expire, generic versions become available and then such drugs are called multiple-source drugs.

New Chemical Entities versus Modified Drugs

Brand name drugs can also be further specified as drugs whose active ingredient has never been introduced before, the so-called *new chemical entities* (NCEs) and ones which are modifications of existing NCE's, the so-called *incremental modified drugs* (IMDs). Recently, the term of me-too drugs has also been increasingly popular for this latter group of drugs. Although there are various interpretations of this term, in this thesis we see *me-too drugs* as NCEs which have a similar therapeutic working as the first NCE introduced in a certain therapeutic market, but which differs in chemical compound. More on this will follow.

Sub-Markets

The pharmaceutical industry consists of many therapeutic markets and sub-markets therein. For example, the antidepressant market is a market of drugs that treats depressions. Based on which chemicals affect the brain and its side effects, this market can further be split into different categories. Figure 2.1 shows sub-markets within the antidepressant market.

Breakthrough versus me-too drugs

The creation of new (sub-)markets within the drug market is driven by both demand and technological advance. The first drug in a new sub-market is called a *breakthrough drug*, which is a result of technological advance. It has significant features such as, for example, reduced side effects compared to the existing drugs in this market. As an example, in the antidepressant market describe in figure 2.1, Prozac is the first antidepressant drug in the sub-market SSRI and is characterized as a breakthrough drug. The action of Prozac was more biologically specific and therefore it had significantly fewer side effects than the earlier class of antidepressants such as Tricyclic and MAOi's (Currie and Park, 2002). Attracted by Prozac success, other drugs such as Celexa and Zoloft were introduced in the SSRI's class. These newcomers have a different chemical entity with a similar working. These types of drugs are the so called *me-too drugs*.

Blockbuster Drugs

Revenue for the pharmaceutical industry comes mainly from the so-called blockbuster drugs, which are drugs with a revenue of more than 1 billion dollars. Blockbusters are cash cows for pharmaceutical firms and therefore, firms' revenue largely depends on these drugs (Craig and Malek, 1995). Figure 2.2 shows some numbers on market share of blockbuster drugs for the period 1999-2001.

Product Life Cycle in Drug Markets

A typical drug product undergoes cyclical development of introduction, growth, maturity, and decline. A successful drug product generates revenue and as its patent expires generic competitors enter the market. To illustrate this cyclical pattern, we take a look at the year 2005. In this year, there were several major brand name drug products that include, among others, Boniva (a treatment of osteoporosis), Byetta (a treatment for diabetes), and Lyrica (a drug to relieve neurophatic pain). None of these drugs are classified as blockbuster (Gebhart, 2006).

At the other side of the cycle, some major drugs were expecting patent expiry in 2005. These include the blockbusters of Allegra and Zithromax. On the generic side, new product introductions contributed 13.6% to generic dollar sales in that year (Gebhart, 2006).

Figure 2.1 The Antidepressant Market

Market 1: Selective serotonin reuptake inhibitors (SSRIs) : These medicines tend to have fewer side effects than other antidepressants. Some of the side effects that can be caused by SSRIs include dry mouth, nausea, nervousness, insomnia, sexual problems and headache. This market consists of the following chemical compounds : citalopram (brand name: Celexa), escitalopram (brand name: Lexapro), fluoxetine (brand name: Prozac), paroxetine (brand names: Paxil, Pexeva), and sertraline (brand name: Zoloft)

Market 2: Tricyclics : Common side effects caused by these medicines include dry mouth, blurred vision, constipation, difficulty urinating, worsening of glaucoma, impaired thinking and tiredness. These antidepressants can also affect a person's blood pressure and heart rate. This market consists of the following products: amitriptyline (brand name: Elavil), desipramine (brand name: Norpramin), imipramine (brand name: Tofranil), and nortriptyline (brand name: Aventyl, Pamelor)

Market 3: Serotonin and norepinephrine reuptake inhibitors (SNRIs) : Some common side effects caused by these medicines include nausea and loss of appetite, anxiety and nervousness, headache, insomnia and tiredness. Dry mouth, constipation, weight loss, sexual problems, increased heart rate and increased cholesterol levels can also occur. This market consists of the following products: venlafaxine (brand name: Effexor), and duloxetine (brand name: Cymbalta)

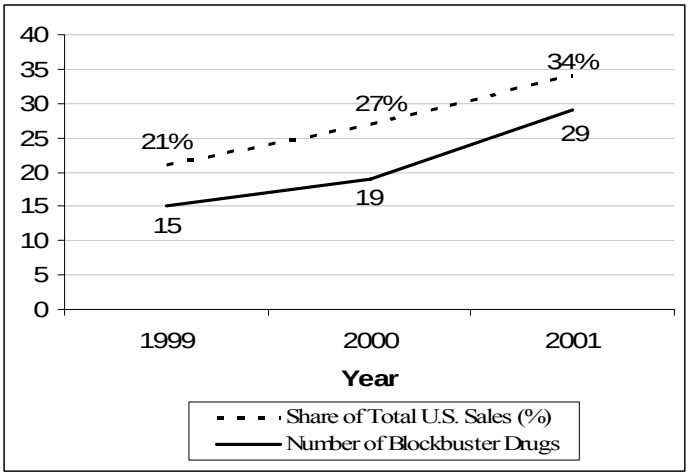
Market 3: Norepinephrine and dopamine reuptake inhibitors (NDRIs) : Some of the common side effects in people taking NDRIs include agitation, nausea, headache, loss of appetite and insomnia. It can also cause increase blood pressure in some people. This market consists of the following products: bupropion (brand name: Wellbutrin)

Market 4: Combined reuptake inhibitors and receptor blockers : Common side effects of these medicines are drowsiness, dry mouth, nausea and dizziness. If you have liver problems, you should not take nefazodone. If you have seizures, you should not take maprotiline. This market consists of the following products: trazodone (brand name: Desyrel), nefazodone (brand name: Serzone), maprotiline, and mirtazpine (brand name: Remeron)

Source: MedLine [1]

[1] http://familydoctor.org/012.xml

Figure 2.2 Shares of Sales and Number of Blockbusters (1999-2001)



Source: Public Citizen (2002)

2.3 THE HATCH-WAXMAN ACT

Prior to 1962, drug products were approved solely based on safety criteria. In the period 1956-1960, the Thalodomide tragedy where 10.000 babies was born with severe malformations because their mothers had taken this drug during pregnancy, brought permanent change to the FDA's approval process. Following this tragedy, a new amendment was added in 1962 that requires stricter regulation in terms of safety as well as *efficacy*. As a consequence, the drug approval process became a time consuming activity for innovator firms, which is at the expense of patent life. This situation was claimed to be a threat for a fall in R&D productivity that could potentially delay the introduction of new life-saving drugs (Wardell, 1975).

At the same time, there was also a concern on the other side of the industry. At that time, generic companies had to go through the same application procedures as companies applying for branded drugs. That means that they had to perform the required *clinical trials* to get an approval and accordingly, limit the incentives to introduce generic versions of drug products. An estimate shows that in the period 1962-1984 there were 150 drugs whose patents expired, but there were no generic alternatives available (Mossinghoff, 1999).

The above development gave a way to a new regulation that would bring a new era in the U.S. pharmaceutical industry. In 1985, the congress passed

the *The Drug Price Competition and Patent Term Restoration Act*, also known as the Hatch-Waxman Act. This Act was aimed to provide a balance in keeping the price of prescription drugs low and at the same time stimulating brand name companies doing innovation research. The Act eliminated the requirement for generic companies to repeat the clinical testing that had been performed by brand name companies. In exchange for allowing generic companies to replicate the findings of brand name companies, the Act contained provisions that would provide several incentives for brand names. These incentives take two major monopoly rights to sell a certain drug products; (1) patent term extension, which is an extension of the effective term of an existing patent and (2) marketing exclusivity. Marketing exclusivity is a form of exclusivity rights to sell a certain drug product and is granted by the FDA. It prevents the agency from approving another firm to market a product with the same active ingredient for a specified period of time. Patents and marketing exclusivity are similar in that both offer market protections for certain drug applications. However, they are legally independent from each other and each run on a separate period that might overlap. Note that while patents are issued by the United States Patent Office (USPTO), marketing exclusivity is awarded by the FDA. Pollock and Johnston (2005) described these two incentives as follows.

2.3.1 Patents

Prior to 1994, patents in the U.S. lasted until 17 years after the time of patents approval. The signing of the General Agreement on Tariffs and Trade (GATT) in 1994 lengthened patent life up to 20 years worldwide, calculated on the date of the first filling of the patent. All patents that were in force at that time had their patent terms revised to 17 years from the patent grant or 20 years from the first filling, whichever is longer.

Patents are often awarded prior to the approval of drugs. Consequently, the effective patent terms were shortened to ensure that the FDA approves the safety and the efficacy of the drugs. To compensate for the time loss between the issuance of the patent and the FDA's approval process, the Act allows NDA applicants to apply for patent extensions. Depending on the length of the approval process, NDA applicants can have a maximum of 5 years patent extension but no more than 14 years from the approval date of NDA. Table 2.1 outlays the change in patent protections for U.S

pharmaceutical firms as a result of the Hatch-Waxman Act and the Uruguay Round Agreements Act.

Table 2.1 Changes in Patent Protection for U.S. Pharmaceuticals

	Before the Hatch-Waxman Act of 1984	After the Hatch-Waxman Act and the Uruguay Round Agreements Act of 1994
Patent Term	17 years from patent grant	20 years from application filling (the earliest relevant filling date)
Average Period of Marketing Under Patent Protection	9 years	11.5 years
Usual Period between Patent Expiration and Generic Entry	3-4 years	1-3 months
Average Generic Market Share for Multiple Source Drugs (in percent)	12.7	57.6

Source: CBO (1998)

The FDA requires that all NDA applications must provide a list with relevant patent information. This list can be found in the FDA publication called *Approved drug products with therapeutic equivalent*, commonly known as the *Orange Book*. The book covers different forms of patents on drug products, such as the approved active ingredient, the approved formulation, and an approved method of use of the drug. The patents list in the Orange Book is particularly important for generic companies that seek approval for certain brand name drugs whose patents are in the Orange Book. We discuss this in more detail below.

The Hatch-Waxman Act's Implication for Generic Drug Applications

Since the implementation of the Act, generic companies can apply ANDA and demonstrate that the generic version has the same characteristics as the brand name version. To do this, ANDA applicants rely on the FDA's previous findings on the safety and efficacy of the corresponding brand name drugs. As a result, generic producers do not have to provide their own clinical studies to demonstrate generics drugs' safety and efficacy, which can save a substantial amount of money.

Additionally, ANDA applicants must contain certifications that refer to the patents listed in the Orange Book. These patents relate to the corresponding

NDA of which the generic applicant aims to make a generic version. There are four types of patent certifications: (1) that the required patents have not been filed; (2) that the patents have expired; (3) that the patent has not expired, but will expire on a certain date and approval is sought after patent expiration; and (4) that the patent is invalid or will not be infringed by the generic version for which the applicant seeks approval. Each of the options is often referred to as paragraph I, II, III, or IV certifications.

If the generic applicants use paragraph I and II, the FDA can approve ANDA immediately. When paragraph III is used, the FDA may approve the ANDA effective on the date when the patent expires. Paragraph IV contains the most complicated arrangement and has triggered controversial issues, which have been the subject of a FTC study (FTC 2002). When a generic applicant makes paragraph IV certifications, generic applicants must notify the patent owner or the holder of the approved NDA (if it is different from the patent holder) that they seek approval for a generic version of the NDA. If the patent owner (mostly the brand name companies) brings an infringement suit within 45 days, the ANDA cannot be approved automatically for a 30 month period (the latter is commonly known as *30-months stay*). If it turns out that patents are not infringed, either by the court or by settlement between generic and brand name companies, the first ANDA applicant has the right of 180 days of marketing exclusivity. This will be explained in more detail below.

2.3.2 Marketing Exclusivity

Marketing exclusivity is the second exclusive right for drug firms, which gives brand name firms a limited protection from new competition in the market. Marketing exclusivity is given to both ANDA and NDA applicants. There are different types of marketing exclusivity, whose period ranges from 6-months to 7 years. *Five-year New Chemical Entity's exclusivity* is awarded to first approval of NCEs. During this period, no generic versions can be approved.

Clinical Investigation Exclusivity applies to drugs for which the applicant performs additional clinical studies to modify the existing drugs. This modification can include change in dosage forms, indications, or switch from prescription to over-the-counter (OTC) (Hathaway and Manthei, 2004). This exclusivity prevents the FDA to approve a competitor's ANDA for a period of *three years*. Exclusivities on clinical investigations can be a

controversial issue. Some claim that this exclusivity stimulates minor modifications of older drugs that have only marginal clinical benefit.

Pediatric exclusivity is a *6-months* exclusivity period, awarded for NDA applications that conduct clinical investigation among children. This exclusivity is added after a drug's patent and/or all other forms of market exclusivity have expired. For example, if an NDA is approved for oral and topical formulations containing the same active ingredient, and thereafter performed pediatric studies conform to FDA regulations for oral formulation, the additional 6-months exclusivity would also be added to topical formulations. In this way, pediatric exclusivity can be awarded to the whole product line, which can give substantial benefit for the brand name companies.

7 years orphan exclusivity is awarded for brand name drugs that are approved to treat rare diseases. The last exclusivity is the only exclusivity awarded to generic applicants.

Generic 180-day exclusivity is awarded to the first generic applicant that challenges a listed patent on the brand name companies' drug products. This exclusivity aims to stimulate generic entry as soon as possible even in the face of potential patent issue. The incentive contains a market protection from other generic companies for a 180 days period. In the next section, we highlight several topics that have become sources of public debate.

2.4 CRITICIMS TOWARD THE PHARMACEUTICAL INDUSTRY

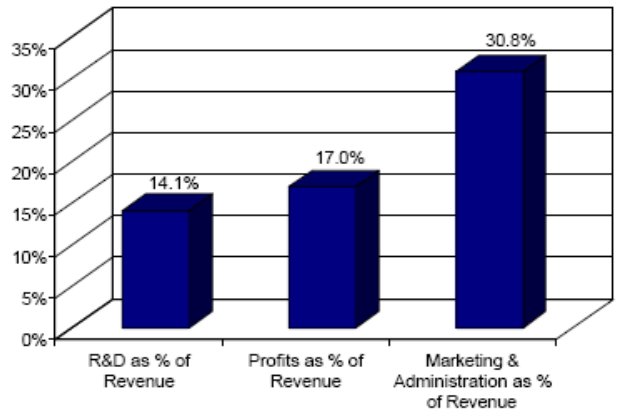
Criticism toward the pharmaceutical industry can generally be classified into the following three interrelated issues; (1) the allocation of resources is suboptimal from a societal point of view, (2) the rate of innovation is slow, and (3) the returns earned by the companies are still high.

Suboptimal Allocation of Resources

Relman and Angell (2002) claimed that most of the basic research which has spurred drugs development was conducted on the expense of public spending. They argued that it is not the industry but public investment in research that has been mostly responsible for the progress in the medical world. In return, pharmaceutical companies are claimed to spend their

resources not on scientific discovery, but to develop variations on existing drugs and to spend a substantial amount on marketing activities. Public citizen (2001) claims that drug firms spend most of their income on marketing, which is far beyond the R&D expenses. Figure 2.3 shows that in 2003 marketing spendings make up a 35 % of total revenue, while R&D comprises of only 14%.

Figure 2.3 Marketing Budget of Pharmaceutical Firms compared to R&D in 2003



Source: Public Citizen (2001)

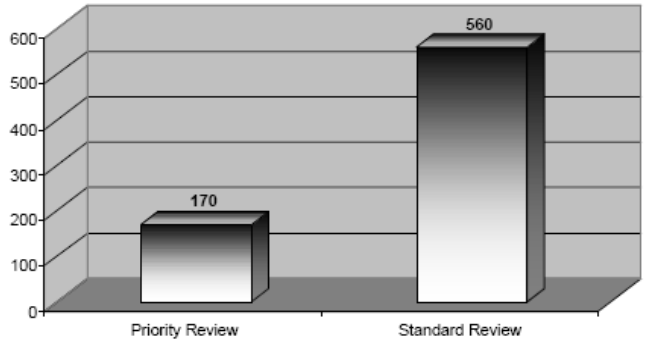
Innovation is slow

A National Institute for Health Care Management study (2002) claimed that the pharmaceutical industry benefits mainly from the growth of less innovative drugs (NIHCM, 2002). For example, between 1989 and 2002, 62% of growth in NDA approvals came mainly from IMDs. In contrast, breakthroughs make up for only 3%. Figure 2.4 shows that the contribution of *priority drugs* is approximately three times lower than that of *standard drug*.

Additionally, firms are increasingly dependent on the sale of blockbusters and their variations. According to an IMS health report, total prescriptions of drugs sales from the 5 largest pharmaceutical companies contain 48% to 80% of blockbuster drugs in 2001 (NIHCM, 2002). As these drugs approach patent expiration, companies often patent new features and obtain three additional years of market exclusivity. Against this setting, brand

name companies are claimed to continue focusing on developing IMDs. This will eventually contribute to increasing costs of prescription drugs, both through their high prices and through keeping away generic competitors from the market (NIHCM, 2002).

Figure 2.4 Therapeutic Importance of Drugs Approved by FDA



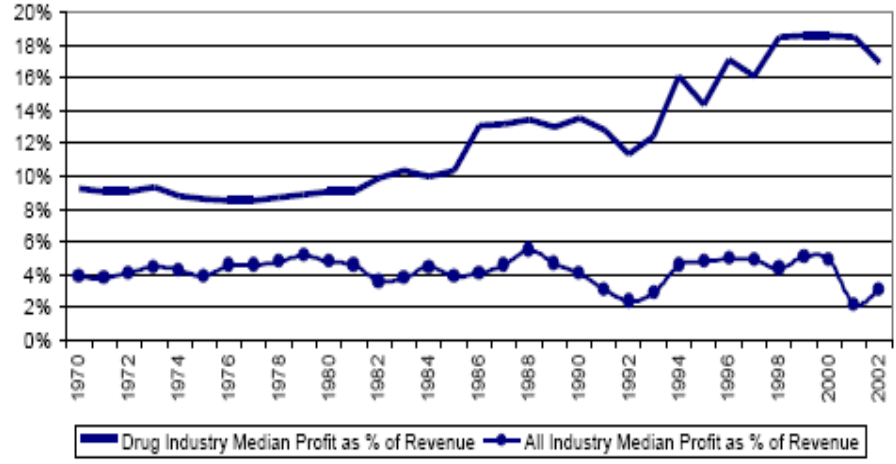
Source: Public Citizen (2001)

Still, the profitability is high

Pharmaceutical firms address the shortfall of NCEs by feeding the growth from extension products (Relman and Angell, 2002). These evergreening practices attract new segments in the market and sustain or further raise the high prices of prescription drugs. The investment in medicine using an active ingredient, whose safety and efficacy have already been approved before, cost much less and are less risky than investing in a new active ingredient about which little is known. The combination of cheaper investment and potential of high prices makes this strategy very attractive and are frequently applied. Additionally, criticisms address various loopholes in the Hatch-Waxman Act that are potential for abuse. Major pharmaceutical firms frequently use legal strategies in order to keep generic competitors out of the market[1]. Pharmaceutical firms' strategies seem to work quite well, as the industry ranks as one of the most profitable industries in the U.S. Figure. Figure 2.5 shows that profitability of pharmaceutical firms is above the average of other industries.

[1] We describe these strategies in more details in the next chapter.

Figure 2.5 Profitability of Fortune 500 Drug Industry and All Fortune 500 Industries (1970-2002)



Source: Public Citizen (2003)

On the other side of the fence, there have been several arguments against the above criticism. Below, we discuss the most important of these counterarguments.

Lag of Productivity

CBO (2006) argued that the figures on productivity of R&D can be misleading since there is a 12 year lag between the initial R&D effort and an NCE's approval. Therefore, it is too soon to know how the sharp rise in R&D spending since the year 2000 will impact the number of future NCE approval. However, the CBO acknowledges that the growth of R&D spending during the 1990s led to a lower average number of approvals in the 2000s than in the previous decades. In other words, using the data on R&D spending in the 1980's and 1990's led to a relatively poor R&D productivity in the 2000's.

Quality is difficult to measure: Not all drugs are the same

The second counterargument is related to the conventional measures in calculating innovation performance. This standard procedure has a potential bias because it ignores the unique characteristics of each drug product. For example, if only few NCEs were approved but they contained important, pioneering, or more effective drug therapies, the industry's actual R&D

productivity would not necessarily be lower (CBO, 2006). Pharmaceutical Research and Manufacturers of America (PhRMA) claimed that the FDA has approved some highly innovative drugs over the past decades, which can improve the quality of life (PhRMA, 2002). For example, in the 1990's some monoclonal antibodies[1] have been approved to treat breast cancer (i.e. the drug Herceptin), to prevent kidney transplant rejection (i.e. Zenapax), and for treatment of complications accompanying angioplasty (i.e. ReoPro). Another example is Regranex, a first biologic drug that stimulates the body to grow new tissue to diabetic ulcer, which was approved in 1997 (PhRMA, 2002). Despite this development, the CBO (2006) argued that increases in the quality of drug products, if it would be ever possible to measure, would have to at least match the substantial rise in the R&D expenditure over the past years.

Me-too drugs and IMDs benefit consumers

The third argument concerns the criticism on the growing number of me-too drugs and IMDs. In spite of the criticism, these drugs can benefit consumers significantly by reducing side effects, being more convenient to take, or treating additional conditions. Furthermore, IMDs are often developed with much lower cost too.

High profitability as an Incentive to Invent

Patent protections have given pharmaceutical firms the ability to set price above competitive level, which in turn increased the ability to generate profit. Although the current patent regulations are frequently under attacks for its counterproductive effects on innovation (Relman and Angell, 2002; NIHCM, 2002; Public Citizen, 2001), economists tend to be more reserved on this matter. One of the reasons is that the rate of inventions and innovations in the pharmaceutical industry depend more on patent protection than any other industry (Mansfield, 1986). A radical change on current patent regulations is likely to affect long term innovation rate and that would not be in the interest of the society. Therefore, the high profitability in this industry is probably justified due to its incentive role to advance technological rate (Waldman and Jensen, 2001). Furthermore, a

[1] Monoclonal antibodies, which have become an important tool in medicine, are antibodies are identical because they were produced by one type of immune cell and are all clones of a single parent cell (Wikipedia).

large part of profit is ploughed back to R&D in order to finance an increasing cost of drug development.

2.5 SUMMARY

This chapter provides three important background characteristics that have influenced the setting in which the pharmaceutical industry operates. To begin with, we show the basic conditions of competition that includes market definition, type of firms, and type of drug products. The industry consists of many sub-markets, which often are driven by technological advances and demand. Noteworthy, this thesis focuses on a conventional definition of drug that is based on chemical entity and therefore does not examine the development in the biopharmaceutical industry.

In addition, we make various distinctions concerning pharmaceutical firms and products that provide a background of firms' competitive environments. First, pharmaceutical firms can be classified into two major groups; innovator firms and generic firms. Innovator firms focus on performing R&D activities and marketing new drugs on the market, while generic firms produce copies of existing drug products. Second, we introduce frequently used terms concerning drug products, which include breakthrough drugs, me-too drugs, NCEs, IMDs, and blockbuster drugs. Additionally, we show that a typical drug product undergoes a cyclical development in the market.

As a second influential setting, we provide a description of the Hatch-Waxman Act. This Act was passed as a response to growing concern on increasing health care costs and aims to facilitate the entry of generic alternatives in the market. Simultaneously, the Act has an objective to keep the incentive of innovative firms intact by giving a variety of market protections based on patent terms and marketing exclusivity. Doing so, the Act strived to create the balance between keeping the drug prices down on the one hand and on the other hand giving incentives for innovation research.

The last part of the chapter is concerned with the growing criticism of the industry, which has put pressure on public policies concerning the industry. The criticism addresses, among others, the slow rate of innovation, despite the persistence of profitability and the continuous rise of R&D expenditure.

This critique has received some counterarguments, which argue that pharmaceutical industry is one the few industries that rely heavily on patent protections. The patent-dependent nature of the technology requires enough incentives in the form of attractive profitability. The counterargument also points at the conventional way of measuring innovation can give an inaccurate picture of innovation in the industry. Furthermore, it is also claimed that novelty of me-too drugs and IMDs has been underestimated.

The next chapter provides an in-depth analysis on pharmaceutical industry, in which we provide the industry performance in term of innovativeness and profitability.

3. THE U.S. PHARMACEUTICAL INDUSTRY: AN IN-DEPTH ANALYSIS

ABSTRACT

In the face of the limited introduction of breakthrough drugs, the pharmaceutical industry becomes increasingly a source of public debate. The industry's increasing incremental drug products and advertising spending are just a few examples of critiques toward the industry that has affected public opinion. However, a careful examination based on economic understanding regarding this phenomenon is essential before any judgment can be made. Against this background, we perform an industry analysis on the drug sector that includes (1) assessments of the demand and supply condition, (2) factors that affect competition, and hence, profit, (3) discussions on several strategies known to deter competitions, and (4) assessment of the performance of the industry in terms of innovativeness and profitability. Although our indications show relatively poor performance, taking into account a dynamic approach that considers long term view gives a more balanced view.

3.1 INTRODUCTION

As has been discussed in the previous chapter, there has been growing public dissatisfaction concerning the pharmaceutical industry in the U.S. For example, popular press often claimed that pharmaceutical firms put greater emphasis on marketing than on R&D and that pharmaceutical firms feed their growth from modified drugs. Another example is the claim that pharmaceutical firms are responsible for the ever increasing drug prices, which further escalate health care cost. Despite that, one needs to examine more closely the economic mechanisms underlying the above phenomenon to be able to provide a balanced view. Indeed, economists have often shown a more reserved attitude toward drastic change in policies regarding the industry because they can have a counterproductive effect on the long term innovation path (Scherer, 2001; Scherer, 1993; Comanor and Wilson, 1979; Mansfield, 1986; Cockburn and Henderson, 1997; CBO 1998; Grabowski and Vernon, 1990). As an example, it is argued that the increasing drug price does not necessarily reflect market power, but it may also indicate the rising fixed cost to cover technological advances. Prescription drugs that

offer new therapies or that substitute for other forms of treatment are likely to cause total drug spending to rise simply because they are expensive to develop (CBO, 2006). Another example, a policy that limits advertising can result in a (partial) loss of information available for consumers and doctors (Comanor and Wilson, 1979), even though some questions the objectivity of pharmaceutical advertising (Scherer, 1970).

In this chapter, we assess the industry performance in terms of profitability and innovativeness. First, we provide several basic analyses such as the demand and supply conditions of the industry and discuss several forces that affect pharmaceutical firm's profitability. We also illustrate pharmaceutical firms' strategies to cope with existing regulations in order to sustain profitability. Having presented this background, we discuss several indications on innovativeness and profitability of major U.S. pharmaceutical firms over time. Our results show a rather poor performance in terms of innovation. At the same time, we found that the stock market value of major pharmaceutical firms by far surpass the industry average.

We structure this chapter as follows. Section 3.2 describes the basic demand and supply conditions in the pharmaceutical markets. Section 3.3 discusses five forces that can drive competition and hence erode profitability of a typical pharmaceutical firm. Section 3.4 presents legal and marketing strategies that have been performed in the past in order to sustain profitability. Section 3.5 assesses industry performance by presenting indications in terms of innovativeness and profitability over time. Section 3.6 gives a summary and conclusion.

3.2 DEMAND AND SUPPLY CONDITION

3.2.1 Demand for Pharmaceuticals

Unlike a typical market, the demand side of the drug markets consists of three separated divisions, namely consumers (patient), decision makers (doctors), and payers (health insurance). This separation weakens the functioning of price as a value indicator. Patients have little information on the drug products while doctors usually base their prescriptions on quality of drugs and less on price. Information from pharmaceutical firms in the forms of sales promotion and DTC advertising are relatively less time consuming and therefore can affect both doctors' decision making and

consumers without any references on price (Steele, 1964). Additionally, prescription costs are to a large extent covered by health insurance, which further contributes to the price-insensitivity of patients and doctors. This inelastic demand is often associated with features such as excessive pricing above the marginal costs of production and misallocation of resources and lower society benefit (Craig and Malek, 1995).

3.2.2 Supply of Pharmaceuticals

The controversy of high profitability in the industry is driven by the relationship between price and cost of drug products. The cost of a drug consists of two parts: manufacturing cost and developing cost. While the cost of manufacturing of an extra bottle of medicine is low, the R&D spending to develop a new drug is extremely expensive. Consequently, drug prices are usually much higher than the cost of producing an additional unit of a drug, because a firm has to ensure that its revenue can cover high fixed R&D cost (CBO, 2006). The ability to set relatively high prices is secured by patents protection for a limited period, which in turn can encourage firms to invest in R&D.

In spite of this novel objective, patent systems often can lead to a direct conflict with society's benefit due to their loopholes that can be exploited by firms. A Congressional Budget Office (CBO) study argued, however, that patents in the drug markets do not necessarily provide monopoly positions due to competition from other brand name firms in the same therapeutic market (CBO, 1998). This is because other firms are allowed to patent drugs that have similar mechanisms with the existing drugs, the so-called "inventing around" (Henderson and Cockburn, 1994). Still, some question the benefits of patents as pharmaceutical firms' resources were mainly withdrawn to finance minor innovations (Craig and Malek, 1995). In the next section, we turn our attention to the several forces that have contributed to high profitability in the pharmaceutical industry.

3.3 FORCES THAT DRIVE PHARMACEUTICAL FIRM PROFIT

We use a five-forces framework to analyze competition in the drugs markets, which consists of five elements: *internal rivalry*, *barrier to entry*, *substitutes and complimentary*, *supplier and buyer power* (Besanko, Dranove and Shanley, 2007). *Internal rivalry* refers to the degree of

competitiveness in the industry that is affected by factors such as price and non-price competitions, market concentrations, potential demand, and degree of product homogeneity in the market. *Barrier to entry forces* include the degree of difficulties for new entrants to enter the market, which include factors such as brand loyalty, economies of scale, patent systems, and incumbents behavior against the new entrants. *Substitute and complementary forces* analyze to what extent the products or technologies outside the industry provide a threat to industry profitability. *Supplier and buyer power forces* refer to the ability of the supplier or buyer to negotiate the price when they make transactions with a pharmaceutical firm.

3.3.1 Internal Rivalry

The force of internal rivalry is considered high when there are relatively many firms, products are perceived to be homogeneous, and consumers have perfect information and switching costs are zero (Besanko et al, 2007). The existing pharmaceutical firms generally enjoy a relatively low degree of internal rivalry. Drug markets have a low market concentration and are dominated by several leading firms with highly differentiated drug products. Additionally, patients and doctors tend not to change drugs easily even when the lower price alternative is available (Coscelli, 2000).

Table 3.1 shows the leading pharmaceutical firms and their market share. At a first glance, the industry does not have extremely high market concentration as none of each player has a market share higher than 15%. However, if we look at sub-markets, the markets are usually highly concentrated. For example, in the period 1987-1989, the anti-ulcer market was dominated by very few products, which enable the sellers of these products to set high prices and consequently earn above-normal profit (Craig and Malek, 1995).

Nevertheless, there are various competition pressures within a typical drug sub-market. These competition threats can be generalized into two categories; (1) a direct threat, a threat that comes from the same sub-market and (2) an indirect threat, a threat that comes from other sub-market but within the same therapeutic market. Innovative as well as generic drugs can pose these two threats. Figure 3.1 describes various competition threats in a typical sub-market by using the breakthrough antidepressant drug of Prozac that belongs to the SSRI sub-market. This figure shows that Prozac competes directly with Zoloft, a brand name drugs. Prozac also competes

directly with its own generic version and generic version of Zoloft. Note that this generic competition occurs only when patents on these brand name drugs expire. Second, Prozac also faces indirect competition from Cymbalta, a brand name antidepressant drug from SNRI sub-market and the (potential) generic versions of Cymbalta.

Table 3.1 Top 10 Pharmaceutical Firms in 2002 by Retail Dollars

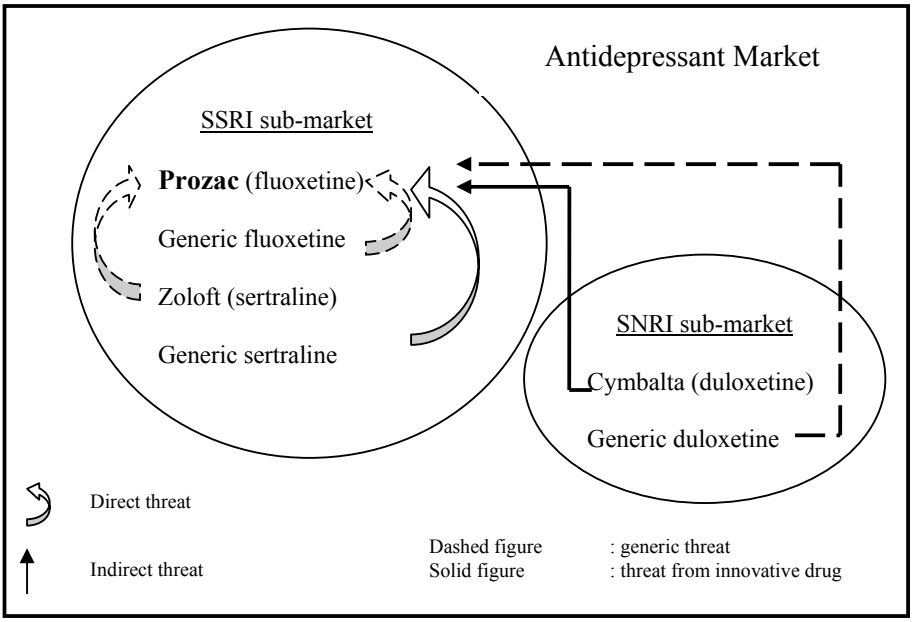
	Total Rxs by retail $ (add 000)	Share %	% change from 2001
Pfizer	17.621.191	10.60%	10.90%
GlaxoSmithKline	15.214.053	9.1	8.5
Merck & Co.	9.657.385	5.8	1
AstraZeneca	9.020.418	5.4	11.3
Johnson & Johnson	8.048.559	4.8	14.1
Novartis	7.638.731	4.6	20.7
Bristol-Myers Squibb	7.058.139	4.2	–7.6
Schering-Plough	6.341.717	3.8	–1.2
Pharmacia	6.212.738	3.7	0.1
Wyeth	5.581.683	3.3	–2.5
All others	74.261.89	44.6	16.7

Source: Gebhart, 2003

While competition concerning innovator drugs are often driven by technological advances, generic competitors compete with incumbents in terms of price. A generic version can be up to 80% cheaper than its brand name counterpart. As has been mentioned in the previous section, however, the weak functioning of price tends to makes price-based competition relatively less threatening. Although the availability of generic drugs in the market has resulted in lower average prices, this reduction of price is only observed in the generic market. Often, the brand name counterpart still has the ability to maintain a much higher price even when generic alternatives are available in the market (Griliches and Cockburn, 1994; Frank and Salkever, 1997).

In spite of the relatively ineffective pricing strategies, brand name companies do use them, albeit that they are usually combined with other strategies such as advertising and product differentiation. We illustrate these in the next sub-section.

Figure 3.1 Competitions in a typical Sub-Market: A Case of Prozac



Another source of profit in the industry is the non-homogeneous nature of drug products. Drug products can de differentiated in various dimensions: new indications, new dosage, new combination, new formulation, etc. The incentive to differentiate is high since launching a new version of existing drug products not only enhances barrier to entry but also can result to granting of marketing exclusivity.

There is an optimistic expectation on profit in the pharmaceutical markets due to the growing demand of drug products. The world will always need health care and more and more of it as developed countries grow older and developing nations grow richer (The Economist, 2007). Facing with high potential demand, advertising plays an important role, especially for certain types of drug categories. For example, intensive direct to consumers (DTC) advertising has been observed in relatively new therapeutical markets such as sleep disorders and erectile dysfunction, with considerable success (Gebhart, 2006).

3.3.2 Barrier to Entry

Incumbent firms relatively enjoy various barriers to entry against new

entrepreneurs that aim to develop new innovative drugs. The high R&D cost in developing a new drug makes the entry extremely difficult. A recent estimate indicates that the cost of developing new products is about $800 million dollar (DiMasi, Hansen, and Grabowski, 2003). High R&D expenditure can deter entry in the drug markets through at least three mechanisms; it can produce economies of scale arising from shared fixed costs; it can produce economics of scope arising from the opportunity to exploit knowledge across program boundaries within a firm; it improves the ability to absorb internal and external spillovers (Henderson and Cockburn, 1994).

Furthermore, advertising and learning effects of existing firms also pose a barrier for newcomers. The effect of advertising is not only present at the current time, but new entry has to take into account the accumulated effects of advertising (Waldman and Jensen, 2001). This threat is especially prevalent as pharmaceutical firms have been increasing their marketing expenditure substantially in recent years (GAO_1, 2006). Additionally, advance in technology has contributed to firms' learning curve. For example, nowadays, a researcher can produce thousand of compounds a year, compared to only 50-100 new compounds a year 15 years ago (Public Citizen, 2001). Furthermore, the improvement in screening technology has accelerated the speed at which compounds can be tested to identify the most promising molecules (Public Citizen, 2001).

From the perspective of generic entry, incumbents benefit from advertising and product differentiation as barriers to entry. In addition, the loopholes in the current patent system provide opportunities for firms to keep generic competitors away from the markets. Incumbents frequently show aggressive behavior to defend their market share in the face of patent expiries (see next section). Even when generic alternatives are available, consumers' and doctors' prescription habit often limit the diffusion of generic versions (Coscelli, 2000). This habit is likely formed by intensive firms' marketing strategies that include sales promotion to doctors as well as DTC advertising. The high level of product differentiation also gives possibility for brand name firms to better position their drug products in the market, and hence limits competition.

As drug firms' sales depend largely on blockbuster drugs and many blockbusters face patent expiry in the near future, threat of generic entry is

evident. Figure 3.2 describe a successful strategy performed by Astra Zeneca as an anticipation of its blockbuster's patent expiry, Prilosec. This example illustrates the importance of the joint effects of barrier to entry discussed above. Figure 3.3 shows another example of how a firm can suffer significant loss after generic entry. In this second example, we show that Pfizer lost a substantial part of its profit due to bad publication on its me-too drug that was developed to anticipate generic competitors.

In contrast to generic entry, the patent system is a less effective instrument to deter entry from innovative firms (CBO, 1998; Henderson and Cockburn, 1994). The possibilities to invent around the existing patents usually results in the introduction of a me-too drug for about six years after the first breakthrough drug is available in the market (CBO, 1998). This "follow the leader strategy", however, has been questioned by Henderson and Cockburn (1994). In their study of racing behavior in the drug markets, they argued that firms' investment behavior can not simply be explained by this type of strategies. Instead, they show that the technological race among innovative pharmaceutical firms and the role of firms' competence are the drivers of competition among brand name drugs.

Figure 3.2 A Successful Strategy: The Case of Nexium

In 2001, Prilosec, a 6$ billion blockbuster drug of AstraZeneca, which is priced at $4/20 mg pil, was facing patent expiry and anticipated generic cost-based competition. Years before, however, the company formed a team to examine all tactical options facing this threat. The company decided to phase out prescription Prilosec and introduce a slightly better efficacy drug product in early 2001 called Nexium (product differentiation strategy). When generics entered the market, Nexium's price was increased to $5/pill (pricing strategy). Additionally, by putting out a me-too, the companies can get new exclusive marketing rights on what are essentially the same old drugs (patent strategy).

In 2003, price of generic versions of Prilosec is between $3.80 and $1.50/20 mg pill. At the same time, the company introduced a non-prescription, over-the-counter version of Prilosec, which is called Prilosec OTC (product differentiation strategy) and priced at approximately $0.71/20 mg pill (pricing strategy). Prilosec OTC's active ingredient offered, then a much lower price then its generic version. The availability of low Prilosec OTC completely undermined the generic competition.Along the way, the company carried out intensive DTC advertising campaign (Gebhart, 2005).As a result of the above strategies, the company's sales in this therapeutic market reached a record amount of $6.4 billion in 2005.

Source: Jain, 2006

Figure 3.3 The Case of Lipitor

When its $13 billion blockbuster cholesterol drug, Lipitor, was facing patent expiry, Pfizer aimed to anticipate it by launching Torcetrapib, a me-too drug that was developed to replace Lipitor. However, concerns over the safety of this new drug have caused financial disaster for the company. Pfizer was dependent on Lipitor as its sales formed for about 40% of total company profit. Net income dropped during the fourth quarter of 2006 by 12%, to approximately $3 billion, compared with the same period in 2005

Source: The Economist, 2007

3.3.3 Threat from Substitutes and Complements

In the past thirty years, drug markets have witnessed one of the most revolutionary technologies; a change from developing drugs based on chemicals into ones that are founded on biological bases. Biotechnology has been widely perceived to play the role of destructive innovation in the pharmaceutical industry (Tushman and Anderson, 1986) and over a thousand of biotechnology firms have been founded in the U.S. (Han,

2004). However, Matraves (1999) questions these claims and argued that this development would not change the current structure of pharmaceutical industry due to its very own nature.

Major pharmaceutical firms have anticipated this new technology by implementing strategic alliances with new biotechnology firms in order to increase their own internal capability on this area (Han, 2004). In return from this cooperation, start-up biotech firms have access to financial resources provided by big pharmaceutical firms. For detailed description on how biotechnology transforms pharmaceutical industry and its effect on established firms, we refer to Galambos and Sturchio (1998) and Matraves (1999).

3.3.4 Supply and Buyer Power

Buyers of drug products generally do not constitute a significant threat in the negotiation of price, due to inelastic price in the demand side as discussed in section 3.2.1. Nevertheless, there has been increasing pressure to implement limit price increase exercised by health insurance organizations (CBO, 2006).

Looking at the supplier side, pharmaceutical firms generally enjoy good access to raw materials, technology and high quality labor. Nowadays, R&D research at the leading pharmaceutical firms can generate thousands of compounds a year at which can be tested to identify the promising chemical entity. In addition, suppliers of technologies are largely fragmented, consisting of biotech firms, universities and other small private firms that provide established pharmaceutical firms with a variety of opportunity such as licensing, joint venture, or acquisitions. Additionally, public funding on basic research has contributed in training researchers, which led to a positive spillover effect for pharmaceutical firms, albeit there is concern of increasing labor wages due to fast rate of R&D expenditures in the industry (CBO, 2006).

3.4 EXPLOITING THE LOOPHOLES OF THE HATCH-WAXMAN ACT

Aside from performing the various marketing strategies described above, brand name companies regularly gain advantage by creatively exploiting the loopholes of the existing regulations (Glasgow, 2001; Bulow, 2004). In

the following we describe several of such strategies.

3.4.1 Legal Strategies Involving Paragraph IV Certification: Patent Infringement and Illegal Settlement

List a new patent just before the patent expires

The study by the FTC (2002) shows that if a brand name firm lists an additional patent in the Orange Book, it can take longer than 30-months before the generic version of the brand name drug enters the market. This can give brand name companies substantial extra time (ranging from 4 to 40 months) to keep generic competition away from the market. This extra time does not include the first 30-months stay[1]. When an additional patent is listed, the generic applicant has to re-certify to the later listed patent. If, upon notice of the generic's re-certification, the brand name firm sues the generic firm within 45 days, the generic has to stay out from the market for 30 months (hence the term 30-months stay) from the notice date or until the court decides upon the newly instituted patent litigation (FTC, 2002).

Figure 3.4 Bristol Myers Squibb Listing a New Patent

BuSpar, an anti-anxiety drug, was launched by Bristol Myers Squibb (BMS) with one patent listed in the Orange Book. This patent was to expire on November 21, 2000. Prior to this date, some generic applicants submitted an ANDA application with paragraph III certification. Only 12 hours before this patent was about to expire, the Patent Office issued an additional patent to BMS relating to BuSpar. BMS directly submitted this patent for listing in the Orange Book. This listing prevented FDA to approve generic versions of this brand name drug. Although the District Court ordered BMS to delist the patent, the company's appeal led to the reversion of the district court decision, holding that generic applicants have no private right of action to delist the existing BMS patent. BMS's action resulted in four months delay of generic entry, excluding the automatic 30-month stay.

Pay Generic Companies to Stay Away

The second strategy brand name companies can apply is to settle a patent dispute with the first generic applicant. These settlements, which appear to be unique to the pharmaceutical industry, occur when a branded company

[1] See also appendix A for explanation of this term.

shares a portion of its future profits with a potential generic entrant in exchange for the generic's agreement not to market its product (FTC, 2006). Bulow (2004) characterizes common features of settlement agreement as follows: (1) each settlement occurred within the complex regulatory provisions of the Act; (2) each settlement involved high amounts of payment from the brand name companies to the potential generic entrants; (3) each settlement contained the agreement that generic entrants stay off the market for a certain period of time.

Figure 3.5 Agreements between Andrx and Hoechst

Andrx, a generic company, made use of paragraph IV to apply ANDA for a generic version of Hoechst's Cardizem CD and therefore had the right of the 180-day exclusivity. Hoechst sued Andrx for patent infringement and is automatically followed by a 30-month stay of FDA approval on Andrx's generic version. Both parties settled the issue by the following items. First, Andrx agreed not to market the generic version, even after the 30-month stay expired. Second, Andrx is paid $40 million each year to stay from the market if it lost the suit and $60 million each year otherwise. Third, Andrx agreed not to relinquish its right on 180-days exclusivity to other generic producers, which is to prevent other potential generic entrants from entering the market. Fourth, Andrx was not to launch any generic versions of Cardizem CD, even if it did not necessarily infringe the Hoechst's patents. FTC has challenged this agreement to be a violation of antitrust policy and shortly before trial Andrx and Hoechst settled with FTC.

Source: FTC, 2002

3.4.2 Product Differentiation Strategies

Besides the potential abuse of paragraph IV certification, many brand name companies apply extensions for existing drugs to lengthen market exclusivity. By far, this strategy is likely the most frequently used tactic. Depending on the type of extensions, brand name companies can have an additional marketing exclusivity that runs from 6 months to 7 years. The line extension activities are less expensive than developing a brand new NCE, which makes them a popular option for brand name companies, especially when one of their blockbuster drugs faces patent expiration. Hathaway and Manthei (2004) described the following example of this strategy.

Figure 3.6 Schering Plough Prolonging Marketing Exclusivity

Claritin, a blockbuster drug of Schering Plough, was approved by the FDA in 1993. The 17-year patent for Claritin was about to expire in 1998, but the firm succeeded to extend its monopoly. Just on time, Claritin was awarded (1) an additional Hatch-Wax exclusivity of two years; (2) an additional 22 months patent extension due to GATT-related patent extension, and (3) an additional 6 months exclusivity for pediatric studies. This summed up to a total of four and a half additional years of monopoly position. Back in 1987, the firm set up a strategic move by patenting the active metabolite of Claritin ─ the molecule into which the body converts Claritin, which accounts entirely for the action of the drug (Relman and Angell, 2002). When the firm started to face the loss from Claritin's sales in 2002, it received a just on time approval in December 2001 for Claritin's metabolite under the name Clarinex. This approval gives the firm 5-year exclusivity under NCE. Additionally, the company received another 6 months pediatric exclusivity on Clarinex. This implies that all existing exclusivities of Clarinex are extended by 6-months. In total, the exclusivity of this drug product does not end until June 21st, 2007.

The above illustrations show that within the current regulatory environment, brand name companies can use a variety of strategies to lengthen monopolies beyond the patent protection scheme. Many times, these actions have been successful to keep generic competitors away from the market and hence bring substantial financial benefit for the brand name companies. As a response to the growing criticism concerning the potential abuse of the Act, the U.S. senate passed the Greater Access to Affordable Pharmaceuticals Act (GAAP) that aims to close loopholes in drug patent law. This regulation limits brand name companies to a 30-month stay of generic competition and prohibits anticompetitive collusions between brand name and generic companies. However, a recent testimony by FTC in front of the Congress argued that this practice worsens competition and society's benefit (FTC, 2007).

3.4.3 Other Strategies

Other strategies that have frequently been observed but are beyond the scope of this book are *mergers* and *political lobby*. For descriptions of mergers in the pharmaceutical industry, we refer to Danzon, Eipstein and Nicholson (2004). In addition, CBO (2006) discusses the effect of mergers

on innovation activities. Balto and Mongove (1999) review several recent mergers that have been under FTC's investigation due to its potential danger in worsening consumer welfare.

Despite its strategic importance, lobbying strategies have mainly been observed by the popular press (Public Citizen, 2002) and have not been investigated carefully, perhaps due to its sensitive nature. An estimate shows that in the period 1999-2000, pharmaceutical firms spend approximately 197 million dollars on lobbying in the Congress (Reisel and Sama, 2003).

3.5 INNOVATION AND PROFITABILITY

In this section, we present (1) indications of innovativeness, in terms of the number of NCEs introduced and the number of drug products per R&D dollar and (2) indications of competitiveness in terms of market value. We use a comprehensive dataset of drug introductions from 1939 to 2005. Earlier studies do not use data prior to 1970. For detailed descriptions on the data and methodology, we refer to appendix B and appendix C.

3.5.1 Innovativeness

Figure 3.7 provides the annual number of drug introductions in the U.S. in the period 1939-2005. This figure shows that drug introductions have increased enormously compared to the early years of the history of modern medicine. While there were only 9 drugs introduced in 1939, this number has increased in 2005 to a total of 587 approvals. When we split these numbers into innovation category, we find a substantial gap between NCEs on the one hand and IMDs and generic drugs on the other hand.

Figure 3.8 presents the annual number of drug approvals for NCE, IMD, and generic approvals. The annual number of NCEs is relatively stable in the past 65 years in comparison to the number of generic and IMD approvals. Even though the rate of NCEs, IMDs and generics were similar prior to 1970, thereafter the IMD and generic approvals rate have been increasing, leaving the rate of NCEs far behind. Generic drug introductions have increased since 1970, but fell significantly at the end of the 1980s. Thereafter, generic drugs increased again to a level higher than ever before in 2005. The IMDs enjoy an increasing trend similar to that of generics, although with a slower rate.

Figure 3.7 Annual Number of Total Drug Introductions (1939-2005)

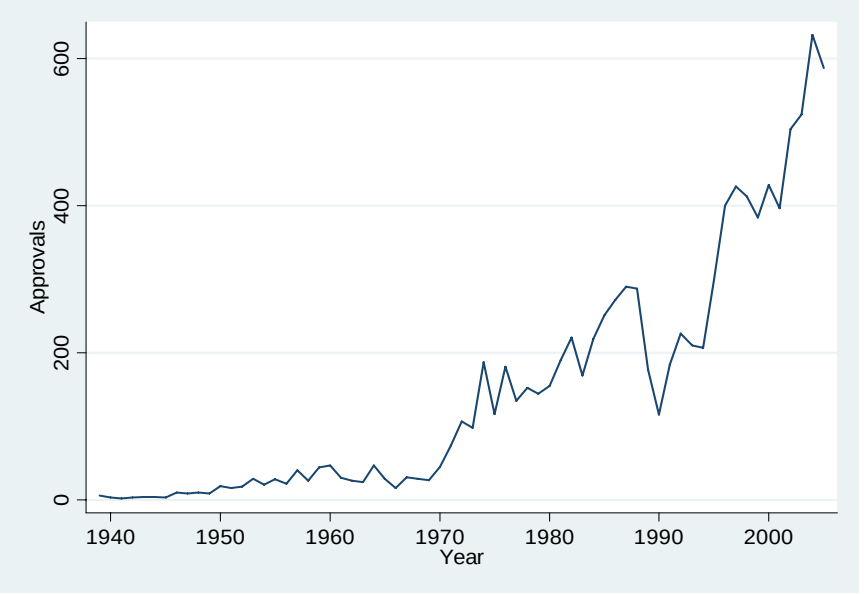


Figure 3.8 Annual Drug Introductions per Category (1939-2005)

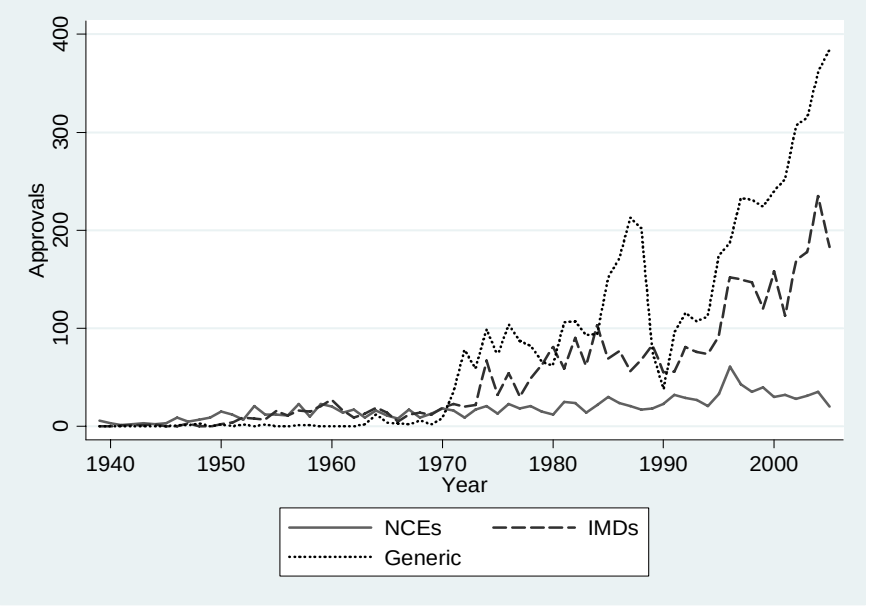
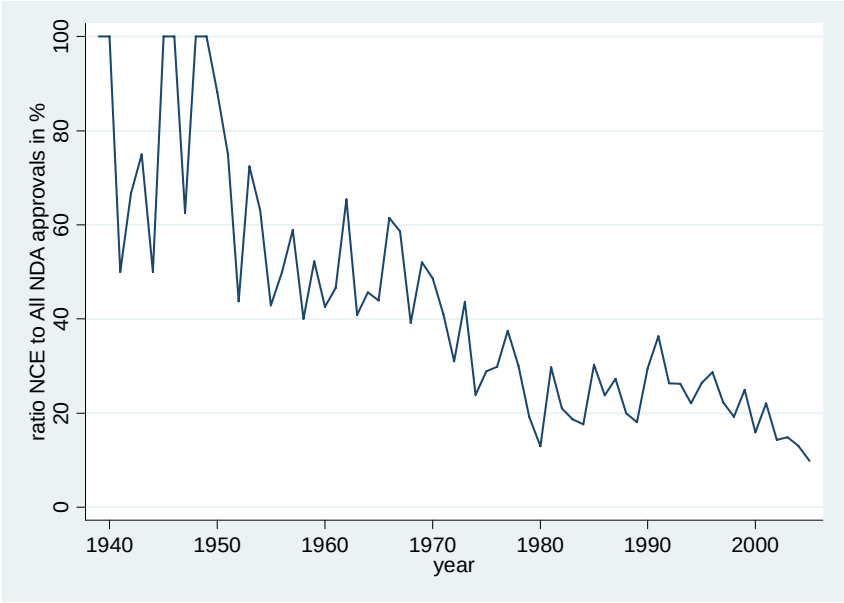


Figure 3.8 shows that NCEs form only a small part of the total of drug approvals. This, however, has not always been the case. Figure 3.9 shows the ratio of NCEs to all brand name drug approvals. According to this figure, NCE contributed to at least 80% of all branded drugs approvals in the 1940's. In the last ten years the average NCE contribution to total NDA approval has dropped to approximately 20%. Our findings show that NCEs' contribution to the growth of drug introductions has been reduced in the past three decades.

Figure 3.10 presents the industry's R&D expenditure in the period 1956-2002. This figure shows that the R&D expenditures have increased strongly in the last four decades. This rise in R&D costs is likely to be a response to the vastly expanded research opportunities created by advances in basic science (Cockburn, 2004). The number of drug targets has increased and research has been expanded to studies on the potential of these drugs. Additionally, the advancement in new technologies in drug development has induced pharmaceutical firms to devote more resources to these technologies on it in order to keep up competitive advantage. Also, a shift of focus from developing drugs for acute to chronic disease, due to the ageing population of baby boom generation in the U.S, has contributed to the rise of R&D spending (Cockburn, 2004; CBO, 2006; Scherer, 1993; Scherer, 2001). Developing drugs for the treatment of chronic disease takes much more time than that of acute disease. Finally, regulatory requirements have become much more stringent over time (Matraves, 1999; Cockburn, 2004).

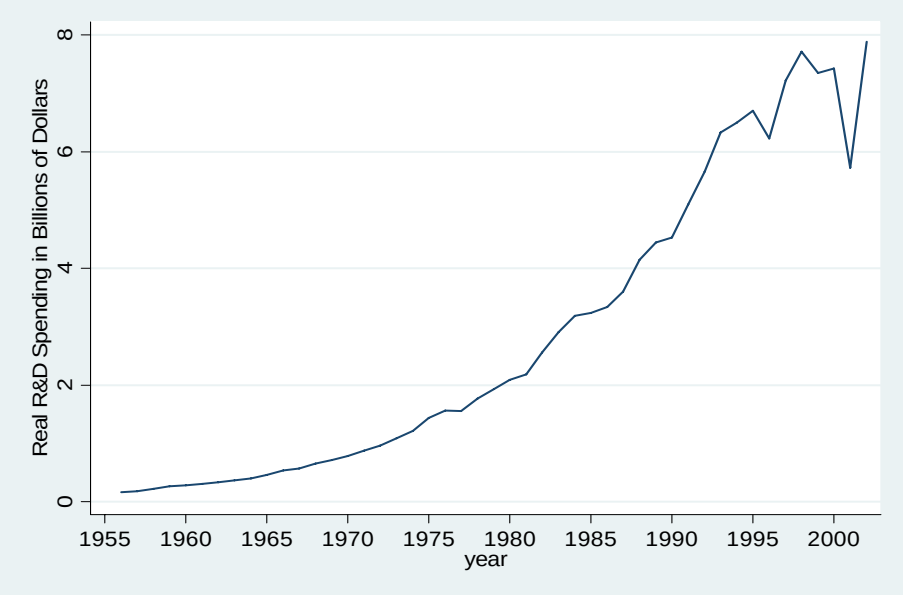
Figure 3.9 Ratio of NCE to all NDA's Approvals (1939-2005)



The increase in R&D spending does not seem to match the number of drugs approvals, however. Figure 3.11 shows the number of NDAs per billion dollar spent on R&D. This figure shows that the number of NDA introductions per billion dollar has decreased significantly in the past 50 years. Between 1956 and 1960, the industry succeeded to introduce 200 to 300 NDA approvals per billion dollar. In contrast, in the last 15 years the industry produces approximately only 20 NDAs for each billion dollar spent on R&D.

Although statistics demonstrate the declining trend of R&D productivity in the industry, some argued that this concern might be an exaggeration (Cockburn, 2004; CBO, 2006). Measures of productivity should take into account the increase in drug quality. If the average quality of drugs has been improving over time, these numbers can understate the true research output (Cockburn, 2004). Furthermore, the long and complex process of drug development indicates that today's drugs are the result of yesterday's R&D effort. Measures of productivity that use current R&D and the number of drugs approved can therefore be misleading.

Figure 3.10 R&D Spending in the Pharmaceutical Industry (1956-2005)[1]



In figure 3.12 we take into account the lag between the initial start of drugs development and the actual drug introduction by using a 12 years lag as an average development time. However, we still find a similar pattern even after taking into account the lag. Based on past figures, CBO (2006) acknowledged that current growth in R&D spending does not necessarily result in an increase in the number of new drugs.

[1] R&D expenditure is adjusted for inflation by using cpi. The sudden drop in 2001 is due to changing industry classification from Standard Industry Classification (SIC) to North American Industry Classification System (NAICS).

Figure 3.11 Number of NDA introduction per Billion Dollar R&D Expenditure (1956-2002)

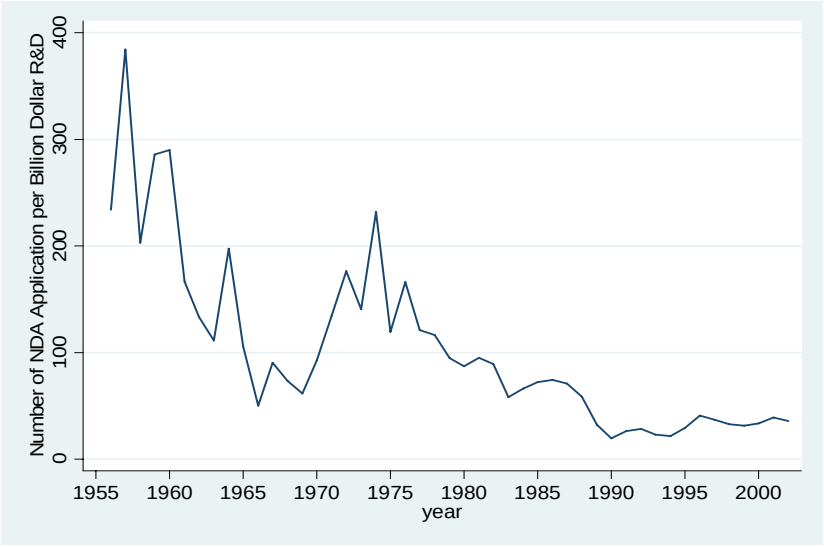
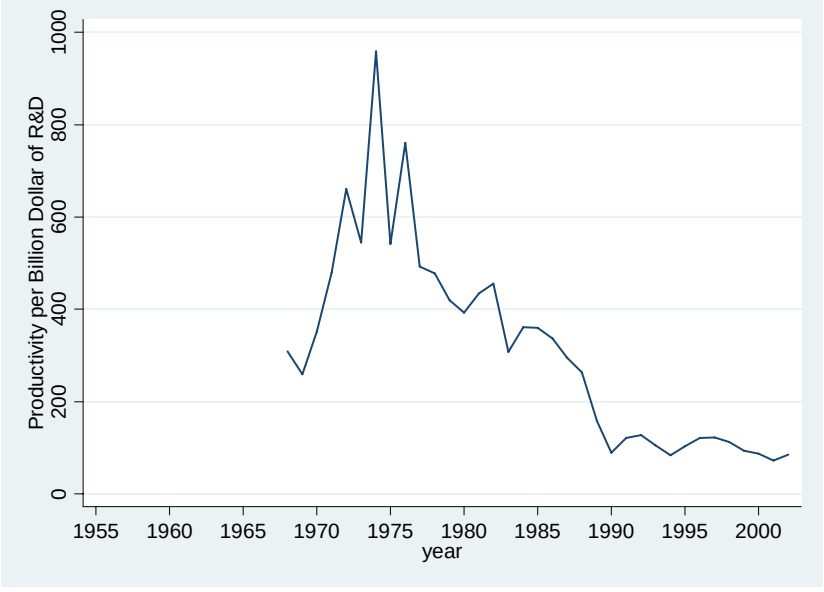


Figure 3.12 taking into account 12 years lag (1968-2002)



3.5.2 Profitability

Unlike the conventional performance of accounting measures such as profit and revenue, market value reflects both firms' tangible and intangible assets. Intangible assets play an important role in the drug industry due to high expenditures of R&D and brand value, reflected in the value of advertising Profitability, measured by the average market value of pharmaceutical companies listed at the U.S. stock exchange, is presented in figure 3.13. Additionally, we also included the market value of all companies in the U.S. for comparison. Figure 3.13 shows that the average market value of companies in the pharmaceutical industry is higher at all periods compared to the rest of the companies. The gap has become larger in the last 20 years. Our findings confirm the idea that the pharmaceutical industry is a highly profitable industry. Our study shows that this idea does not only apply in terms of profit measured by accounting standard, but also in terms of investors' valuation in the stock market.

In terms of returns, pharmaceutical companies earn more and more per NDA approval. The contribution of each drug approval on market value is substantially high, as figure 3.9 shows. The figure shows the ratio of market value in million dollars to the number of NDA approvals in the period 1950-2005. While companies on average earned less than 10 million dollars per drug approval in 1950, companies can earn nearly 0.7 billion dollar per drug approval in 2005.

Figure 3.13 Market Value of Pharmaceutical Companies Compared to All Other Companies (1971-2005)

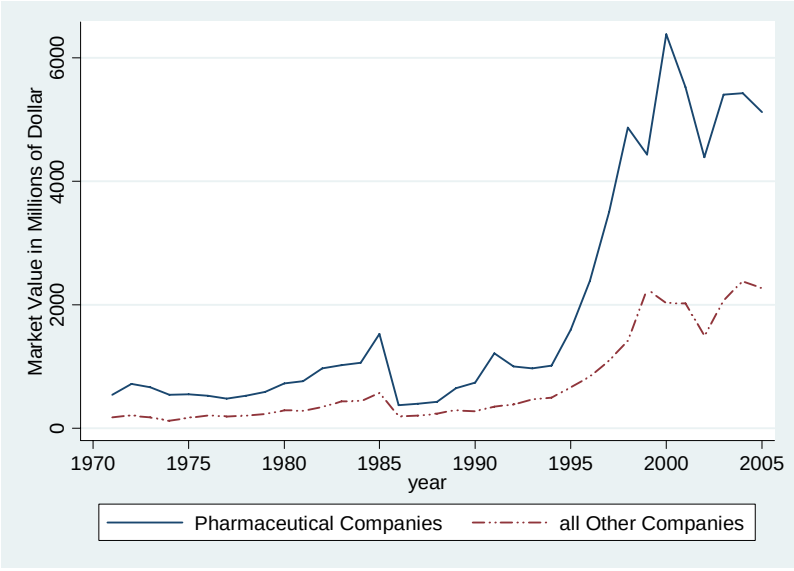
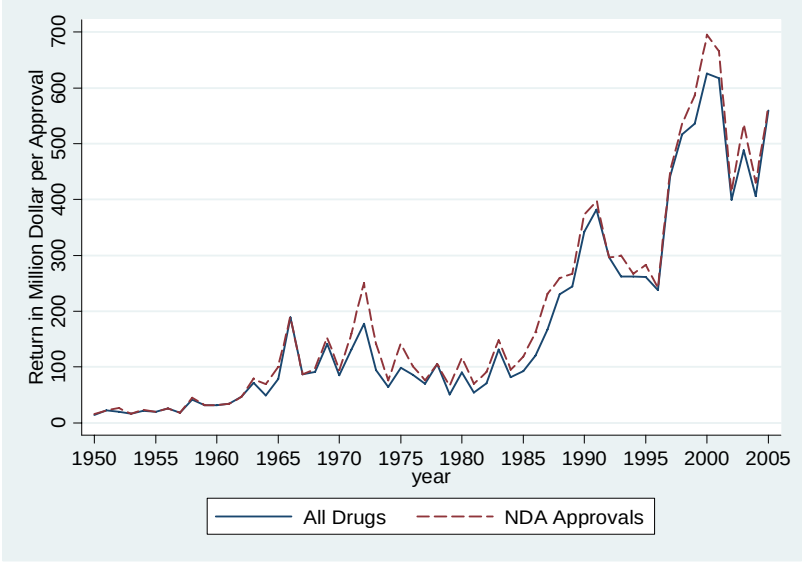


Figure 3.14 Returns in Million Dollar Market Value per Approval (1950-2005)



3.5.3 Other Considerations: Dynamic Efficiency

Our findings above seem to coincide with the existing critiques. First, consistent with previous studies (NIHCM, 2001; CBO, 2006), we show that the relative number of the most innovative drug products has been declining over time. At the same time, the market has been dominated by incremental product innovations. Second, the number of drug approvals per R&D dollar has been declining over the years. With respect to profitability the returns per drug approval has become almost 50 times higher in the last 50 years.

Nonetheless, the above view concerns static performance and a dynamic setting could provide a more balanced view. While static efficiency concerns whether price is equal to marginal cost and long-run average cost, dynamic efficiency requires a long term consideration in obtaining an optimal rate of technological advance. From the latter perspective, the acceptable innovation rate can exist hand in hand with the situations described in the previous sub-section (Waldman and Jensen, 2001; CBO 2006, Craig and Malek, 1995). Therefore, it is difficult to judge the innovation performance of the industry. Below, we provide several considerations that balance the indications that are provided in the previous sub-section.

High return compensates high cost of capital

Practice in the pharmaceutical industry has been described as a virtuous pattern of profit-seeking behavior (Scherer, 2001), which means that only a small fraction of drugs that were introduced can recover the R&D costs and the overall industry's returns were only moderately above the industry's cost of capital. The attractive returns in certain therapeutic markets increases R&D expenditure as firms compete to exploit these opportunities until the return become unattractive (Grabowski, Vernon, and DiMasi, 2001). The sustaining high profitability in the pharmaceutical industry might just reflect a high cost of capital in that industry. The long and uncertain drug development process is a unique characteristic to pharmaceutical industry and makes it more risky than any other industry. As a result, outside financing is more difficult to obtain in this sector. The increasing cost of developing a new product and high risks associated with it must be compensated with relatively high returns.

Slow adjustment of R&D toward growing demand

The current low R&D output per dollar is likely part of profit maximizing behavior as anticipation to strong consumer demand. A high demand can push firms to invest to the point beyond diminishing marginal returns through two mechanisms; (1) increased R&D spending could put upward pressure on researchers' wages, and (2) higher demand could encourage companies to reach more deeply into their inventories of potential R&D projects to ones with lower expected returns (CBO, 2006). In a study of various industries, Lanjouw and Schakermann (2002) found that decreasing R&D output was negatively related with increasing R&D expenditure and once the R&D growth has slowed the R&D productivity has recovered. The study argued that this pattern is a part of profit-maximizing behavior in a well-functioning market. We note, however, that this latter assumption should be taken into consideration on whether to accept the current productivity as reasonable from society's welfare point of view.

3.6 CONCLUSIONS

This chapter argues that assessing the performance of drug industries requires an understanding of economic mechanisms underlying phenomena that were frequently used by the critics. Against this background, we describe several forces that affect the profitability of a typical pharmaceutical firm. Given the price-inelastic nature of demand and supply side characterized by high fixed cost and returns secured by a patents system, we describe several forces that affect pharmaceutical firms.

We show that drug markets enjoy a relatively low level of competition, which is partly due to intensive patent regulations. Competition is also lessened by the growing demand of drug products and high level of product differentiation. In addition, consumers and doctors generally show persistent behavior in their preference towards specific branded drugs, which makes generic entry a less competitive threat. Nonetheless, in many sub-markets innovator firms compete intensely against each other. Often, however, innovator firms merge with each other to benefit of large, diversified R&D programs.

Generally, the barrier to entry for generic and other small firms works in favor of leading pharmaceutical firms. Except the current patent system, a

high and growing R&D expenditure makes entry extremely difficult. Additionally, new entry has to take into account the cumulated effect of advertising, product differentiation strategies, and learning advantage of incumbents. Incumbents firms also show aggressive behavior toward generic firms that threaten to infringe the existing drug patents. In many occasions, entry to barrier is magnified due to joint effects of several barriers at the same times.

Looking at the industry's performance, our findings coincide with the established criticisms. We show that the proportion of most innovative drug products has been declining over time. At the same time, the market has been dominated by incremental product innovations. The rise in drug approval did not seem to match the significant increase in R&D expenditures. With respect to profitability, in the last 50 years, the return per drug approval has become almost 50 times higher.

In spite of this decreasing performance, a dynamic consideration can provide a more balanced view on the subject matter. The costs of discovering and developing drug products have increased substantially over the years, and therefore high profitability might indicate a high cost of capital and the required high returns needed to compensate the cost and the risk. In addition, a low ratio of drug output to R&D dollars is likely a result of adjustment of R&D expenditures to the increasing demand of drug products.

Driven by the increasing critics on the escalation of advertising expenditure and the increasing number of modified drugs, the next chapter seeks whether these phenomena have contributed to the substantial rise of stock market value of major U.S. firms.

4. THE EFFECT OF ADVERTISING AND PRODUCT DIFFERENTIATION ON THE PERFORMANCE OF U.S. PHARMACEUTICAL FIRMS

ABSTRACT

Despite the important role of advertising and product differentiation, studies on the profitability of pharmaceutical firms mainly focus on the role of R&D. In this chapter, we investigate the impact of advertising and product differentiation on pharmaceutical firms' market value. Especially, we examine whether there has been a change in the pattern of returns of these variables over time. Our results show that, nowadays, pharmaceutical firms' performance is not only closely linked to their R&D activities but also to advertising activities and product differentiation. Since the 1990s, the return of advertising has become three times larger than that of R&D. In addition, we found that the impact of product differentiation came largely from the introduction of IMDs. The vast increase of the number of IMDs since the 1990s is likely to contribute to this development. Our results emphasize the role of advertising and product differentiation in the virtuous rent-seeking behavior in the pharmaceutical industry.

4.1 INTRODUCTION

Next to R&D expenditure, advertising expenditure is of strategic importance for firms' survival. Firms can use R&D and/or advertising expenditure as choice variables responding to increased competition. Indeed, past empirical studies in the various industries demonstrate the significant effect of R&D and advertising on firms' profitability (Griliches, 1981; Jaffe, 1986; Hall, 1993). The roles of R&D and advertising, as well as product differentiation, are especially important in the pharmaceutical industry where firms do not fully compete in terms of price and products are highly differentiated (Matraves, 1999). The escalation of R&D, advertising and the vast increase of product modifications have been claimed to increase the economies of scale and contribute to the industry's high profitability (Matraves, 1999; Craig and Malek, 1995).

Scherer (2001) points out several ways in which R&D investment can be linked with profitability. First, successful R&D projects result in new products in the next period that eventually lead to profit. Second, high

profitability can lead to increase in R&D expenditure in the next period. Although findings from studies on the link between internal funding and R&D are still mixed, pharmaceutical firms probably depend more on internal funding to finance their R&D activities than on external resources (Himmelberg and Peterson, 1994; McCutchen, Jr., 1993). Third, the link between profitability and R&D can be traced through the demand-pull mechanism in which expected profitability in certain therapeutical markets increases firms' R&D expenditure on that area (CBO, 2006).

Simultaneously, advertising can be linked with profitability in various ways (Erickson and Jacobson, 1991). First, advertising seeks to differentiate the firms' products and therefore can enhance brand loyalty and reputation. This loyalty and reputation can in turn enable firms to set higher prices than products with similar qualities. In addition, the long term effect of advertising can discourage potential entrants to enter in an intensive advertised industry (Waldman and Jensen, 2001).

Popular press often claims that major pharmaceutical companies put more emphasis on marketing than on R&D (Public Citizen, 2001; Rellman and Angell, 2002). As a result of the entire lift of DTC advertising in 1997, drug companies' spendings on DTC advertising of drug products increased twice as fast as spending on promotion to physicians or on research and development in the period 1997-2005 (GAO_1, 2006). Over this period, drug companies spent less each year on DTC advertising ($4.2 billion in 2005) than on promotion to physicians ($7.2 billion in 2005) or R&D ($31.4 billion in 2005) ($GAO_1$, 2006).

Product differentiation is closely related with firms' advertising activities. In highly advertised industries, products are usually differentiated (Matraves, 1999). Product differentiation, accompanied with advertising campaigns, can affect performance through the process of enlarging consumer choice and through market segmentation that satisfies consumer demand more precisely (Connor, 1981). Additionally, in the U.S., product differentiation enables drug firms to obtain market exclusivity as has been illustrated in chapter 2. For example, when a drug company introduces an NCE, it will be granted a marketing exclusivity for a period of five years. Within this period, the company can invest in brand names and the launch of product extensions that can lead to additional marketing exclusivity.

Scherer (2001) emphasizes the importance of R&D and advertising activities and argues that they play an important role in the concept of "virtuous rent-seeking" that characterizes pharmaceutical markets (Scherer, 2001). He describes this concept as follows: "… that is, as profit opportunities expand, firms compete to exploit them by increasing R&D investments, and perhaps also promotional costs, until the increases in costs dissipate most, if not all, supranormal profit returns…" However, despite the vast increase of advertising expenditure, as well as the high degree of product differentiation associated with it, few empirical studies examine their relationship with the profitability of pharmaceutical firms. Instead, the focus has been on the R&D role on pharmaceutical firms' profitability (Scherer, 2001; Grabowski and Vernon, 1990; Grabowski, Vernon and DiMasi, 2001; OTA, 1993).

Against this background, this chapter studies the role of advertising and product differentiation for pharmaceutical firms' market value. Additionally, we want to compare the returns of advertising with that of R&D. Our study provides an opportunity to test the proposition that drug firms in fact put more emphasis on marketing activities than on R&D. Our study contributes to the existing research in the following three ways. First, our approach enables us to investigate simultaneously the return of various intangibles assets of pharmaceutical firms that include R&D, advertising and product differentiation. Doing so allows us to compare the pattern of advertising returns with that of R&D over time.

Second, we are one of the first to study the impact of various intangible assets such as innovation, brand names and product introduction on U.S. pharmaceutical firms' market value over a long time period. Despite their valuable contributions, studies on the return of R&D in the pharmaceutical firms cover a relatively short period of time (Grabowski, Vernon, and DiMasi, 2001; Grabowski and Vernon, 1990). The relatively long study coverage allows us to asses whether there has been a shift in the patterns of the return of various assets of pharmaceutical firms. Furthermore, by examining these returns over a long time period we can gain a better understanding of pharmaceutical firms' behavior. This understanding can eventually be used to reduce the gap between private and social return (Hall, 2000).

Third, studies on R&D return in the pharmaceutical industry generally use

accounting measures such as profits, sales or cash flows (Grabowski, Vernon, and DiMasi, 2001; Grabowski and Vernon, 1990). The time lags between the initial R&D decision and its final output in the form of new drug products provide limitations in measuring the direct impact of R&D on firms' profitability. Our study uses a market valuation model that provides an alternative solution to this problem (Griliches, 1981; Hall, 1993). This approach leaves the valuation of firms' strategic decision, including R&D, advertising and product differentiation strategies, to the financial markets. Using financial markets' evaluation avoids the problem of timing of costs and revenue described above and is capable of forward-looking evaluation, which traditional accounting approaches do not do well (Hall, 1993).

This chapter is structured as follows. In the next section, we outline the theoretical framework based on the seminal work of Griliches (1981). Section 4.3 presents the methodology where we explain the independent variables in our model. This section also provides the data and the sample selection we used. Additionally, we present the estimation procedures we used and our model specifications. Section 4.4 discusses the results. Section 4.5 concludes the present chapter by discussing the most important findings and their implications for innovation in the U.S. pharmaceutical industry.

4.2 THEORETICAL FRAMEWORK

Using market value to measure the return of intangible assets is based on the assumption that the value of firm intangible assets, that include R&D, patents, advertising, and product differentiation, are determined frequently in the financial markets. The basic model hypothesizes that the market value of a pharmaceutical firm is a function of all firm assets, both tangible and intangible (Griliches 1981; Hall 2000).

$$V(A_1, A_2, A_3, \ldots) = f(A_1, A_2, A_3, \ldots) \qquad (4.1)$$

where f is an unknown function that describes how the combination of firm assets creates value. Since the functional form of (4.1) is unknown, economists usually use an ad hoc linear function. Pioneered by Griliches (1981), this model gained popularity as indicated by a considerable number of papers using this model (for a review see Hall, 2000). This model is expressed as follows (for simplicity reasons we omit the time aspect):

$$V_i(A,K) = q\,(A_i + \sum_{j=1}^{N} \gamma_j K_{ji})^{\sigma} \qquad (4.2)$$

where V_i is the current market value of firm *i* as by the end of the year and A_i is the current value of the firm's conventional assets. K_{ij} denotes the *j*th intangible asset of firm *i*, and N is the total number of intangible assets. γ_j denotes the parameter of variable K, while *q* is the current market valuation coefficient of the firm's assets, reflecting its differential risk and monopoly position (Griliches, 1981). From equation (4.2), we take the logarithm of both sides:

$\log V_i = \log q + \sigma \log (A_i + \sum_{j=1}^{N} \gamma_j K_{ji})$, which is equal to:

$$\log V_i = \log q + \sigma \log [A_i(1 + \sum_{j=1}^{N} \gamma_j \frac{K_{ji}}{A_i})].$$

Using the approximation that log (1+ x) = x, we get:

$$\log V_i = \log q + \sigma \log A_i + \sigma(\sum_{j=1}^{N} \gamma_j \frac{K_{ji}}{A_i})$$

Letting $K_{ji}/A_i = I_{ji}$ and adding a disturbance term, we get the following empirical equation

$$\log V_i = \log q + \sigma \log A_i + \sigma \sum_{j=1}^{N} \gamma_j I_{ji} + u_i \qquad (4.3)$$

Under constant return to scale, this model implies that σ, the coefficient of log A_i, is unity. Furthermore, the intercept of the model (log q) can be interpreted as an estimate of the logarithmic average of Tobin's q for the sampled companies during the sample period (Hall, 2000).

4.3 METHODOLOGY

4.3.1 Independent Variables Included in the Model

We include the variables of interest in the equation 4.3; *R&D*, *advertising*, and *product differentiation*. As a measure of *product differentiation*, we use the annual number of product introductions that include NCEs and IMDs. Following Hall (1993), we include several control variables. We included *cash flow* (net of advertising and R&D) as a proxy for any market power or long-run profitability of companies. We also included the *growth rate of sales* in the present year to capture the prospects for future growth of pharmaceutical companies in our sample. Even though this variable might be a product of firm's R&D and other investments, we assume that it is not completely captured by the current level of R&D expenditure (Hall 1993). To control for specific industry movement, we included the weighted average of *industry return* in our model.

We excluded patent variables because we did not find any significant effect of patent variables in the initial analysis. For this purpose, we used several measures of patents, such as patent counts, patent citations, and importance of patent such as patent originality and generality[1]. The weak relation between patents and market values can be traced to several factors. First, a review of existing studies shows that the patent is an indication of the same phenomenon as R&D variables but in a noisier way (Hall 2000; Bosworth and Mahdian 1999). Second, R&D variables and patents did not always play significant roles when jointly included (Stoneman and Bosworth, 1994). Griliches, Pakes and Hall (1987) argued that patent count is a noisy measure of the underlying economic value of the innovations to which they are associated. Furthermore, patents have highly skewed distributions suggesting that few patents are highly valued and that many are worth little. Nevertheless, Hall (2000) argued that *weighted* patent, such as patent citation index, provides a better measure than simply counting the granted patent different measures of patent citations and the importance of patents. Our preliminary analysis showed, however, that these measures also had a negligible effect on firms' market value.

[1] For more explanations on these terms see http://www.nber.org/patents/pat63_99.txt.

4.3.2 Model Specification

We specify two models. In the first model, we include the annual number of total products introduction as a proxy for product differentiation. In the second model, we split the product introductions into two categories; NCEs and IMDs. Doing so enables us to look at the individual effect of each of this product group.[1] In addition, we include the interaction variable of R&D and advertising to check whether the impact of R&D is strengthened by advertising and vice versa. Table 4.1 provides the definition of the variables used in the models. The two models can be specified as follows.

Model (1)

$$\log V_{it} = \log q_t + \sigma \log A_{it} + \gamma_1 R\&D/A_{it} + \gamma_2 Adv/A_{it} + \gamma_3 CF/A_{it} + \gamma_4 \Delta\log S_{it} + \gamma_5 DCE_{it} + \gamma_6 (R\&D/A)*(Adv/A)_{it} + \gamma_7 Total_{it} + \gamma_8 Index_t + u_{it}$$

Model (2)

$$\log V_{it} = \log q_t + \sigma \log A_{it} + \gamma_1 R\&D/A_{it} + \gamma_2 Adv/A_{it} + \gamma_3 CF/A_{it} + \gamma_4 \Delta\log S_{it} + \gamma_5 DCE_{it} + \gamma_6 (R\&D/A)*(Adv/A)_{it} + \gamma_7 NCE_{it} + \gamma_8 IMD_{it} + \gamma_9 Index_t + u_{it}$$

We perform regression analysis for the period 1971-2005. In addition, we also run a separate analysis for the two periods and see whether there is any shift of assets return from the first period (1971-1989) to the second period (1990-2005).

[1] In the preliminary analysis, we also included the square terms of IMDs and the interaction term between IMDs and NCE, but we removed these terms because they did not have significant coefficient in any of the equation.

Table 4.1 Definition and Operationalization of Variables

Variables	*Definition*
Log V_{it}	logarithm of market value of firm *i* at time *t*; market value is defined as stock price multiplied by number of outstanding stocks plus debt
Log q_t	intercept
Log A_{it}	logarithm of total tangible assets of firm *i* at time *t*
$R\&D/A_{it}$	ratio of R&D expenditure to total assets
Adv/A_{it}	advertising to assets ratio
CF/A_{it}	cash flow to assets ratio
$\Delta \log S_{it}$	growth of sales
DCE_{it}	debt to equity ratio; represents the capital structure of the firm
$R\&D/A_{it} * Adv/A_{it}$	Interaction between R&D and advertising[1]
$Total_{it}$	number of total products launched (NCEs, IMDs and generics) in year *t* by firm *i*[2]
NCE_{it}	number of NCEs introduced in year *t* by firm *i*
IMD_{it}	number of IMDs introduced in year *t* by firm *i*
$Index_t$	value weighted average of industry return

4.3.3 Estimation Procedure

A pooled test (Breusch Pagan multiplier test)[3], which tests the null hypothesis of whether a firm's specific error term is zero, is significant at the 1% level (χ^2=25.66). This indicates that performing ordinary least square (OLS) on pooled data will result in inefficient estimates. Therefore, we use *fixed effect* (FE) and *random effect* (RE) estimators that take into account companies' specific error terms (Verbeek 2000). The FE estimator assumes that a firm's specific effects are constant and do not vary over time. This is comparable to inserting a dummy for each firm and applying OLS to the regression equation that is transformed into deviations from

[1] We standardize R&D/A and Adv/A in the operationalization of this interaction variable.
[2] We do not divide the number of product introduction with total assets because it produces very small quantities that lead to substantially high coefficients. Therefore, we include the product's variable in absolute form, not in ratio like any other intangible assets.
[3] This test investigates whether the data can be pooled and ordinary least square (OLS) estimation can be performed.

individual means.

The RE estimator, on the other hand, treats a firm's specific error as a part of the error term. The RE estimator is a generalized least square (GLS) estimator that is obtained by exploiting the structure of the error covariance matrix (Verbeek 2000). The Hausman test (Hausman 1978) can be performed to choose between the FE- or RE- estimator. Under the null hypothesis that there is no correlation between firm specific effects with the regressors both estimators are consistent but the RE estimate is efficient, while fixed effects are not. Under the alternative hypothesis that a firm's specific effects are correlated with the regressors, RE estimators are inconsistent, while FE estimators are consistent and efficient.

4.3.4 Data Descriptions

For a detailed description on the selection of drug products and companies we refer to appendix B. We link the product database with financial data from COMPUSTAT. We replace missing values in advertising by using information from annual reports and by using extrapolation. For more details on this procedure we refer to appendix D. Industry index is obtained from the Kenneth R. French website[1]. The resulting database, after merging financial data and drugs approval data, comprises of 27 companies in the period 1971-2005. The minimal number of observation within one firm is 6 and the maximal number is 35. As such, we have unbalanced panel data with 599 firm-year observations.

4.4 RESULTS

In figure 4.1 we present the trend in the market value of pharmaceutical firms in our sample in comparison with the trend in NCE and IMD introductions in the period 1971-2005. This figure shows that there was a simultaneously sharp increase in the number of NCEs, IMDs and market value in the period 1994-1997. In 1996, the number of NCEs was at the highest in the history. At the same year, the number of IMDs also increased significantly compared to the previous years. A similar trend applies to the stocks valuation of pharmaceutical firms. After 1996, the number of NCEs has somewhat slowed down and reached the lowest in the past 30 years level in 2005. Meanwhile the market value and the number of IMDs stay at

[1] http://mba.tuck.dartmouth.edu/pages/faculty/ken.french/data_library.html

a relatively high level in that period.

Figure 4.1 Market Value and the Annual Number of NCEs and IMDs (1971-2005)

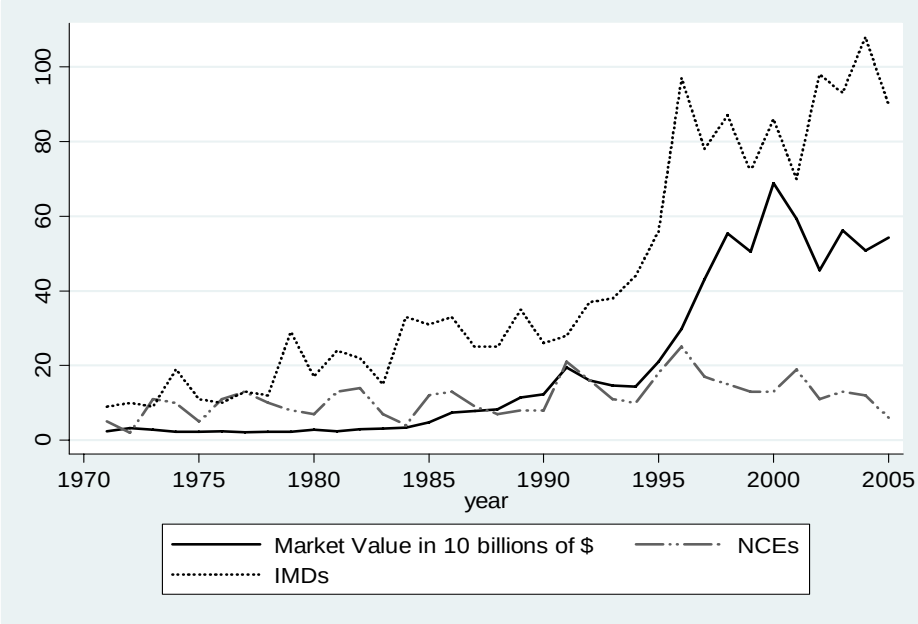
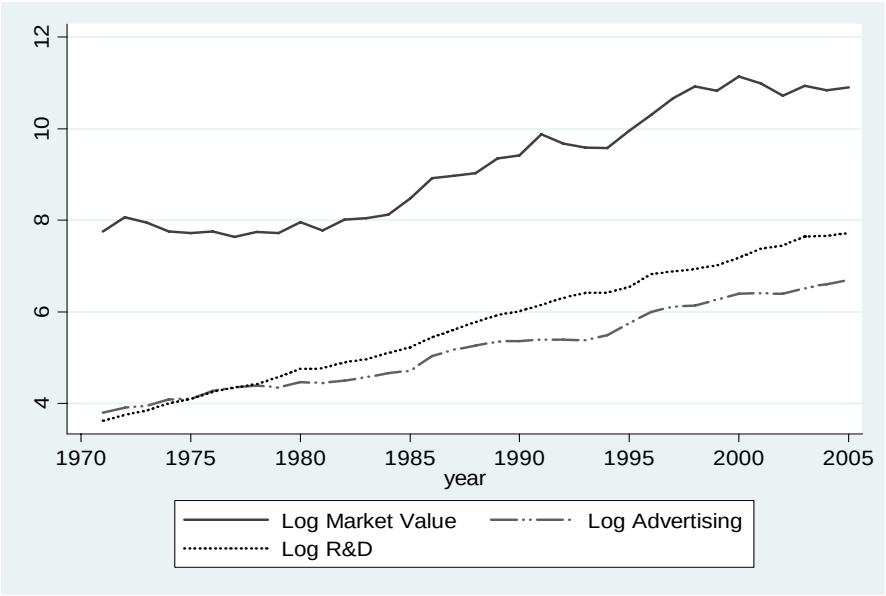


Figure 4.2 shows the trend of R&D and advertising expenditures in comparison with market value. Both R&D and advertising expenditures have been increasing in the period 1971-2005. There has been, however, an increasing gap between these two figures. Since 1975, the R&D expenditure increased faster than that of advertising expenditure. Based on this figure, we can reject the claims that pharmaceutical firms spent more on advertising than on R&D expenditure (Public Citizen, 2001). However, we cautiously note that in our data advertising expenditure is likely an underestimation of the real figure, due to substantially missing values of advertising in COMPUSTAT (see also appendix D).

Figure 4.2 Market Value, R&D and Advertising expenditure of Pharmaceutical Firms (1971-2005)



We present the descriptive statistics of the variables in table 4.2. We also provide separate descriptive statistics for period 1971-1989 and 1990-2005 in table 4.3 and table 4.4, respectively. On average, almost all assets increased from the first period to the second period. For example, the average of market value (in logarithm) has increased from 7.50 in the period 1970-1989 to 9.79 within the period 1990-2005. At the same time, its volatility was somewhat reduced, as the standard deviation of this variable has decreased from the first to the second period. R&D to assets ratio and the degree of product differentiation in the second period was also higher than the first one. While a firm introduced on average 1.55 products in the period 1970-1989, it increased to 3.62 in the second period. A remarkable growth is observed for incremental products, which have increased from an average 0.86 to 2.90 introductions a year. There was also a slight increase in the average number of NCEs from the first to the second period.

Curiously, the intensity of outside debt has decreased. In the period 1970-1989, an average debt to equity ratio was 0.36, while in the period 1989-2005 it was only 0.16. This figure might support the position that

pharmaceutical firms' are increasingly dependent on internal resources in financing investment activities (Scherer, 2001). Furthermore, despite the vast increase of advertising expenditure, the ratio of advertising to assets is relatively stable in the period under study. The same also applies to growth variable.

The estimation results of the three models for the whole period (1971-2005) are presented in table 4.5. Each model is estimated by three estimation procedures (OLS, FE and RE). The first three columns in table 4.5 present the estimates of model 1. The last three columns present the estimates of model 2, in which we split the product variable into NCEs and IMDs. The estimation results in the period 1971-1989 and the period 1990-2005 are presented in table 4.6 and table 4.7, respectively. All regressions are performed with robust variance estimate (Huber, 1967; White 1980; Rogers, 1993). Additionally, we exclude outliers that were under the 5% percentile and above the 95% percentile of the log of market value. As a result, the observations were reduced from 599 to 538. The minimal number of observation within one firm was reduced to 2 and the maximal number stayed at 35.

Table 4.2 Descriptive Statistics, 1971-2005 (N=599)

Variable	*Definition*	*Mean*	*St. Deviation*
LogMV	Log market value	8.74	2.04
LogAssets	Log Assets	7.90	1.77
R&D/A	R&D to assets	0.09	0.05
Advertising	Advertising to assets	0.04	0.05
DCE	Debt to Equity	0.25	0.32
D log sales	Change in log sales	0.14	0.23
Product	Total products	2.68	3.14
CFA	Cash Flow to Assets	0.04	0.04
NCE	Innovative drug products	0.49	0.79
IMD	Incremental drug products	1.97	2.73

Table 4.3 Descriptive Statistics, 1971-1989 (N=271)

Variable	*Definition*	*Mean*	*St. Deviation*
LogMV	Log market value	7.50	1.81
LogAssets	Log Assets	6.96	1.52
R&D/A	R&D to assets	0.07	0.05
Advertising	Advertising to assets	0.05	0.06
DCE	Debt to Equity	0.36	0.43
D log sales	Change in log sales	0.14	0.25
CFA	Cash Flow to Assets	0.04	0.04
Product	Total products	1.55	1.86
NCE	Innovative drug products	0.40	0.69
IMD	Incremental drug products	0.86	1.26

Table 4.4 Descriptive Statistics, 1990-2005 (N=328)

Variable	*Definition*	*Mean*	*St. Deviation*
LogMV	Log market value	9.79	1.60
LogAssets	Log Assets	8.68	1.57
R&D/A	R&D to assets	0.10	0.05
Advertising	Advertising to assets	0.04	0.03
DCE	Debt to Equity	0.16	0.15
D log sales	Change in log sales	0.14	0.21
CFA	Cash Flow to Assets	0.04	0.05
Product	Total products	3.62	3.64
NCE	Innovative drug products	0.58	0.87
IMD	Incremental drug products	2.90	3.24

Table 4.5 OLS, Fixed Effects and Random Effects Estimation, 1971-2005 (27 companies, N= 538)

	Model 1			Model 2		
	OLS	**FE**	**RE**	**OLS**	**FE**	**RE**
Logarithm of Assets	0.929***	0.936***	0.926***	0.927***	0.935***	0.926***
	(0.018)	(0.019)	(0.019)	(0.018)	(0.020)	(0.019)
R&D to assets	2.266***	2.479***	2.388***	2.249***	2.481***	2.390***
	(0.670)	(0.579)	(0.528)	(0.702)	(0.578)	(0.528)
Advertising to assets	1.364*	1.801**	1.622***	1.351*	1.791**	1.614***
	(0.734)	(0.707)	(0.615)	(0.737)	(0.711)	(0.624)
Cash Flow to Assets	2.793***	2.870***	2.983***	2.807***	2.819***	2.940***
	(0.713)	(0.513)	(0.477)	(0.712)	(0.516)	(0.480)
Δ log sales	0.098	0.062	0.047	0.099	0.064	0.049
	(0.141)	(0.137)	(0.122)	(0.142)	(0.138)	(0.123)
Debt to equity	-1.685***	-1.662***	-1.579***	-1.675***	-1.663***	-1.580***
	(0.173)	(0.155)	(0.145)	(0.173)	(0.154)	(0.144)
Advertising x R&D	0.033	0.085**	0.077**	0.031	0.083**	0.076**
	(0.045)	(0.034)	(0.031)	(0.048)	(0.034)	(0.031)
Total	0.019**	0.018***	0.018***	_	_	_
	(0.008)	(0.006)	(0.006)	_	_	_
NCE	_	_	_	0.027	0.024	0.024
	_	_	_	(0.020)	(0.015)	(0.016)
IMD	_	_	_	0.019*	0.017**	0.017
	_	_	_	(0.009)	(0.008)	(0.007)
Industry Index	-1.565***	-1.684***	-1.704***	-1.568***	-1.680***	-1.701***
	(0.246)	(0.133)	(0.128)	(0.236)	(0.134)	(0.128)
R^2 ~	0.959	0.952	0.958	0.959	0.952	0.958
X^2 (Hausman Test) +	n.a. ^			n.a. ^		

Standard errors are in parentheses; *significantly different from 0 at 10%;** significantly different from 0 at 5%;*** significantly different from 0 at 1%;
+ Prob> χ^2 is in parenthesis; ~ R^2 refers to within R^2 and overall R^2 for respectively FE and RE. ^ not available due to small sample property

Table 4.6 OLS, Fixed Effects and Random Effects Estimation, 1971-1989 (18 Companies, N= 246)

	Model 1			Model 2		
	OLS	**FE**	**RE**	**OLS**	**FE**	**RE**
Logarithm of Assets	0.864***	0.816***	0.823***	0.865***	0.817***	0.826***
	(0.031)	(0.031)	(0.025)	(0.031)	(0.031)	(0.025)
R&D to assets	3.652***	4.035**	4.092***	3.646*	4.081**	4.134***
	(1.779)	(1.647)	(1.294)	(1.800)	(1.665)	(1.302)
Advertising to assets	2.096*	4.758*	3.851***	2.098*	4.779*	3.857***
	(1.125)	(2.739)	(1.213)	(1.133)	(2.756)	(1.213)
Cash Flow to Assets	2.501***	3.315***	3.146***	2.493**	3.227***	3.103***
	(1.085)	(0.775)	(0.725)	(1.101)	(0.780)	(0.731)
Δ log sales	-0.238***	-0.183***	-0.197***	-0.236***	-0.179***	-0.196***
	(0.054)	(0.067)	(0.063)	(0.055)	(0.068)	(0.063)
Debt to equity	-1.571***	-1.504***	-1.492***	-1.569***	-1.504***	-1.491***
	(0.194)	(0.197)	(0.170)	(0.193)	(0.119)	(0.170)
Advertising x R&D	0.111	0.252***	0.218***	0.111	0.255***	0.219***
	(0.090)	(0.091)	(0.059)	(0.092)	(0.092)	(0.060)
Total Product	0.016	0.017**	0.015*	_	_	_
	(0.010)	(0.008)	(0.012)	_	_	_
NCE	_	_	_	0.015	0.015	0.018
	_	_	_	(0.027)	(0.020)	(0.021)
IMD	_	_	_	0.018	0.021	0.015
	_	_	_	(0.016)	(0.014)	(0.014)
Industry Index	-1.388***	-1.169***	-1.216***	-1.391***	-1.166***	-1.217***
	(0.294)	(0.161)	(0.159)	(0.300)	(0.161)	(0.160)
R^2 ~	0.948	0.964	0.945	0.948	0.897	0.945
X^2 (Hausman Test) +		n.a. ^			1.22 (0.995)	

Standard errors are in parentheses; *significantly different from 0 at 10%;** significantly different from 0 at 5%;*** significantly different from 0 at 1%;
+ Prob> χ^2 is in parenthesis; ~ R^2 refers to within R^2 and overall R^2 for respectively FE and RE. ^ not available due to small sample property

Table 4.7 OLS, Fixed Effects and Random Effects Estimation, 1990-2005 (25 Companies, N= 292)

	Model 1			Model 2		
	OLS	**FE**	**RE**	**OLS**	**FE**	**RE**
Logarithm of Assets	0.999***	0.998***	0.992***	0.999***	0.996***	0.991***
	(0.026)	(0.054)	(0.043)	(0.027)	(0.055)	(0.044)
R&D to assets	1.741**	1.888***	1.795***	1.752***	1.900***	1.804***
	(0.721)	(0.395)	(0.366)	(0.713)	(0.392)	(0.366)
Advertising to assets	3.625***	4.249***	3.741***	3.594***	4.209**	3.706***
	(1.039)	(1.185)	(0.956)	(1.055)	(1.194)	(0.977)
Cash Flow to Assets	3.239***	2.684***	2.861***	3.246***	2.640***	2.828***
	(0.709)	(0.965)	(0.764)	(0.709)	(0.966)	(0.771)
Δ log sales	0.540***	0.513***	0.516***	0.541***	0.517***	0.519***
	(0.121)	(0.113)	(0.108)	(0.120)	(0.111)	(0.108)
Debt to equity	-2.044***	-1.891***	-1.930***	-2.031***	-1.882***	-1.920***
	(0.230)	(0.268)	(0.210)	(0.233)	(0.268)	(0.210)
Advertising x R&D	-0.039	0.000	-0.008	-0.039	-0.003	-0.009
	(0.051)	(0.029)	(0.024)	(0.050)	(0.029)	(0.024)
Total Product	0.010	0.019**	0.016**	_	_	_
	(0.009)	(0.008)	(0.008)	_	_	_
NCE	_	_	_	0.016	0.020	0.017
	_	_	_	(0.026)	(0.018)	(0.019)
IMD	_	_	_	0.009	0.020**	0.017*
	_	_	_	(0.009)	(0.010)	(0.009)
Industry Index	-1.800***	-2.104***	-2.032***	-1.825***	-2.134***	-2.057***
	(0.350)	(0.353)	(0.361)	(0.341)	(0.349)	(0.357)
R^2 ~	0.949	0.875	0.948	0.949	0.876	0.948
X^2 (Hausman Test) +	1.84 (0.994)			1.29 (0.999)		

Standard errors are in parentheses; *significantly different from 0 at 10%;** significantly different from 0 at 5%;*** significantly different from 0 at 1%;
+ Prob> χ^2 is in parenthesis; ~ R^2 refers to within R^2 and overall R^2 for respectively FE and RE.

The R&D coefficients for the total period (1971-2005) are positive and significant, although they are relatively low compared to the past findings (Hall, 2000). Our R&D coefficients are centered approximately on 2.4, while findings from the past studies are centered on 5 or 6. Still, our R&D coefficients are within the range. The advertising coefficient is somewhat lower than R&D, which is approximately 1.8 in the regression over the whole period (1971-2005). Looking at the effect of product differentiation, our results show that product differentiation have positive impact on market value. In the period under study, an introduction of a new product increases the market value by approximately 18%. This effect is likely a result of the vast increase of IMD introductions since none of NCE coefficients is significant.

Comparing the results in the period 1971-1989 and that of 1990-2005, we found somewhat different patterns. In the period 1990-2005, we found that the coefficient of advertising to assets is almost three times as large as the coefficient of R&D to assets, while their coefficients are more or less similar in the period 1971-1989. In other words, the gap between the return of advertising and that of R&D becomes larger as we move from the first to the second period. Compared to Hall (1993) that found 4 to 5 times smaller advertising coefficients than that of R&D expenditures, our findings seem to show the opposite. The difference might be due to the nature of the industry; Hall (1993) study covered various U.S. industries, while we concentrate on U.S. pharmaceutical firms.

Additionally, we found a positive interaction effect between R&D and advertising intensities in the first period, which implies that their effects on market value strengthen each other. Nonetheless, this interaction effect is relatively small compared to the main effects. In the period 1990-2005, we do not find a significant interaction effect.

In the period 1971-1989, the impact of total product introduction on firms' market value is positive and significant. When we move from the first to the second period, this effect becomes slightly bigger. According to fixed effect estimator, an introduction of a new product in the period 1990-2005 will on average increase market value by 19%. Interestingly, similar with the regression results from the whole period, NCEs do not have significant

impact on the market value in the period 1990-2005, while IMDs do. This is probably due to the relatively stable and small number of NCE introductions compared to that of IMDs.

Looking at the control variables, the coefficients of cash flow to assets are positive and significant, which is line with the findings by Hall (1993). The impact of cash flow in the latter period, however, is slightly reduced compared to the period 1971-1989. As expected, the effect of higher debt leverage is negative and significant, which confirms previous findings (Toivanen, Stoneman, and Bosworth, 2002). This finding implies that high debt leveraged pharmaceutical firms are less valued than their peers with a relatively low level of external financing. The magnitude of leverage effects increases as we move from period 1971-1989 to the period 1990-2005. This finding shows that nowadays pharmaceutical firms are likely to be less dependent on external financing compared to the earlier period (1970-1989). The coefficient of industry index is negative and significant in all regressions, which indicates a negative relationship between pharmaceutical firms' market performance in our sample and the average return of all drugs firms. Note that the latter includes not only drug firms, but also, for example, biotech firms, medicine and chemical firms, and pharmaceutical preparation firms[1].

In contrast to previous findings (Hall, 1993), the coefficient of growth is not significant. This might indicate that pharmaceutical firms feed their growth mainly from R&D activities. In the period 1971-1989, the coefficients of growth of sales are negative and significant, while they are positive and significant in the second period. Looking at the whole period, the effects are negligible, perhaps as a result of the opposite results in the two periods. Assuming that we have specified the model correctly, one of the explanations of these findings is as follows. In the period 1971-1989, investors' expectations regarding the pharmaceutical firms' profitability was less optimistic than in the period 1990-2005. Prior to the 1990s, the increase in profitability due to the rise in sales was probably spent on the

[1] For details definitions of the industry portfolio we refer to http://mba.tuck.dartmouth.edu/pages/faculty/ken.french/Data_Library/det_49_ind_port.html

next period R&D, which eventually reduced the total amount for the dividend pay out. This is in contrast with the second period where investors' confidence was rising due to the vast increase of profitability. Noteworthy, this increasing optimism is probably due to the U.S. market trend in general (see figure 3.13).

Summarizing, our results show the importance of advertising and product differentiation in stock market valuation of the U.S. pharmaceutical firms. Although the R&D expenditure is much higher than advertising over the years, since 1990, the returns of advertising have become three times as high as that of R&D. In addition, product differentiation has positive and significant effects on market value. This effect is probably a result of the vast increase of IMD introductions over the years.

4.5 CONCLUSIONS

In this chapter, we examine the impact of advertising and product differentiation on pharmaceutical firms' performance. Our results emphasize the role of advertising and product differentiation in the virtuous rent-seeking behavior in the pharmaceutical industry. Despite the theoretical importance of these variables, the existing empirical studies mainly concentrated on the role of R&D in the profitability of pharmaceutical firms. Our study is important in that it provides a better understanding of pharmaceutical firms' behavior. This understanding can be used as part of policy makers and economists attempt to quantify the private returns on innovation and advertising activities in order assess their contribution to industry growth. In turn, this understanding can be a guide for strategies that aim to close the gap between private and social returns (Hall, 2000). In addition, our study also provides a possibility to test the claim of popular press that pharmaceutical firms put more emphasis on advertising than on R&D activities.

Our findings show significant impacts of advertising and product differentiation on firms' market value. In terms of expenditure, we do not find any evidence that pharmaceutical firms spend more on advertising than on R&D. After 1980, the R&D expenditure has always surpassed the advertising expenditure. However, our regression results show that

nowadays the returns of advertising have become three times as large as that of R&D. This "opposite" findings can be interpreted in several ways. First, although the R&D is higher in the absolute terms, firms might use advertising more effectively. Furthermore, the rise in R&D expenditure does not necessarily lead to the corresponding increase of investors' optimism regarding firms' innovation performance. This is perhaps due to the fact that R&D expenditure is mainly withdrawn to finance minor innovations.

As expected, product differentiation has a positive and significant contribution to firms' market value. On average, an introduction of a new drug product increases market value by 18%. The role of IMDs herein is presumably of major importance since we found that the NCE introductions do not have significant effects. Nevertheless, the magnitude of the coefficients is larger than that of IMDs.

Relating our findings to the pattern of innovation in the industry, we argue that the explosion of market value has not been the sole consequence of more innovation in the industry. The current behavior of drug companies, i.e. frequent launching of incremental drugs accompanied by effective use of advertising and the escalation of R&D expenditure, seems to get its reward in the financial market.

From the academic perspective, we show that incorporating a proxy for product differentiation can give a more complete picture of the fundamental values of publicly traded pharmaceutical companies. Although a firm valuation has been intensively studied, existing research focuses primarily on the innovation input, i.e. R&D, or intermediate output (i.e. patents). Our study complements the existing literature by including final output of innovation activities in the model, measured by the number of product introductions.

As all research, we acknowledge limitations of our results. We have a considerable number of missing values for advertising in our dataset. Therefore, our results are depending on the accuracy of our estimates on the missing values of advertising. This, however, would have been overcome if pharmaceutical companies provided data on their advertising expenditures. Hence, we recommend that the drug companies should provide information

on their advertising expenditures, aside from their administration and distribution expenditures. Additionally, information on DTC advertising can facilitate further research on the evaluation of public policy concerning advertising in the U.S. pharmaceutical industry.

In light of increasing attempts to limit consumers' exposure to false or misleading DTC advertising (GAO_1, 2006), studies on the persuasive versus informative role of DTC advertising will be an interesting and useful endeavor for future studies. Furthermore, we encourage future research to investigate the role of advertising and product differentiation at the product level. For example, one could investigate the impact of DTC advertising of a blockbuster on its sales. Such studies could give more details on the contribution of advertising. Additionally, such studies could compare R&D and advertising returns at the project level in order to assess their effectiveness. It is also interesting to generalize our findings to other high tech industries to see whether similar patterns exist.

5. PRODUCT DIFFERENTIATION STRATEGY: WHAT DRIVES LINE EXTENSIONS?

ABSTRACT

Despite the predominant existence of modified drug products, drug companies' motivation in launching product extensions has received little attention. We use a real option framework to explain companies' decisions on this issue by assuming that a product extension is a response to uncertainty both within and outside the firm. Additionally, we propose that the extension decision is influenced by brand building activities. Using the repeated events duration model, we identify several determinants that affect companies' decisions to extend or modify an existing NCE. These determinants include uncertainty regarding the firm's stock volatility, financial constraints, competitive pressure and advertising growth. We test our model by using a dataset of 335 NCE extensions in the period 1971-2005.

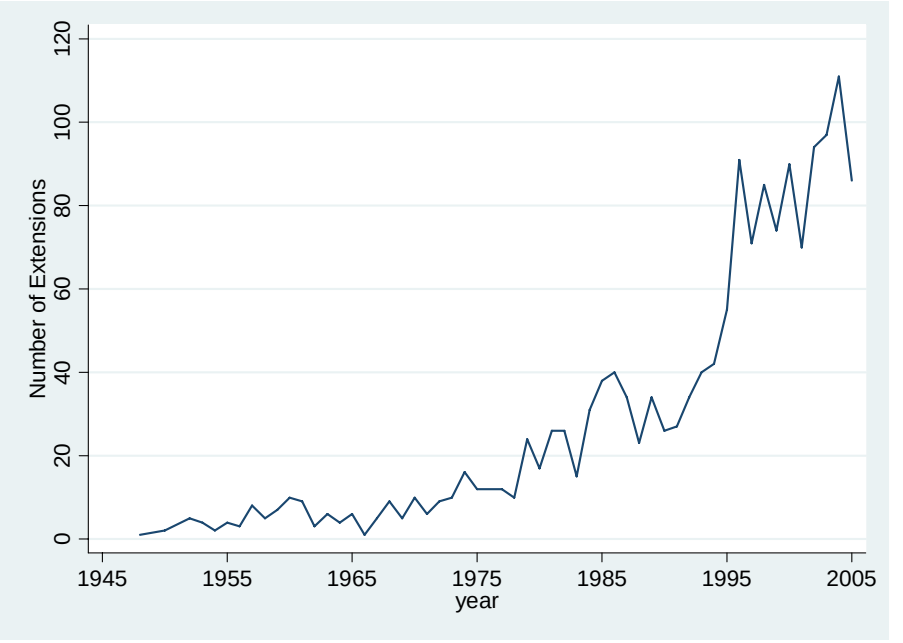
5.1 INTRODUCTION

There has been a growing concern that a substantial amount of R&D activities performed by pharmaceutical companies is not spent on new drugs for serious and life-threatening conditions, but instead focused on producing modified drugs (Public Citizen, 2001; Craig and Malek, 1995, Relman and Angell, 2002; GAO_2, 2006). Figure 5.1 presents the annual number of drug extensions performed by the pharmaceutical companies in our sample. This figure indicates that the practice of line extension has increased strongly over the past 30 years. Despite its prominent existence, pharmaceutical companies' behavior concerning line extensions is little studied. This is a peculiar state of affair considering the wide criticism on the slow growth of innovation in the industry.

From an economic point view, introducing line extensions can be an effective strategy to deter competition. Product extensions in the pharmaceutical industry can provide a low-cost and low-risk alternative to developing an entirely new drug, which is expensive and involves high uncertainty. The development of a new drug can last up to 20 years and its

cost can reach up to $ 800 millions (OTA, 1993; DiMasi, Hansen and Grabowski, 2004). The odds of successfully launching a new molecule is very small, as only one drug reaches the launch phase out of 10.000 potential molecules that are considered in the initial phase (OTA, 1993).

Figure 5.1 Annual Number of Line Extensions (1950-2005)



Next to its cost advantage, line extensions can provide pharmaceutical companies with an additional time of market exclusivity, both via patents and marketing exclusivity, as has been discussed in chapter 2. In the coming years, the threat of losing market exclusivity is significant. About $ 11 billion worth of brand-name drug lose patent protection in 2007, followed by $ 10 billion in 2008, and even more in 2009 and 2010 (Gebhart, 2006).

The benefits of a drug extension are summarized by Baichwal and Neville (2001) as follows. First, in the threat of a competitor that is about to launch a superior product, launching a drug extension that has new benefits such as reduced side effects can revive a firm's market position. Second, by using

the so called *drug delivery* system technology, drug companies can prolong market exclusivity by developing an enhanced version with therapeutic benefits. These benefits include improved efficacy or dosing frequency or new therapeutic indication.

As an example, in 1989 Biovail Inc. modified its blockbuster drug *Cardizem*, a three-times-daily cardiovascular drug, by introducing *Cardizem SR*, that has a twice daily dosage. In 1991, the company introduced another modified version of *Cardizem*, namely *Cardizem CD* that has a once daily dosage (Baichwal and Neville, 2001). As a result of this action, Biovail's revenue peaked from $ 260 million in 1988 to $ 400 million in 1989 and remained steady in 1991.

In addition, the current rebate agreement between health insurance and pharmaceutical firms provides great incentives to launch modifications of existing drugs (CBO, 2006). Medicaid, a U.S. health insurance program for low income groups, currently involves with pharmaceutical firms in a program in which firms have to enter a discount agreement in order to have their products covered by Medicaid. The level of discount is often linked with the inflation rate. When the branded drug price increases faster than the rate of inflation, firms have to offer a larger rebate. This rule, however, does not apply to IMDs. Thus, if a manufacturer wants to raise the price of a drug more quickly while avoiding the additional rebate, it can develop a new version of the drug—for example, with a different dosage or form of delivery—and introduce it at a higher price (CBO, 2006). As a consequence, this policy gives firms extra incentive to introduce modified drugs.

In this present chapter, we study companies' motivation to extend their existing NCE. The central question of this chapter is: What drives drug companies in extending their NCEs? We use a real option approach, an established framework in economic literature, to explain this behavior. We start with the premise that companies use line extensions to cope with uncertainties, both in the market place and within the companies themselves. We identify variables that represent these uncertainties on the basis of economic and marketing literature.

We arrange this chapter as follows. In the next section we discuss relevant

literature from marketing and economics on product extensions. Section 5.3 presents our theoretical framework, where we explain how real option theory can be used to model firm behavior concerning line extensions. Section 5.4 describes how we modeled a firm's decision to extend an NCE. Section 5.5 explains the data that we used and how we selected our sample. Section 5.6 presents the results of our study. Section 5.7 summarizes our findings and discusses the implications for future research.

5.2 LINE EXTENSIONS

In marketing terms, a line extension is a part of product differentiation strategy, which is also frequently referred to as proliferation strategy. This strategy includes a large number of new product introductions, enlarging product variety and creating a long product line (Connor 1981, Bayus and Pitsus, 1999). A line extension can be defined as adding up a new product to an existing product line (Kadiyali, Vilcassim, and Chintagunta, 1998). The new product that is included to the line differs from their parent product in relatively minor ways, such as type, size, quality or price.

The phenomenon of line extensions is not unique to the pharmaceutical industry; previous research has documented a highly frequent application of line extensions in other industries. For example, Aaker (1991) shows that 95% of new products in the consumer product industry are line extensions. Putsis and Bayus (2001) argue that this strategy is also common in the personal computer industry. Generally, the marketing literature acknowledges the cost advantage of line extension compared to developing a new product, which is more expensive and involves high risk of failure (Booz, Allen and Hamilton, 1980; Crawford, 1987).

Looking at the literature of line extensions within a single brand, we found that launching a product extension of an established brand provides a stock of information about the product's quality and can reduce the marginal benefit of quality-assuring advertising (DeGraba and Sullivan, 1995). This implies that line extensions enjoy lower advertising expenditures for a given level of sales (Smith and Park, 1992). In the economic literature, the motivations behind product extensions have also been studied from a theoretical perspective. Choi (1998) presented a theoretical framework of

product extension in which a company stakes its reputation as a bond for quality in using product extension as a signal for quality. Wernerfelt (1988) provides a signaling model in which a multi-product company can use its reputation as a bond for quality by using a product name for an established product when it introduces a new experience product.

Although we found quite intensive empirical literature on line extensions, the focus is merely on extensions within a single brand (Reddy, Holak, and Bhat, 1994; Swaminathan, Fox, and Reddy, 2001). Nevertheless, research on product line extension is not new. One of the first empirical studies on this topic by Connor (1981), investigated the effect of market structure on product proliferation strategy. Connor's study concluded that an imperfect market structure is related with the high levels of product proliferation. In more recent papers, some authors began to study the determinants of product line extension. Bayus and Putsis (1999) conducted an empirical study on product proliferation by taking into account both the supply and demand side. They found that the length of a product line is positively related to both demand and supply. The same authors also investigated the determinants of product line change and found that high industry barriers, high market share, and companies with short product lines are likely to increase the number of product extensions (Putsis and Bayus, 2001). Shankar (2006) used a rational expectation framework to identify reactions and anticipation to product line decisions and other marketing actions. He found that a firm is likely to engage in product line actions when its competitors changed their product line in the past when the firm's size is large, and when product price is high.

Following Bayus and Pitsus (1999), Pitsus and Bayus (2001) and Shankar (2006), our study contributes to the existing empirical literature on line extension that concentrates on product line decisions. Our contribution to the empirical literature lies on the use of financial option theory to understand companies' behavior concerning line extensions. Our highly-detailed data on drug introductions is well-suited for examining line extension behavior of pharmaceutical firms, since the introduction of modified drugs has increased substantially over the past decades.

5.3 A REAL OPTION FRAMEWORK FOR LINE EXTENSION DECISIONS

A real option is the right to undertake some business decision (McGrath and Nerkar, 2004). Option comes from financial terminology that refers to the right, not the obligation, to either buy or sell an underlying asset at a given price within a specified time. The real options framework has gained popularity in recent years in both business and economics applications. For example, Bulan (2005) investigated whether real option models can explain the relationship between firm investment and uncertainty. The study shows that higher uncertainty reduced firm incentives for investing. McGrath and Nerkar (2004) investigate a firm's R&D investment behavior in applying a second patent as the commitment to grow further in that area. They found that the impact of the first patent, firm experience, and competition influence the propensity to apply for the second patent, which shows a commitment to invest further in that area. Another study on the application of real option is performed by Quigg (1993), which examined the empirical predictions of a real option pricing model. Her model has explanatory power for predicting transaction prices over and above the intrinsic value. In marketing field, Dias and Ryals (2002) present a conceptual paper on using a real option framework in explaining brand extensions. They argued that investment in advertising increases brand equity and therefore provides a firm with an opportunity to extend the existing product line.

To apply the real option framework in the decision to extend a product, we start from the premise that a launch of a product extension is a signal of a firm's commitment to further invest in the existing product (Dias and Ryals, 2002). By using an analogy with the financial terminology, an investment in a certain product line can be compared to *buying* a call-option. This means that a firm has the right but not the obligation to make further investment or to delay or even to stop investing in that product line. Therefore, launching a line extension can be seen as *exercising* the call-option, namely that the firm decides to invest further in the existing product line.

By definition, an (real) option can only have value if there is uncertainty in the future. In other words, the decision to exercise an option depends on the agent's perception of the current period on uncertainty in the future period.

Applying this to line extensions, we assume that the decision to extend a certain product depends on companies' perception of uncertainties about the future. Based on theoretical and empirical studies, we propose that the probability of a line extension is a function of: (1) uncertainty regarding the stock market volatility; (2) uncertainty regarding financial constraints; (3) uncertainty regarding the level of competition. Furthermore, we argue that the decision to launch line extensions also depends on (4) the amount of effort that has already been invested in building a brand reputation. Below, we explain each of these drivers and propose some hypothesis on the relationship between these variables and the rate of line extensions.

5.3.1 Uncertainty Regarding the Stock's Return

By using a real option framework, Bulan (2005) studied the relationship between a firm's investment in capital ratio and a firm's uncertainty, measured as the volatility of the firm's equity return. The paper assumes that the ability to delay investment decisions is valuable when the investment is irreversible and the future is uncertain. This irreversibility stems from the fact that capital is specific at the industry and/or firm level. The study decomposed total uncertainty faced by an individual firm into its systematic and firm-specific components, and then related these uncertainty measures to the firm's investment behavior. Doing so implies that the effect of industry-wide volatility can be controlled for by firm-specific risk. Bulan (2005) found that periods of higher industry and firm-specific uncertainty are related to lower investment by companies.

In our case, we assume that when a firm faces the decision to extend a product, it has spent a considerable investment on the parent product in the previous period. In other words, we assume that the decision to launch an extension can only be made after the parent product has already been developed and launched. This implies that after having developed and introduced an NCE, pharmaceutical companies can choose whether to stop, to delay or to continue investing in the NCE's product line. We propose, that periods of higher industry and firm uncertainty will have a positive relation with the likelihood of line extensions. An option to extend offers a viable alternative in the situation of high uncertainty, especially in the pharmaceutical industry where line extensions provide a cost advantage and a potential extension of market exclusivity.

Hypothesis 1

The higher the uncertainty about to the firm's stock price, the higher a firm's likelihood to launch a product extension.

5.3.2 Uncertainty Regarding Financial Constraints

Financial constraints form a restriction to firm investments, which occurs when it lacks internal funds to finance investment and therefore it faces a higher cost of raising fund at any given amount (Cleary, Povel, and Raith, 2004). Conducting a product development project is likely to undergo financial constraints. A firm that is less constrained is more inclined to take up riskier projects, such as developing a new product. On the contrary, a firm that is more financially constrained tends to continue on the current project.

Empirical evidence on the effect of financial constraints on innovation generally points out a negative relationship between financial constraints and taking up an innovation activities. For instance, using a qualitative construct of financial constraints, Savignac (2005) found that the higher the financial constraint, the less likely a firm engages in an innovation activity. Bond, Harhoff, and Van Reenen (1999) showed that cash flows have a positive impact on the likelihood to perform research and development.

Applying this to the context of line extensions, we argue that in the face of high financial constraint, companies tend to invest in less costly and less risky projects such as line extensions. In other words, the less financial resources a firm has, the more likely it launches line extensions.

Hypothesis 2

The higher the financial constraints, the higher a firm's likelihood to launch a product extension.

5.3.3 The Level of Competition

In a highly competitive industry, consumers have more options in choosing competitive products from a number of companies than in a less competitive industry. Hendrick and Singhal (1997) argued that the ability to introduce new products faster and on time is likely to be an important source of differentiation and competitive advantage. In the empirical literature, the effect of competition on new product introductions is

generally positive. Roder, Hermann and Connor (2000) investigated the effect of market structure on product proliferation. They found that increasing competition raised the number of product introductions in the market. In their study on the computer industry, Bayus and Putsis (1999) found that an increased likelihood of expanding a product line is associated with a low concentration ratio. Their findings imply that companies are more likely to introduce line extension when competition is relatively high. In a study that used a real option framework, McGrath and Nerkar (2004) found that competition in a certain patent area has a positive association with the likelihood of applying a second patent. In other words, competitive threat stimulates companies to exercise an option by investing further in the patented innovation. Following this line of reasoning, we argue that the higher the competitive pressure, the higher the likelihood that a firm produces a line extension to protect its market share.

Hypothesis 3

The higher the competitive pressure, the higher a firm's likelihood to launch a product extension.

5.3.4 Brand Building

As has been mentioned in the previous chapter, the role of advertising has become increasingly important in the pharmaceutical industry. Dias and Ryals (2002) argued that investment in advertising increases brand equity and eventually provides a firm with an opportunity to extend the existing product line. Hence, we propose that a high growth in advertising expenditure is likely to increase the rate of product extensions in the following period.

Hypothesis 4

The higher the advertising level, the higher a firm's likelihood to launch a product extension.

5.4 METHODOLOGY

5.4.1 How to Handle Repeated Extensions

The dependent variable in our study is the rate of extension, which is measured over time until the next extension is launched. As we have time

as a dependent variable, survival analysis is the common method to apply. The traditional survival analysis assumes, however, that event times are independent. In our dataset we generally have extensions per product. Multiple extensions within one product raises three complications that traditional survival analysis does not address: (1) the order in which product extensions occur, (2) the dependence among extensions within the same product, (3) the delineation of analysis time (Kam and Indridason, 2004). Treating each extension as an independent random variable can yield misleading results. Standard errors are incorrect, it means that one implicitly restricted the influence of covariates to be the same across extensions, when in fact there might be varying effects from one extension to the next (Box-Steffenmeier and Zorn, 2000).

There are several ways to deal with these issues. The common way is to use the so called *variance corrected approach* (Wei, Lin and Weissfeld, 1989). This variance corrected approach consists of three widely used variants; the *independent increments model* (Andersen and Gill, 1982), the *marginal model* (Wei, Lin and Weissfeld, 1989) and the *conditional model* (Prentice, Williamd, and Peterson, 1981). These models are different in the way they define the risk set at each extension (Cleves, Gould, Gutierrez, 2004). Note, risk set is the collection of products which are at risk at a certain point in time and this risk set defines which product may be extended at a particular time (Box-Steffenmeier and Zorn, 2002).

In the *Andersen and Gill model* (1982), henceforth *AG model*, extensions are assumed to follow a nonhomogeneous Poisson distribution. This implies that the chance of extension for a certain product is independent of any earlier extension that occurred within the same product. Note that this assumption might be questioned if the ordering of extensions is important. Furthermore, the AG model restricts the baseline hazard rate for all order of product extensions to be the same.

The *marginal model* is based on the idea of marginal risk set. In this model, the data is treated as a competing risk dataset as if the extensions were unordered. Each extension has its own stratum and each extension appears in all strata (Cleves, 1999). The main characteristic of this model is that all observations are at risk for all extensions at all time prior to experiencing

extension. For example, the tenth extension of a certain product can occur at any time, even prior to the first, second, third, etc. events.

In the *conditional model*, a sequential ordering is imposed: a product is not at risk for a later extension until all prior extensions have occurred. The *conditional model* has two variations (Cleves, 1999). First, time to each extension can be measured from the introduction of the parent product (i.e. NCE). This variation is also called the *Conditional Elapse Time* (CET) model. In the second variation, the time to each extension is measured from the previous extension, the so called *Conditional Inter event Time* (CIT) model.

5.4.2 Model Specification

We modeled the rate of extension as a function of the several lagged covariates that were discussed in the previous sections. These were lagged of R&D growth, lagged of cash flows' growth, lagged leverage, lagged advertising growth, and lagged of competition. Note that R&D growth, cash flows growth, and leverage are measures of firm's financial constraints. Furthermore, we also related the rate of extensions to companies' expectation on the stock market's volatility (Bulan 2005). Due to considerably high correlation between industry- and firm-specific uncertainties, we dropped industry's uncertainty in our model. We specified our model as follows.

$$\ln r(t) = \lambda_0(t) + \beta_1 grR\,\&\,D_{it-1} + \beta_2 grCFA_{it-1} + \beta_3 De_{it-1} +$$
$$\beta_4 AgrAdv_{it-1} + \beta_5 C_{it-1} + \beta_6 C^2{}_{it-1} + \beta_7 NCE_{it-1} + \beta_8 \hat{\sigma}_{\varepsilon it} + \eta_{it} \qquad (5.1)$$

$r(t)$ = the hazard rate of extension
$\lambda_0(t)$ = baseline hazard rate
$grR\,\&\,D_{it-1}$ = R & D's growth at period $t-1$
$grCFA_{it-1}$ = cash flow's growth at period $t-1$
De_{it-1} = debt to equity's ratio at period $t-1$
$grAdv_{it-1}$ = advertising's growth at period $t-1$
C_{it-1} = competition at period $t-1$
$C^2{}_{it-1}$ = the square of C $_{it-1}$
NCE_{it-1} = Number of NCE launched by company i at period $t-1$
$\hat{\sigma}_{\varepsilon it}$ = company i volatility at time t

The dependent variable was the hazard rate of product extension, i.e. the rate at which products are extended at a given instant in time. The hazard rate was measured as the logarithm of time until a product extension is launched. The decision to exercise the option to extend was assumed to be made at the beginning of the year *t*. R&D growth (*grR&D*), Leverage (*De*), cash flows' growth (*grCFA*), Advertising growth (*grAdv*), and Competition (*C*) were measured as the value at the end of year *t*-1, and hence are predetermined repressors. We added variable *NCE*, which referred to the total number of NCEs that a firm launched in the previous year and the square of Competition (C^2) to investigate whether its has a non-linear relationship with the rate of extension[1].

Unlike any other covariates, we did not use the lagged variables for firm uncertainty. This was to account for the forward looking feature of stock market movement. Under the rational expectation assumption, we could not use realized values of volatility to proxy for expected volatility (Bulan, 2005). Hence, firm uncertainty represented rational expectations of the

[1] In the preliminary analysis, we found a negative relationship between competition and the rate of extension, which is in contrast with the literature. Consequently, we were curious whether competition has a non-linear effect with the rate of extensions.

variability in the company's profits over year *t*. We refer to Appendix D for more details on how we constructed our covariates

We estimated the above equation by using all four models described above; the *AG model*, *marginal model*, *CET* and *CIT model*. We allowed the baseline hazards to differ for the *order* of extensions and for the multiple extensions within the same *firm*. The latter allowed us to control for firm specific effects. As a comparison, we began with a model that only considers the first extension, i.e. henceforth the "*First model*". This model only includes the time until each product's first extension and implicitly assumes that the first extension is representative of all extensions. This is, however, a questionable assumption because it wastes possibly relevant information (Cleves, 1999).

5.5 DATA AND SAMPLE SELECTION

We defined extension as any modification or repetition of an existing NCE. Data on NCEs and extensions were obtained from the CDER database. The CDER database provides the date of approval for each drug product. We used this information to gather the data on the duration to the next extension. For details on how we processed the dataset we refer to appendix B. For financial data we used the COMPUSTAT database. We used the Kenneth French database to obtain the daily industry index[1]. For details on the variables' construction we refer to appendix D. The variable competition was obtained from the CDER database. We defined competition as the total number of total NCEs launched by competitors in the market; thus the total number of NCEs launched in the industry minus the ones of the specific firm.

We matched the financial data with the product extensions dataset which resulted in a sample on drug extensions in the period 1971-2005. Our sample did not cover the period prior to 1971 because the data on advertising expenditure was not available. As an example, Premarin, a drug product launched by Wyeth for the first time in 1942, has undergone several extensions; the first one in 1956 and the second one in 1978. We did

[1] http://mba.tuck.dartmouth.edu/pages/faculty/ken.french/data_library.html

not include the first extension, but we included the second one. Note that in *AG-*, *Marginal*, and *CET models*, the clock starts ticking when the product is launched for the first time. Consequently, we started to measure Premarin's clock in 1942. For the CIT model, the clock is reset after each extension. Accordingly, the Premarin's clock was reset to zero again after each extension. The observation was defined censored when (i) the product is not yet extended at 31-12-2005 or (ii) the firm is acquired or ended its business activities[1].

5.6 RESULTS

We found in total 556 NCEs that were introduced by companies in our sample. Until 31 December 2005, 36% of these NCEs has never been extended. This is shown in figure 5.2. The rest of NCEs had experienced in total 1203 extensions until the end of 2005. Companies in our sample began to launch line extension in 1950. The last observed line extension is in 2005. The majority of extensions occur in the 1980s as approximately 85% of the extensions were launched in the period 1980-2005. Figure 5.3 shows the annual number of drugs, which were modifications of the 356 NCEs for the period 1950-2005.

Figure 5.4 shows the order of extensions for the 356 NCEs that have been modified. This figure shows, for example, that the higher the order of the extension, the lower its frequency. For example, for the 356 NCEs that underwent the first extension, 65% of them (N=230) were extended for a second time. NCEs that underwent 18 extensions occured only three times.

[1] This applies, for example, to Mallinckordt Inc., which was acquired in 1999.

Figure 5.2 Number of Extended vs. Not Extended NCE (1939-2005)

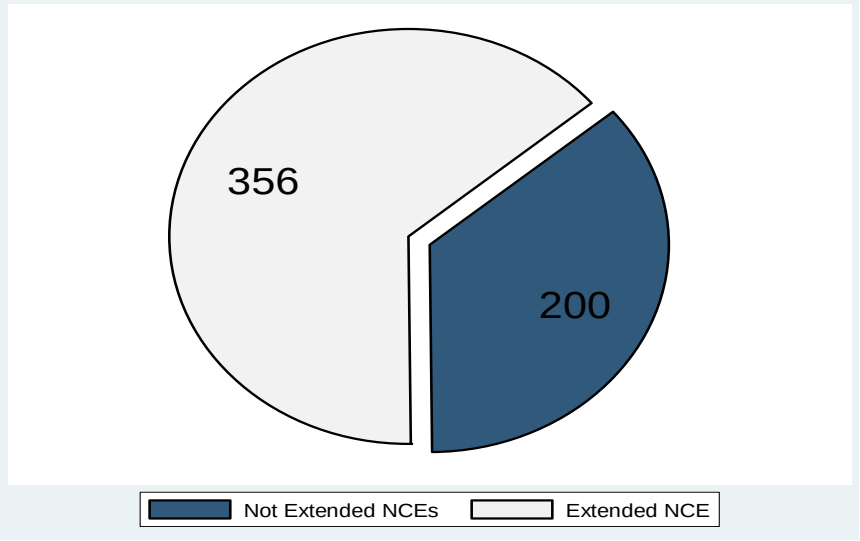


Figure 5.3 Annual Extension of NCE (1950-2005)

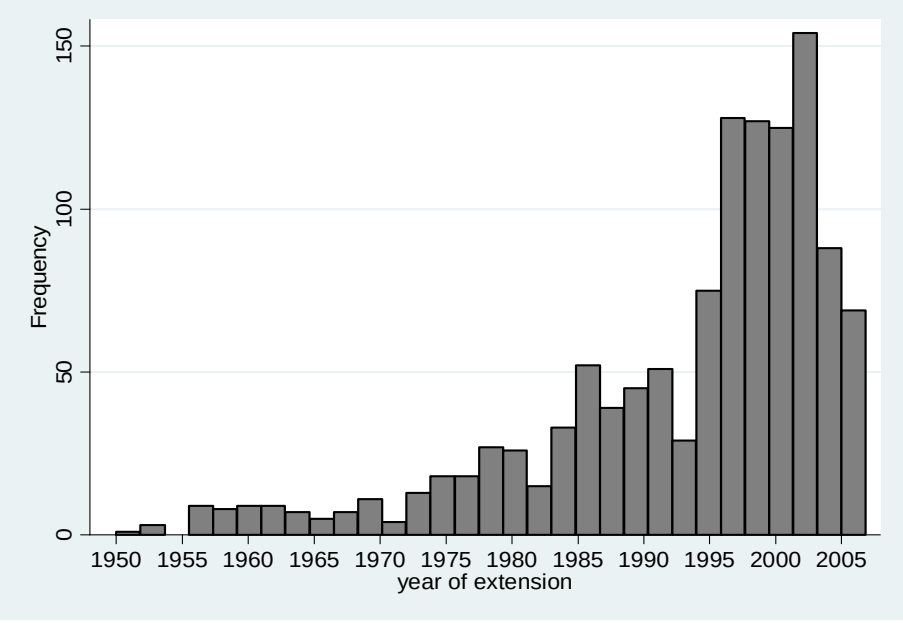
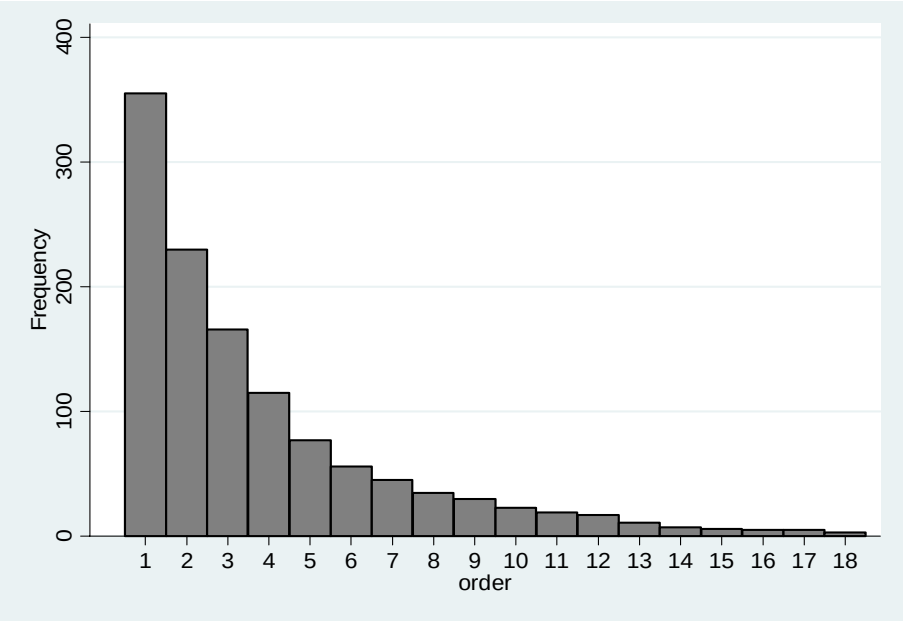
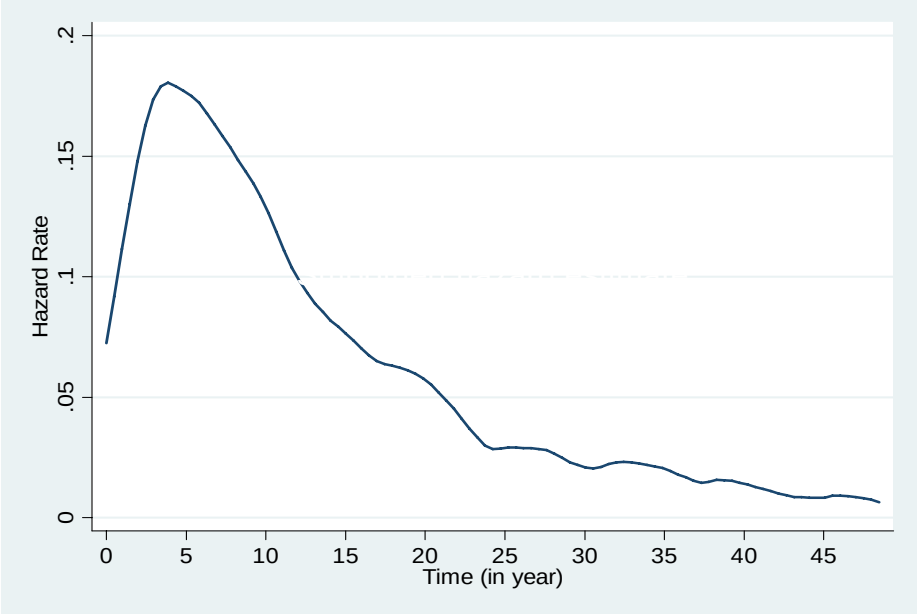


Figure 5.4 Number of Extensions (N=356)



We present two non-parametric estimates of the hazard function in figure 5.5 and figure 5.6. Figure 5.5 shows the rate of extension as a function of time for all 356 NCE launched by the companies in our sample. Note that time to each extension is measured from the introduction of parent product instead of from the previous extension (see also section 5.4.1). Figure 5.5 illustrates a high likelihood of launching a line extension within five years after the introduction of the parent NCE. The rate of extension increases sharply in these first 5 years and thereafter it gradually decreases. Figure 5.5 suggests that the companies in our sample generally intensify the introduction of line extensions within the 5 years period after the NCE's introduction, which suggests that pharmaceutical companies tend to increase the extension rate within the 5 years period of marketing exclusivity.

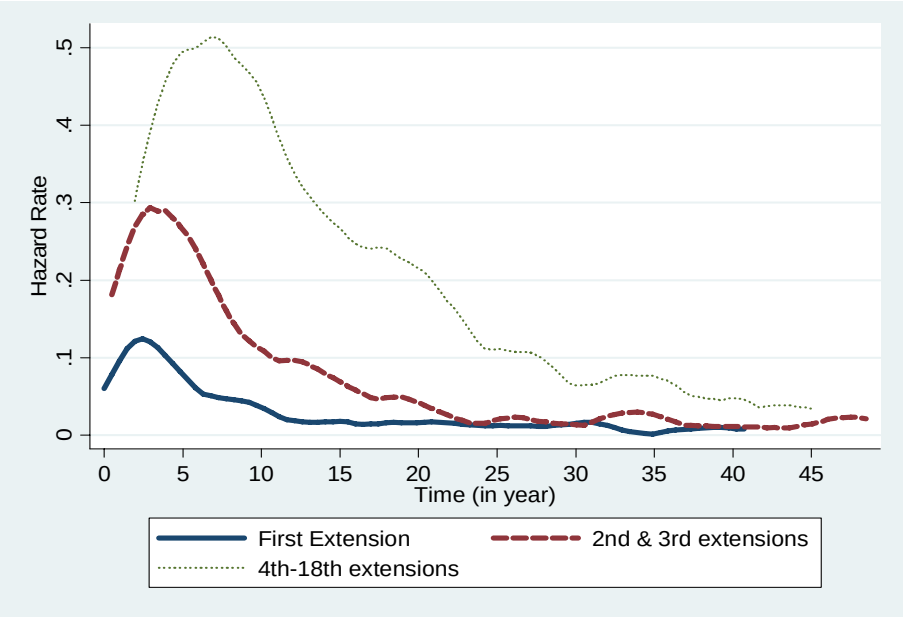
Figure 5.5 Drug Extensions as a Function of Time



In figure 5.6, we split the hazard function based on the order of extensions. Specifically, we divided line extensions into the following categories: (1) first time extensions, (2) second and third time extensions, and (3) fourth to 18th time extensions. This figure shows that the rate of the first extension of NCE (the solid line) is the highest in the first two or three years after the launch of NCE. Higher order extensions are most likely introduced within 10 years period after the NCE is launched (the thinnest line). This figure suggests that the more frequent the NCE was extended, the higher the hazard rate. For example, while the optimum hazard rate of the first extension is approximately 0.12, the hazard rate of fourth to 18th extensions can reach up to 0.5, which is almost five times faster than the optimum hazard rate of the first extension. This implies that, given that an NCE has been extended before, the chance is high that it will be extended again in the future. The numbers of observations for each category are more or less comparable; 31% of all NCEs have been modified once and approximately 35% of the NCEs has been extended for more than four times. So, about one third of all NCEs has been frequently extended. A Wilcoxon test showed that there is a significant difference of survivor functions among

the different orders of extensions (p<0.000).

Figure 5.6 Drug's Extensions Rate by Order of Extension



The remaining sample after merging the product extension data with financial data consisted of 335 NCEs. Depending on how the risk time is defined, we had 1142 to 8739 observations in our regressions. For example, regressions based on the *AG model* and *Conditional models* involved 1142 observations. Simultaneously, we had 8739 observations in the regressions based on the *marginal model*. This large number of observations was due to the assumption of this model that all NCEs had *n* chances to be extended, where *n* referred to the highest possible number of NCE extensions in the dataset (Cleves, 1999). The number of observations in the regressions that used first extension only, i.e. *First model*, was 335, which corresponds to the total number of NCEs used for the regression analysis.

The earliest extension observed in our data was launched in 1971 and the last extension was launched in 2005. Table 5.1 presents the regression estimates of the five models that were described in the previous section. The first column presents the results that use first extensions only, i.e. the *First model*; followed by the *AG model*, *marginal model*, *CET* and *CIT*

model. A log likelihood value is given for each model. This value indicates the best fitting model when we want to compare models using the same data. The model is considered to describe the data well when this value is near to zero. In terms of the log likelihood value, the *AG models* seem to be the best models as their log likelihood values are closest to zero compared to the conditional and marginal models.

In all models, the proposed positive relationship between firm's stock market volatility and the likelihood of extension behavior is confirmed. The hazard ratio is bigger than one, which indicates a positive relationship. For example, according to the *AG model*, the hazard ratio of firm's volatility is 1.55. In the *CIT model*, the hazard ratio of firm volatility is a bit lower, i.e. 1.37. The impact of firm's volatility was the highest for an NCE that was about to be extended for the first time. The hazard ratio of firm's volatility is close to 2 in the *First model*.

Regarding the effects of financial constraints on the rate of extension, our findings are mixed. As has been mentioned in section 5.4.2, we use three measures of financial constraints, namely R&D growth, cash flows growth and leverage. As expected, cash flow growth and leverage, which represent companies financial constraints, have negative relationships with the likelihood of extension. In all models, the hazard ratios of these two variables are less than zero and are all significant, except for the *CIT model*. The effect of cash flows' growth is bigger than the leverage effects. Looking at the *CET model*, for example, one unit increase of cash flows will lead to an approximately 25% decrease in the number of extensions in the next period. Furthermore, one unit increase of leverage will only lead to an approximate 7% fall in the number of extensions in the next period. Contrary to our hypothesis, R&D growth has a positive association with the likelihood of extension. Its coefficient is not statistically significant in the *AG*- and *CIT models*. In the *CET model*, an increase in one unit R&D growth leads to a 2.35 times higher level of line extensions in the next period.

Confirming hypothesis 4, the effect of advertising on the probability of extensions was positive. A higher level of advertising growth increases the rate of product extensions in the next period. In all models, the hazard ratios

are significant and are higher than one, which indicates positive relationships. For an NCE that was about to be extended for the first time, the effect of advertising growth is the largest. According to the *First model*, one unit increase in advertising growth in the previous period can increase the probability of extension about five times. When we included all extensions, the hazard ratio became much lower. For example, according to the *CIT model*, the hazard ratio of advertising growth is only 1.3.

In contrast to our third hypothesis, we found a negative relationship between extension rate and competitive pressure, measured by the number of NCEs launched by competitors. Hazard ratios of competition in all models are significant and are less than one. The *marginal model* has the lowest hazard ratio of competition of 0.78 while the *CET model* has the highest hazard ratio of 0.90. This indicates that an introduction of an NCE by a competitor in the previous period reduces the number of a firm's line extensions by approximately 10 to 22%. Nevertheless, the effect seemed to be non-linear. The square term of competition is greater than one and significant in all models. This suggests that competition reduces the chance of line extensions up to certain point; thereafter, competition seems to increase the likelihood of launching a line extension.

Our control variable, the number of NCEs launched by the firm, does not seem to affect the extension rate in the next period apart from the first model. Introducing an NCE will increase the likelihood of a first extension by 20%, as the hazard ratio in the first model is 1.2.

5.7 CONCLUSIONS

Driven by the substantial rise in the number of drug extensions in the pharmaceutical market, this chapter presents a study on companies' motivation for launching line extensions. Despite the prevalent behavior of line extensions in this industry, scholars have not given much attention to this topic. This chapter used a real option framework in which we propose some determinants that might affect companies' decisions to extend an existing NCE. Our study aims to enhance the understanding of companies' behavior concerning line extensions, which is not only important for companies' strategic insights, but also provides the stakeholders with

economic explanations, which in turn, can be used for improving the industry's policies.

Using a real option framework allowed us to make a parallel comparison between the launch of product extensions with an agent exercising a call option in a financial market. We propose that launching a line extension can be seen as a firm's response to cope with uncertainties that come from inside as well as outside the firm. Additionally, we propose that advertising activities play an important role in this situation. We used several types of repeated event models to test our hypotheses on the nature of the relationship between our proposed determinants and the rate of extension. Our expectations are largely confirmed.

Our findings show the important role of advertising in companies' decision to launch a line extension. This result provides empirical support on the existing theoretical view that advertising increases brand equity and opens opportunities for companies to launch a line extension (Dias and Ryal, 2002). We argue, therefore, that the increasing trend in advertising expenditures has strongly contributed to the rise in the number of line extensions. Besides brand building activities, companies seem to be affected by their own expectation on their stock market volatility in their decision to launch a line extension. The more uncertain a firm's perception of its stock volatility, the more likely line extensions will be launched as a response to this uncertainty.

Uncertainty regarding companies' financial constraints also seems to influence companies' decision to extend, although its impact depends on the type of the financial source. Cash flows affect companies' decisions the most. A period of low cash flow growth seems to result in a higher number of extensions in the next period. The same applies to the effect of leverage, although its impact is generally lower. These findings might suggest that line extensions provide a 'buffer' against financial uncertainties.

Contrary to our hypothesis, we found a positive relation between growth in R&D and companies' decision to extend. An increase in R&D seems to be an opportunity for pharmaceutical companies to launch line extensions. One of the explanations of this positive relationship can be due to the fact that, unlike cash flows and leverage, R&D budget is determined within firm

strategic policy. This suggests that R&D expenditure does not necessarily form a financial constraint, but R&D expenditure and how it is spent might just reflect firm policies.

Contrary to our hypothesis, we found that when competitors introduced an NCE, a firm reduces its number of line extensions in the next period. An introduction of NCEs by competitors might be a signal of superiority of the competitors toward the company. As a response, a firm might attempt to concentrate its resources on new innovative products, instead of launching a line extension. This, however, is an issue that needs further empirical testing.

This chapter contributes to the literature of product extensions by opening up a research agenda on modeling companies' behavior in product extensions. The assumption that product extensions are merely a routine does not seem plausible, especially in the pharmaceutical industry. With respect to innovation, we argue that market protection regulations influence the pattern of line extensions over the years. We have shown, for example, that the majority of extensions took place since the 1980's, the time when the Hatch-Waxman Act was implemented. Additionally, our results show that line extensions are to a large extent launched within the period of marketing exclusivity. As expected, we have shown that the introduction of line extensions were the most intensive in the period when the product was protected by marketing exclusivity.

This study is limited in several ways, which can be a topic for future research. First, our study did not show how time interacts with the variables in the model in affecting the extension rate. The test of the proportional hazard assumption[1] is rejected in our model, which indicates a potential interaction between time and our covariates. Furthermore, we used an overall measure of advertising, despite the use of product level as our unit of analysis. As this data is not available to us, we acknowledge that it would be better to use advertising data at the product level in order to

[1] This is a specification test to check whether the hazard ratio is proportional over time. The result is a chi-square value which indicates deviation from the proportional hazard assumption. In the preliminary analysis we cannot reject the null hypothesis of specification test based on Schoenfeld residuals (Schoenfeld, 1982).

measure its impact more directly. We recommend future research to exploit this research potential.

Table 5.1. Variance Corrected Models for Product Extension

Covariates	Cox Regression Time to First Event (First)	Andersen-Gill (AG)	Wei et al. (Marginal)	Conditional Elapsed Time (CET)	Conditional Intervent Time (CIT)
Firm Volatility	1.993***	1.546***	1.981***	1.585***	1.371***
	(0.307)	(0.186)	(0.261)	(0.013)	(0.118)
Cash flow growth	0.586**	0.657***	0.685**	0.765*	0.910
	(0.129)	(0.088)	(0.110)	(0.123)	(0.111)
Debt to equity ratio	0.959***	0.939***	0.894***	0.925***	0.940***
	(0.013)	(0.011)	(0.016)	(0.013)	(0.008)
R&D Growth	2.021*	1.241	2.281**	2.352***	1.267
	(0.853)	(0.284)	(0.732)	(0.547)	(0.239)
Advertising growth	5.078***	2.624**	3.731**	1.779	1.267*
	(3.157)	(1.004)	(1.939)	(0.696)	(0.657)
Competition	0.83***	0.834***	0.784***	0.897***	0.872***
	(0.032)	(0.028)	(0.029)	(0.032)	(0.026)
Competition square	1.002***	1.002***	1.003***	1.0001**	1.001***
	(0.001)	(0.000)	(0.001)	(0.000)	(0.000)
NCE	1.228**	1.070	1.157	1.096	1.069
	(0.124)	(0.077)	(0.131)	(0.111)	(0.065)
N observations	335	1142	8739	1142	1142
N subject	335	500	8739	500	1141
N extensions	167	662	662	662	662
Schoenfeld PH test (χ^2)	12.46	29.04***	256.59**	231.21***	37.00***
Log Likelihood	-374.792	-703.289	-1402.4911	-1660.7168	-1025.287

Cell entries are hazard ratios; standard errors are in parentheses. Models in the last three columns have robust standard errors (adjusted by clustering within product) and allow the baseline hazard rates to differ by the order of extensions. *p<0.05 **p<0.05***p<0.01. CIT does not have the same number of observations as CET due to splitting procedure in Stata (the time origin is different between CIT and CET).

6. DISCUSSION AND IMPLICATIONS

6.1 INTRODUCTION

In this thesis, we discuss several topics that are related with innovation performance in the U.S. pharmaceutical industry. We aim to answer the following questions. (1) What is the performance of the pharmaceutical industry in terms of innovativeness and profitability? (2) What is the role of advertising and product differentiation for pharmaceutical firms' profitability over time? (3) What are the drivers behind pharmaceutical companies' motivation to introduce drug extensions? Throughout chapter 3 to chapter 5, we provide answers to the above questions.

In chapter 1, we provide an introduction and present our motivation to conduct these studies. This motivation originates from the growing criticism and skepticism of consumers and public organizations regarding the slow innovation rate and the persistence of high return in the industry. We also present our research questions in chapter 1. Chapter 2 presents an overview on basic conditions of the industry that includes market definition and several terminologies frequently used in the industry. We also describe the Hatch-Waxman Act, a regulatory framework aimed to balance incentives for continued innovation among brand-name pharmaceutical firms with opportunities for market entry by generic firms. Finally, we discuss the major criticisms toward the pharmaceutical industry and their counterarguments.

Chapter 3 analyzes the main features of the U.S. pharmaceutical industry. We present the basic demand and supply conditions, we analyze the forces that affect profitability of a typical pharmaceutical firm, we discuss several firms' strategies, and we present the industry's performance in terms of innovativeness and profitability. Chapter 4 investigates the role of advertising and product differentiation for the stock market value of U.S. pharmaceutical firms. Chapter 5 provides a model of pharmaceutical companies' behavior concerning product line extensions.

We arranged the current chapter as follows. In section 6.2, we present the summary and main findings as well as the academic implications of our studies that were described in the preceding chapters. We present some

implications for firm strategies in section 6.3. Section 6.4 presents several recommendations for public policy and section 6.5 concludes with some directions for future research.

6.2 SUMMARY OF KEY FINDINGS

6.2.1 Chapter 2: The U.S. Pharmaceutical Industry: An Introduction

In this chapter we describe three features that characterize the modern U.S. pharmaceutical industry. First, we present several basic conditions for competition in the industry that include market definition and the different types of firms and drug products. We also describe a typical product life cycle in the industry. Second, we discuss the Hatch-Waxman Act and its two important forms of exclusivity rights to sell drug products, namely (1) patent protections and (2) *marketing exclusivity*. Finally, we take a look on several prominent criticisms addressed toward the industry and we also present their counterarguments.

Market Definition and Terminology

Pharmaceutical companies perform business activities concerning research, development, and the marketing of drugs that aim to improve the well-being of patients. Generally, pharmaceutical companies can be classified into two groups: brand-name companies and generic companies. The former group concentrates on research and development of new innovative drugs or develops new drugs from existing drugs. The drug products produced by this group of companies are often referred to as branded drugs, as they are often patented. The latter group of companies produces imitations of existing drugs, the so called generic drugs. I this book, we use the terms firms, pharmaceutical firms, innovative firms, and research-based firms interchangeably to refer to brand name pharmaceutical firms.

Brand name drugs can also be further divided in drugs whose active ingredients have never been introduced before, the so-called NCE (*new chemical entity*) and drugs which are modifications of existing NCEs, the so-called IMDs (*incremental modified drugs*).

Other important terms are breakthrough and me-too drugs. A first drug in a new (sub)-market is called a *breakthrough drug*, which has significant

features such as, for example, reduced side effects compared to the existing drugs in this market. *Me-too drugs* are drugs that have a different chemical entity albeit with a similar working as breakthrough drugs.

Blockbusters drugs are drugs that have a revenue of more than $ 1 million. Due to their size, pharmaceutical firms depend largely on blockbusters. The typical *product life cycle of a drug* starts with its introduction, followed by generating revenue, reaching maturity and eventually decline as its patent expires and generic competitors enter the market.

The Hatch-Waxman Act

Prior to the 1980s, generic companies had to follow a strict procedure in order to achieve a drug approval. This procedure was similar to that of applying for brand-name drugs. As a result, the number of generic drug approvals was small in that period. In order to improve this situation, the Hatch-Waxman Act was passed by the Congress in 1982. This Act eliminated the requirements for generic companies to repeat the procedure that had been performed by brand-name companies. In exchange, the Act provided brand-name companies with various marketing exclusivities, which are forms of exclusivity rights that enable a brand-name firm to sell its product exclusively during a certain period. Together with patent arrangements, marketing exclusivities provide firms with opportunities to earn back the expensive cost they made to develop a new drug. The implementation of the Act has lengthened the effective patent terms that were previously reduced due to the increasing regulatory requirements concerning drug approval. In addition, in order to stimulate generic entry, the Act grants the first generic alternative a period 180-days exclusivity.

Major Criticisms and Their Counterarguments

Innovation, productivity and profitability form the core targets of criticism on the industry. Pharmaceutical companies are claimed to mainly concentrate their resources on incremental innovations and less on breakthrough medicines despite the spur of public funding into the industry. As a result, the number of innovative drugs is small. Compared to other high tech industries, the productivity of the pharmaceutical industry is one of the lowest, despite the escalation of R&D expenditure. At the same time,

the industry's profitability has claimed to be one of the highest in the U.S.

These criticisms, however, have been attacked for their oversimplification. First, conventional productivity measurements can be misleading because a drug introduction today is a result of yesterday's R&D activities. Second, the criticisms do not take into account the fact that the quality of drugs is probably increasing over the years. Conventional measurements without giving quality weights are likely to underestimate industry innovation performance. Third, the benefit of me-too drugs and modified drugs are often underestimated. These products offer varieties that probably increase consumers' welfare. Finally, developing a new drug is highly risky and can only be compensated with an attractive rate of return. Indeed, it is argued that the profit rates in the industry tend to exceed the risk-adjusted cost of capital by only modest amount.

6.2.2 Chapter 3: The U.S. Pharmaceutical Industry: An In-Depth Analysis

Chapter 3 provides an industry analysis that includes the discussion of the following topics. First, we describe the basic demand and supply conditions of drug markets. Second, we discuss forces that affect the profitability of a typical pharmaceutical firm. Third, we present several firm strategies that have been performed in the past in order to deter generic competitors. Fourth, we discuss industry performance in terms of innovativeness and profitability. This chapter aims to answer the first question of this thesis, namely: What is the performance of the pharmaceutical industry in terms of innovativeness and profitability?

Demand and Supply Sides

The demand side of pharmaceutical markets is characterized by the separation of consumer, decision maker, and payers of drug products that hardly refer to price. In addition, it is argued that consumers and doctors show persistence habit prescriptions. The demand is, therefore, relatively price inelastic; price is likely to be a weak indicator of drug products. The supply side is characterized by relatively low manufacturing cost but extremely high fixed cost, a situation in which a patents regime is argued to be necessary.

What Forces Affect Profitability of a Typical Pharmaceutical Firm

We use a five-forces analysis to identify features that affect competition in the pharmaceutical industry; *internal rivalry*, *barrier to entry*, *substitute threat*, and *supply and buyer power*.

The *internal rivalry* among pharmaceutical firms is relatively low due to several factors. First, it is an oligopoly market; there are only few players in each sub-market. Second, drug products can be differentiated in various dimensions such as new indications, new dosage, new combination, or new formulation. Product differentiation, accompanied by effective advertising, enables firms to deter competition. Additionally, patents and marketing exclusivity allow firms to set prices higher than the competitive level. The high potential growth of demand for drug products also contributes to the positive expectation of profitability.

The high R&D and advertising expenditure, high degree of product differentiation, and patent regimes provide an effective *barrier to entry*. Nevertheless, the competition is relatively intense among major pharmaceutical firms, where the possibility to "invent around" the existing patents somewhat limits the monopoly positions.

The biotech era is considered to pose a threat of *substitute products*. Some argue that the advances in biotechnology act as a disruptive innovation, which can overturn the existing chemical based drug industry. Others argue, however, that this threat is insignificant. Additionally, pharmaceutical firms have a generally low degree of *supplier power*; raw materials, technology and high quality labor are relatively easy to obtain. However, there is a concern of increasing labor wages due to the fast rate of R&D expenditure in the industry (CBO, 2006).

Table 6.1 provides a summary of the current and future effects of the five-forces described above for pharmaceutical firms.

Table 6.1 Five-Forces Analysis of a typical drug market

Force	*Threat to Profits*
Internal Rivalry	Medium
Entry	Medium
Substitute/complement	Low, but is expected to increase in the future due to biotechnology revolution
Supplier Power	Low, but there are concerns in increasing real wages of researchers
Buyer Power	Low, but is expected to increase due to increasing health care costs

Pharmaceutical Firms' Strategies

We show that various strategies of pharmaceutical firms aimed to deter generic competition. These include legal and marketing strategies and are often used simultaneously. First, pharmaceutical companies can apply for a new patent just before the patent of a certain drug is expired. In the past, this conduct has led to a substantial extension of the exclusivity period. Second, brand-name companies often arranged settlements with generic companies, in which brand-name companies paid generic companies to stay out of the market. Third, and by far the most frequently used, we show that the current regulations enable firms to lengthen market exclusivity by launching various modifications of existing drugs. We illustrate that despite its idealism, the Act contains loopholes that have several counterproductive effect on both innovation and competition.

What is the performance of U.S. the pharmaceutical industry in terms of innovativeness and profitability?

Using new evidence and an alternative measure, we provide the following indications on the innovativeness and profitability in the pharmaceutical industry.

- *How innovative is the pharmaceutical industry?*

We show that the incremental drug products have dominated the market. At the same time, the contribution of innovative drug products is small.

Productivity has also decreased over the years. The increase in R&D spending does not seem to match the number of drugs approval. We show that the number of NDA introductions per billion dollar spent on R&D has decreased significantly in the past 50 years. Between 1956 and 1960, the industry succeeded in introducing 200 to 300 NDA approvals per billion dollar R&D. In contrast, in the last 15 years the industry produces approximately only 20 NDAs per billion dollar R&D.

- *How profitable is the pharmaceutical industry?*

Unlike existing research, we use stock market value as an indication of profitability of pharmaceutical firms. We demonstrate that the average market value of companies in the pharmaceutical industry is higher at all periods compared to companies from other industries. This gap has become larger in the last 20 years. In addition, we show that the industry's return has also increased strongly in the past two decades.

Other Considerations: Dynamic Efficiency

In general, we found several indications that support the current criticisms and we will now mention several factors that might have contributed to this phenomenon. First, the inelastic price due to the separation at the demand side has slowed down the competition. Second, the regulations have several loopholes that have not been beneficial for the allocation of innovation resources. Third, perhaps distinctive to the pharmaceutical industry, the important role of advertising and product differentiation, accompanied with the escalation of R&D, have provided an effective barrier to entry that might have worsened competition. As a consequence, health care cost is expected to continue rising in the future and the claim on the slow innovation rate is here to stay.

However, taking into account a dynamic approach that considers a long term innovation path can give a more balanced view. It is extremely difficult to determine the socially optimal amount of R&D. It is argued that the acceptable innovation rate can co-exist with the current performance of the industry. We provide the following explanations for this.

- *High return compensates high cost of capital*

One argument against the current criticisms is that the high profitability in the industry might just reflect the high cost of capital in developing new drugs. The long and uncertain drug development process is perhaps a unique feature of the industry and makes it relatively more risky than any other industries. For example, it is argued that outside financing is relatively more difficult to obtain in this industry. Therefore, the increasing cost of developing a new product and high risk associated with it must be compensated with relatively high returns.

- *Slow adjustment of R&D toward growing demand*

It is argued that the current low R&D output per dollar is likely part of profit maximizing behavior as anticipation to strong consumer demand. A high demand can push firms to invest to the point beyond diminishing marginal returns. Past studies on various industries showed that decreasing R&D output has been negatively associated with increasing R&D expenditure, which is indeed the case in the U.S. pharmaceutical industry. These studies argue that once the R&D growth slows down, the R&D productivity will recover, which is part of profit-maximizing behavior in a well-functioning market.

Based on the above discussion, we argue that any change in public policy must be a result of a careful consideration in order to keep the innovation intact.

6.2.3 Chapter 4: The impact of Advertising and Product Differentiation on the Stock Market's Valuation of Pharmaceutical Companies

In the past two decades the market valuation of pharmaceutical companies has increased substantially. Criticisms argue that high profitability is a consequence of escalation of advertising expenditure and an increasing amount of resources devoted to develop modified drugs. In this chapter, we investigate the impacts of advertising and product differentiation on the pharmaceutical firms' market value. Especially, we examine whether there has been a change in the pattern of returns of these variables over time. In addition, this study gives an opportunity to test the claim that pharmaceutical firms put more emphasis on advertising than on R&D.

What is the impact of advertising on the stock market value of pharmaceutical firms, and how does it compare to that of R&D?

In terms of total expenditure, we find little evidence that pharmaceutical firms spend more on advertising than on R&D. However, we show that the role of advertising has become more important than that of R&D. Despite the rise of R&D expenditures in the period under study, nowadays the R&D's return is three times lower than that of advertising. This suggests that pharmaceutical companies might use advertising resources in a more effective way than their R&D resources.

What is the impact of product differentiation on the stock market value of pharmaceutical firms?

The rise in drug approvals over time seems to get its reward in the financial market, which is shown by a significant relationship between product introductions and firms' market value. On average, an introduction of a new drug product increases market value by 18%. The role of IMDs in this is presumably of major importance. We found that NCE introductions do not have significant effects. Nevertheless, the magnitude of the NCE coefficients is larger than that of IMDs. The non-significant impact of NCE introductions might be due to the relatively small number of NCEs that were introduced during the study period compared to the number of IMDs.

What are the academic implications?

First, our approach enables us to investigate simultaneously the return of various intangibles assets of pharmaceutical firms that include R&D, advertising and product differentiation. Doing so allows us to compare, among others, the pattern of advertising return with that of R&D over time.

Second, we are one of the first to study the impact of various intangible assets such as innovation, brand names and product introduction on the U.S. pharmaceutical firms' market value over a long time period. Despite their valuable contributions, studies on the return of R&D in the pharmaceutical firms cover relatively short period of. The relatively long study coverage enables us to asses whether there has been a shift in the patterns of the return of various assets of pharmaceutical firms. Furthermore, by examining these returns over a long time period we can

gain a better understanding in the pharmaceutical firms' behavior. This understanding can eventually be used to reduce the gap between private and social return.

Third, studies on the R&D return in the pharmaceutical industry generally use accounting measures such as profits, sales or cash flows. The time lags between the initial R&D decision and its final output in the form of new drug products provide a limitation in measuring the direct impact of R&D on firms' profitability. Our approach leaves the valuation of firms' strategic decision, including R&D, advertising and product differentiation strategies, to the financial markets.

Finally, we show that incorporating innovation output can give a more complete picture of the fundamental values of publicly traded pharmaceutical companies. Although firm valuation has been intensively studied, existing research focuses primarily on the innovation input, i.e. R&D, or intermediate output (i.e. patents). Our study complements the existing literature by focusing on the final output of innovation activities, measured in the number of product introductions. We argue that incorporating product introduction in the market valuation model can improve our insights on the return of innovation activities.

6.2.4 Chapter 5: Pharmaceutical Companies' Behavior Concerning Product Line Extensions

Despite the predominant existence of modified drug products, drug companies' motivation in launching product extensions is little studied. This is a curious state of affairs considering the wide criticism on the slow growth of innovation in the industry. We investigate the determinants of line extension by using a real option framework. By doing this, we assume that launching a line extension can be seen as a firm's response to uncertainty that comes from within as well as outside the firm. These uncertainties include factors such as stock price volatility, financial constraints, and competition. We also argue that advertising acts as a brand building activity that provides a firm with an option to extend existing products in the next period.

What are the determinants of the launch of line extensions?

This study shows that a positive growth of advertising and an increasing uncertainty regarding firm's stock price volatility increase the propensity to launch line extensions. Second, we found that cash flow and leverage growth act as financial constraints to launching line extensions. A period of low growth of these variables is followed by a lower rate of extensions. However, in contrast to our hypothesis, R&D expenditures do not constrain the extension rate. Our findings show that high growth of R&D expenditure increases the likelihood of a line extension in the next period. This is perhaps due to the fact that R&D expenditures are determined to a certain extent within companies strategic decisions. Financial resources such as cash flow and leverage are influenced by firm's revenue and firm's ability to attract external financing.

The findings on the effect of competition on the propensity to extend are mixed. We found a non-linear relationship between competition and the rate of extension. In contrast to our expectation, the increase of competition lowers the rate of extension, albeit up to a certain point. Thereafter, the competition has a positive relationship with the rate of line extensions. We think that this non-linearity is due to firm's perception of competition. If the competition pressure is relatively low, a firm might use this opportunity to capture the market by differentiation activities such as line extensions. However, when the competitive pressure becomes stronger, the firm will focus more on launching innovative products and therefore the rate of line extensions is reduced. This, however, is an issue that requires further empirical testing.

What are the academic contributions?

This study contributes to the existing research by opening up a research agenda on modeling a firm's behavior concerning product extensions by using a real option framework. The pharmaceutical industry provides a suitable setting for line extension study due to the predominant existence of line extensions in this market. We provide new empirical evidence for the application of real option theory in explaining line extension behavior.

6.3 IMPLICATIONS FOR FIRM STRATEGY

We list several implications of our studies for firm strategies. The following strategies should not be considered as being independent from each other. Instead, we argue that they are often simultaneously implemented and they can strengthen each other's effects.

6.3.1 R&D based strategies

High R&D expenditure is one of the features of the pharmaceutical industry and is likely to be so in the future. *Strategies based on R&D activities* will maintain an important role in the future. Noteworthy, higher R&D expenditure does not automatically lead to higher performance if the firm is unable to deliver successful products that are not readily imitable and imperfectly substitutable (Yeao and Roth, 1999). Resources should be concentrated on firms' therapeutic specialization. Henderson and Cockburn (1994) argued that successful drug projects are related to a firm's unique disciplinary expertise, which is largely tacit. They also argue that firms can increase the chance of successful new products by facilitating information across the boundaries of the firm and by enhancing information flows between scientific and therapeutic classes within the firm. At the same time, firm can sustain performance by expanding existing therapeutic categories into new emerging research areas (Yeoh and Roth, 1999).

6.3.2 Strategies focused on Lengthening the Product Life Cycle

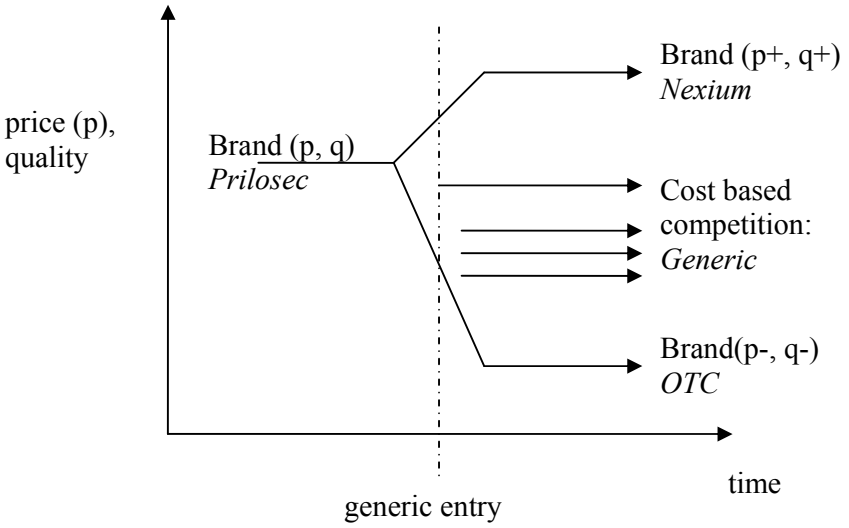
Despite the emphasis on radical innovations withinin management research on pharmaceutical firms (Yeoh and Roth, 1999; Sorescu, Chandy, and Prabhu, 2003), we propose the importance of a complementary relationship in increasing firm performance. We argue that managers should focus on *strategies on lengthening the product life cycle*, instead of thinking in terms of each category independently. The small odds of bringing new, successful blockbusters and the threat of patent expiry of existing blockbusters are the main driving forces for enhancing the product life cycle. Within this framework, drug delivery technology can be a powerful in revitalizing the existing drug products. It is argued that this technology makes medicines more convenient and acceptable to patients by, for example, simplifying the dosing regimen and improving administration (Baichwal and Neville, 2001).

In light of lengthening the life cycle of drug products several strategies can be used, which include *advertising and product differentiation strategies*, *patent and legal strategies*. We expect that pharmaceutical firms will maintain and strengthen legal strategies in the future concerning patent infringements from generic firms. Despite the increasing legal costs, pharmaceutical firms have accumulated their knowledge and capabilities throughout the years, which can increase the chance of future success on patent infringement. Furthermore, this strategy is worth its cost due to the high stake involved. Nevertheless, we argue that firms can benefit more from a combination of marketing strategies; i.e. advertising, product and pricing strategies, which will be summarized in the next section.

6.3.3 Marketing Strategies: Advertising, Product and Pricing Strategies

Pharmaceutical firms can implement various combinations of marketing strategies to limit the competition from generic firms. Figure 6.1 illustrates a successful marketing strategy conducted by AstraZeneca, which is also briefly discussed in chapter 3. In the face of patent expiry, Astra Zeneca launched a low cost over the counter (OTC) version of Prilosec. Simultaneously, the firm launched Nexium, with a slightly higher marginal benefit than Prilosec. Nexium was sold with much higher price than Prilosec and other generic versions. The intensive advertising helped promoting the brand recognition of Nexium. In 2003, Nexium had the highest DTC advertising wih more than $200 million (Gebhart, 2004).

Figure 6.1 Combinations of Marketing Strategies (Jain, 2006)



As concluding remarks, we argue that the pharmaceutical firms cannot survive without truly innovations. Despite the escalation of the number of modified drug products, there is a limit of gaining competitive advantage from modified firms in the pharmaceutical industry. First, from a practical point of view, firms can have at maximum a 14 year patent protection. Any modified drugs launched after this period will not be granted marketing exclusivity. Second, from a strategic point of view, a pharmaceutical firm is not only threatened by generic competitors, but also, to a large extent, by other research-based pharmaceutical firms. Launching a high quality NCE might be the most powerful strategy against this threat.

6.4 IMPLICATIONS FOR PUBLIC POLICY

Although our indications on industry performance show relatively poor performance, taking into account a dynamic approach that considers long term view gives a more balanced view. Nevertheless, we point several directions in which current policies can be improved. We focus our attention on improving the quality and the flow of information, combined with the assessment of loopholes of the current regulations. These two are

interconnected; effective regulations depend to a large extent on access to high-quality information. Although costs for providing such information are high, we argue that it can eventually improve industry performance.

Access to high-quality innovation performance of drug products is useful for several reasons. First, giving more accurate weights to existing drug products can provide a better judgment on current innovation performance and productivity performance. Access to information on drugs can also improve information flow among patients, doctors, and health insurance, and eventually drug firms. A prescription decision that is based on high quality and easily obtainable information can encourage choosing the best quality drug products in relation to price. In addition, access to this information can provide alternatives other than the existing information from pharmaceutical firms, of which its impartiality is sometimes questioned (Scherer, 1970). As decision making will be more efficient, both based on the quality price of drug products, it provides firms with a more accurate signal about the relative value of different drug treatments. Better signals would lead to greater efficiency in the use of drug treatments as well as in the research and development of new treatments (CBO, 2006). In addition, policies on patent grants, marketing exclusivity and rebate programs can benefit from this information.

6.4.1 Implications on Policies on Patent Grants and Marketing Exclusivity

In chapter 3, we show that pharmaceutical companies have frequently applied strategies within the legal framework to keep generic competitors away from the market. Additionally, drug markets are flooded with me-too drugs and modified drugs, probably at the expense of resources that could be devoted to develop breakthrough drugs. We argue that the current regulatory framework can be improved in order to give better incentives that eventually lead to a higher innovativeness in the industry. We therefore propose a policy that strongly discriminates between innovative and less innovative drug products. This can be realized by giving longer market exclusivity to a highly innovative drug product than current regulations offer. A discriminative incentive based on innovation can be applied to the NCEs as well as the IMDs that are based on clinical investigation. Remember that the current regulatory framework grants all

NCEs a five-year period of marketing exclusivity and grants all improvements based on new clinical investigations with three years marketing exclusivity. We propose that breakthrough NCEs should be given a higher reward than me-too NCEs. The same applies to IMDs based on clinical investigations. As has been shown in the previous section, clinical investigation exclusivity can be controversial. It has been granted for slight changes in, for example, dosage form and for changes in the relatively minor ingredient of drug products. We argue that a slight modification such as changing the dosage form should be given a smaller incentive than, for example, new clinical investigations that offer new indications of an existing drug, assuming that the former involves less thorough clinical studies.

A similar concept can be applied to the process of patent grants. Not all inventions and innovations are worth granting a patent. Waldman and Jensen (2001) argue that some innovations are patent-dependent and others are not; that is, some technology would become available just as quickly, or even more quickly, without a patent system. There is variety of reasons why many high-technology innovations would be developed without patents. First, many inventions and innovations result from human curiosity and genius. Such inventions are driven primarily by a need to understand. Second, sufficient economic incentives for inventions and innovation often result from first-mover advantages or an ability to move rapidly down a learning curve. Third, complementary investments in marketing and service can provide sufficient protection from competition for new inventions and innovations. Finally, secrecy may provide better protection against imitation than patents because with patents protection the new technology is made public, whereas with secrecy competitors are prevented from gaining insights into the new invention or innovation.

In line with the above framework, we argue that granting a certain category of pharmaceutical innovation can actually worsen the rate of innovation. For example, while patenting the process of producing probably increases social value, patenting a chemical product does not. The rationale behind process versus product patents is that the same chemical product can be obtained by different processes and methods and even starting from initially different material and components (Boldrine and Levinee, 2007). Indeed,

modern pharmaceutical industries in countries where patents are fewer and weaker have had faster innovation rates than countries such as the U.S. (Boldrine and Levinee, 2007).

Nevertheless, it is not realistic to implement drastic changes toward the current patents system in the industry. However, we believe that the current patent regime should be revised by reducing or even eliminating exclusivity rights for innovations that are considered not worth granting. Brand loyalty, through advertising and product differentiation perhaps provides an effective protection on 'minor' innovations (Waldman and Jensen, 2001). We emphasize, however, that access to quality information regarding drug characteristics can facilitate such policy.

6.4.2 Implications for Rebate Policy

As we have mentioned in chapter 5, rebate agreement between health insurance organizations and pharmaceutical firms has given incentive for firms to launch modified drugs. This example shows how firms' investments decisions depend not only to market forces but also to public policy—sometimes in unanticipated ways (CBO, 2006). We argue that a change in current rebate policies that aims to stimulate high innovative drug products is considered necessary. An access to information of the quality of drugs can facilitate this policy change.

6.4.3 Disclosure of Information of Advertising

Another type of information whose availability can be beneficial for industry performance is the disclosure of information on R&D and advertising expenditure. We have shown in chapter 4 that the advertising expenditures of pharmaceutical companies have increased tremendously. The lift of the direct to consumer (DTC) advertising prohibition in 1997 has contributed to this phenomenon (GAO_1, 2006). In addition, we have shown that the return of advertising on pharmaceutical companies is significant and even higher than R&D expenditures. Curiously, the pharmaceutical companies have not provided data on their advertising expenditures for a rather long period of time. Therefore, we propose a policy that requires pharmaceutical companies to disclose advertising expenses. This not only can improve public attitudes, but it can also improve the quality of future research on the industry.

In line with GAO current recommendations (GAO_1, 2006), we argue that the authorities should also evaluate their regulations on the policy of DTC advertising. Advertising in this industry is controversial, because it does not only have an informative role, but also a persuasive role (Commanor and Wilson, 1979).

6.5 SUGGESTIONS FOR FUTURE RESEARCH

We provide several suggestions for future research that are derived from the empirical studies in this dissertation. These suggestions are often direct consequences of our studies' limitations. Some suggestions concern new questions that rise from the findings of our research. Finally, we provide a general idea for future research that looks at the innovation in the pharmaceutical industry in general.

First, our indications of product innovation are relatively simple and provide opportunities for improvement. The distinction of NCEs versus IMDs is a crude indication of innovation, which provides room for improvement. For example, one can further separate NCEs into breakthrough drugs and me-too drugs. This classification requires a thorough examination of each therapeutic category to which the NCEs belong; a demanding task that requires insights from a multidisciplinary team.

Despite the vast increase of studies on a structured, rational approach to prescription, there is still a weak relationship between the cost effectiveness of lifesaving programs and their implementations in the U.S. (Neumann, 2004). Therefore, we suggest more studies on factors that might influence the diffusion of rational prescription approaches. Results of such studies can improve the adoption by doctors, patients and health insurance organizations of more rational prescription behavior that maximizes the value of drug products related to their price.

Third, we recommend more research on the industry's innovation productivity. The investigations can use several indications of productivity to improve the reliability of the productivity construct. For example, besides the number of drug approvals, future research can use weighted

patents and weighted measurements of the quality of drugs with respect to innovativeness. In addition, productivity in human capital can provide new insights on this issue. For example, future studies can also assess the quality of labor measured through indicators such as level of education and professional experience, and relate them to productivity measures.

Fourth, future research could validate our studies by using more accurate advertising data, provided that the data on advertising will be available in the future. Concerning advertising activities, a topic for future research could be the role of advertising in the industry. Research that investigates the direct effect of advertising on the pharmaceutical industry's innovation can provide valuable insights. Instead of looking at the aggregate level as we did, another line of research in this area can be directed at the product level. For example, one can relate the line extension of a blockbuster product to the advertising that is associated with it.

As a final remark on future research in general, we invite more researchers to conduct studies on the area of innovation in the pharmaceutical industry. The increasing availability of datasets on innovation in the pharmaceutical industry combined with the ever increasing progress in information technology provides a great potential for high quality research.

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APPENDIX A: GLOSSARY OF TERMS[1]

Active ingredient is any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention disease, or to affect the structure or any function of the body of human or animals.

ANDA means Abbreviated New Drug Application, an application submitted to FDA for approval to market a generic version of an already approved drug. ANDA contains data that when submitted to the FDA, provides for the review and ultimate approval of a generic drug product. Generic drug applications are called 'abbreviated' because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, a generic applicant must scientifically demonstrate that its product is *bioequivalent* (i.e. performs in the same manner as its relevant brand-name drug). Once approved, an applicant may manufacture and market the generic drug product to provide safe, low cost alternative to the U.S. consumers.

Bioequivalent is defined as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Brand-name drug is a drug marketed under a proprietary, trademark-protected name.

Breakthrough drug is a first drug introduced in a (sub) therapeutic market that has distinct advantage(s) compared to the existing ones.

Clinical trial is a study that evaluates new drug or other interventions on patients in strictly scientifically controlled settings, and are required for regulatory authority (in the USA, the FDA).

Drug delivery is a term that refers to the delivery of a pharmaceutical

[1] This appendix is based on information provided by FTC's study (2002), CDER frequently asked questions (http://www.fda.gov/cder/ob/faqs.htm), Parker & Manning (2002), and Wikipedia

compound to humans or animals.

Efficacy is the ability to produce a desired amount of a desired effect; it indicates that the effect of a given intervention (e.g. intake of a medicine, an operation, or a public health measure) is acceptable. 'Acceptable' in that context refers to a consensus that it is at least as good as other available interventions to which it will have ideally been compared to in a clinical trial.

The **Federal Trade Commission** (or **FTC**) is an independent agency of the United States government that aims to promote consumer protection and the elimination and prevention of anticompetitive business practices.

Generic drug is the same as a brand-name drug in dosage, safety, strength, how it is taken, quality, performance, and intended use. Before approving a generic drug product, FDA requires many rigorous tests and procedures to assure that generic drug can be substituted for the brand-name drug. The FDA bases evaluation of substitutability, or therapeutic equivalence, of generic drugs on scientific evaluations. By law, generic drug product must contain the identical amounts of the same active ingredient(s) as the brand-name alternative. Generic drug can be expected to have equal effect and no difference when substituted for the brand-name product.

Hatch-Waxman Act or Drug Competition and Patent Term Restoration Act is an complex combination of patent and regulatory laws. Under the act, brand-name drug applicants are encouraged to obtain FDA approval for drugs through patent term extensions and market exclusivity. This Act also facilitate generic applicant by awarding *180-days exclusivity* to the first generic entrant in the market.

Market Exclusivity is a form of market protection granted by FDA. It prevents the agency from approving another company to market a product with the same active ingredient for a specified period of time. Under the Hatch-Waxman Act, there are five types of marketing exclusivity: (1) five years given for new compounds, (2) three years for new uses of an existing compound, such as new indications, formulations, or combinations, (3) 180-days for the first generic entrant of a specific NDA, (4) seven years for drugs that treat rare disease, and (5) 6-months for pediatric studies.

Me-too drugs is an a NCE drug which has a sight variations on the existing drugs. It has similar therapeutic working with the first NCE introduced in the market, but differs in chemical compound. Because it has a new compound, it is rewarded 5 years NCE exclusivity, the same period as a breakthrough drug.

New chemical entity (NCE) means a drug that contains no active compound that has been approved b FDA in any other application.

New clinical investigation is an investigation in humans, the results of which (1) have not been relied upon by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety in new patient population and (2) do not duplicate the results of another investigation relied upon by FDA to demonstrate a previously approved drug's effectiveness or safety in a new patient population. A clinical investigation that provides a 'new' basis for approval of an application can qualify for exclusivity. In this context, 'new' is intended to convey a lack of prior use of a clinical investigation rather than any temporal requirement.

New Drug Application (NDA) means New Drug Application. Pursuant to the FDA, a brand-name company seeking to market a new drug product must first obtain FDA approval by filling an NDA.

Paragraph I certification means a certification that a generic applicant seeks FDA approval of its ANDA for a relevant NDA for which no patent information has been filled in the Orange Book.

Paragraph II certification means a certification that a generic applicant seeks FDA approval of its ANDA for a relevant NDA for which a patent filed in the Orange Book has expired.

Paragraph III certification means a certification that a generic applicant seeks FDA approval of its ANDA as of the date a patent listed in the Orange Book has expired.

Paragraph IV certification means a certification that a patent listed in the Orange Book is invalid or will not be infringed by the generic drug for which the ANDA applicant seeks approval.

Patent Term is the period of time during which a patent is in effect, currently 20 years beginning on the date the patent's application is filed by USPTO. Market exclusivity and patent term are separate and have distinct time periods that can overlap.

Pediatric studies are defined as at least one clinical investigation, in a pediatric age group (up to 16 years old).

Priority drugs are drugs that receive priority review from FDA and represent drugs that have significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease.

Settlements means agreements settling patent litigation between brand-name companies and a generic applicant that has filed ANDA containing paragraph IV certification.

Standard drugs are drugs that receive standard review from FDA and represent drugs that appear to have therapeutic qualities similar to those of one or more already marketed drugs.

30-month stay prohibits the FDA form approving an ANDA with a paeagraph IV certification for 30 months if the relevant brand-name company brings a patent infringement suit within 45 days of notice of the generic applicant's paragraph IV certification. The 30-month stay is terminated by (1) the expiration of the patents; (2) a final determination of non-infringement or patent invalidity by a court in the patent litigation; or (3) the expiration of thirty months form the receipt of notice of the Paragraph IV certification.

APPENDIX B: DATA AND SAMPLE SELECTION OF DRUG PRODUCTS AND COMPANIES

The data of drug products are obtained from the Drugs@fda website.[1] This website provides a downloadable database file, which contains a zip file with seven text file documents containing a dataset on product approvals. For the purpose of our studies, we used three of them, namely: (1) RegActionDate.txt; (2) Application.txt; and (3) Product.txt.

For the explanation of each document, we refer to the website. We included only approvals with type N, S, SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8, SES, SED. These are approval types for NDA, ANDA, biologic drugs, and supplement types. For more detailed explanations of approval types we refer to the file DocType_lookup.txt on the website. We merged all three documents using STATA and produced 12.699 drugs approvals. The first approval date is on 11 November 1911 and the latest is on 26 August 2006[2]. Note that the next approval after 11 November 1911 is on 9 February 1939. Because of this large gap, we excluded the first approval of drug products in 1911 and therefore we cover the drugs approvals between the period 1939-2005. To avoid multiple counting, we count only once for drugs with the same active ingredient that was approved on the same day. For example, Ziagen, with active ingredient Abacavir Sulfate, was approved for the first time on 17 December 1998. This NCE was approved in two dosage forms, so it appears in the database twice. We count this only once and therefore the applicant had only one NCE approved on this date according the final data. Eliminating multiple approvals on the same day with the same active ingredients brings us to a number of 10.368 approvals in total. We assume that the day of approval is equal to the day of introduction.

[1] (http://www.accessdata.fda.gov/scripts/cder/drugsatfda)

[2] This is a generic application whose date is an expected date of approval. In many occasions, the expected date can be known in advance due to regulations (see section 2.2.1).

B.1 CLASSIFICATION OF DRUG PRODUCTS: NCE, IMD AND GENERIC

The dataset provided by drugs@FDA does not allow us directly to distinguish drug products into NCE, IMD or generic. We used the following procedure. First, we identified generic applications as follows. We observed that generic application has application numbers between 40000 and 49999 or between 60000 and 89999[1]. Our procedure successfully traces generic drug applications and found that 5614 approvals (54%) are categorized as generic applications. This implies that the rest of the drug approvals, i.e. 46%, are NDA applications.

From the population of NDA applications, we distinguished NCE as the drug approval whose active ingredient has never been approved before. This implies that we categorized all drug products based on its active ingredient and ranked them by date of approval. The first drug product approved in a certain active ingredient category, i.e. the drug product that has the earliest date of approval, is classified as NCE. This procedure is performed in STATA. We found 1243 NCEs, or 12% of all drugs approved in the period 1939-2005. The rest is classified as incrementally modified drugs (IMDs). For example, fluoxetine chloride, known with trade marks Prozac or Sarafem, is first approved in 29 December 1987. Since that time until 31 December 2005, there were 67 additional drug approvals with this active ingredient (excluding drugs that combine this active ingredient with others), of which 55 are ANDA applications. The first approval in 1987 is classified as NCE, 55 are classified as generic and the rest (12 approvals) are categorized as IMDs. Note that we took into account combinations and derivations of active ingredients in defining NCEs.

B.2 FIRM SELECTION

The dataset that is provided by drugs@FDA provides information on the sponsor companies of drug applications. In total, there are 596 different sponsor companies in the dataset in the period 1939-2005. We choose 27 companies in our final sample based on the following criteria. First,

[1] This is after years of examination of the database. Additionally we took a random sample and check it manually. The results show that we can be confident about this classification.

companies had to be listed in the U.S. stock market. Second, selected companies must have the majority of their product portfolios consisting of brand-name drugs, i.e. NDA approval. Especially, we limited the final companies to ones that have at least 50% of their total products consisting of NDA approvals. By doing this, we concentrated only on brand-name pharmaceutical companies and therefore excluded pharmaceutical companies that focus on producing generic drug products. Lastly, we required that selected companies must have at least four years of data on drug approvals and financial data. The final companies are the so-called *brand-name* companies, i.e. pharmaceutical companies that specialize in producing brand-name drugs.

We also took into account some major mergers and acquisitions in the pharmaceutical industry. From company website we traced that companies underwent a merger and/or acquisition. This is not always processed on time by FDA. We take this into account by looking at the year of the merger or acquisition and grouping drug approvals of both companies into one entity after the date of the merger. For example, Pfizer acquired Warner-Lambert Pharmaceutical in June 2000. Warner-Lambert brought two subsidiary companies; Agouron and Parke Davis. We grouped all drugs sponsored by Warner, Agouron and Parke Davies into Pfizer starting on 1 January 2001.

Figure B.1 provides the comparison of total NDA approvals and NDA approvals from our final sample. This figure shows that even though our sample does not cover the whole population, it does represent the industry trend.

Figure B.1 Comparison of NDA approvals in the population and in the sample

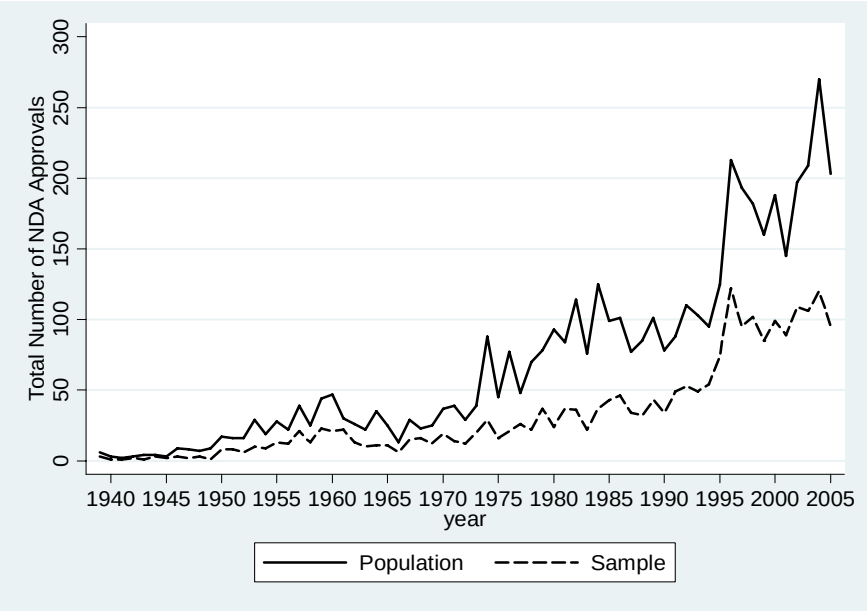


Table B.1 U.S. Pharmaceutical Firms Included in the Study

3M	Mallinckrodt
Abbott	McNeil Corp.
Allergan	Medicis
Amgen	Merck
AstraZeneca	Novartis
Bayer	Novo
Biovail	Pfizer
BristolMyersSquibb	Pharmacia
Forest Labs	Schering
Genentech	Schering Plough
GD Searle	Serono
GlaxoSmithKline	Shire
King Pharmaceuticals	Wyeth
Eli Lilly	

B.3 LIMITATIONS OF THE FDA DATABASE

The CDER database is limited in the sense that it only registers the latest sponsor of the drugs, not necessarily the one that introduced them in the first place. Once a company was taken over by another firm or merged with other companies, the database put all the drugs introduced by the initial companies into the new company[1]. Therefore, we only used data on introduction preceding a merger or acquisition. For example, we do not include GlaxoSmithKline, one of the big pharmaceutical companies, because we only have three years of accurate data after the big merger between Glaxo Wellcome and SmithKline in 2001. Before 2001, we cannot trace whether a particular drug belonged to Glaxo Wellcome or to SmithKline. Furthermore, we only include observations after year 1989 for Bristol Myers Squibb, the year in which Bristol Myers merged with Squibb.

[1] We obtain data on merger and acquisition by consulting the company's history from the company, the Financial Times database, and CRSP.

APPENDIX C: SAMPLE AND METHODOLOGY FOR ASSESSING INDUSTRY PERFORMANCE (CHAPTER 3)

We used the FDA website to obtain the data. The detailed description of how we compiled and processed this data is given in appendix B. We grouped the approvals in three categories. The first category concerns NCEs, drugs that had new or a combination of chemical entities that had never been marketed before. This category is considered to have the highest innovation level. The second category concerns the so called extension drugs or IMDs: drugs whose active ingredients have been marketed before but approved for modification such as a new target population, new indication, or new dosage/route. The last category is that of generic drugs, which have the lowest level of innovation, as it is an imitation of existing drugs. Note that the NCEs and IMDs are NDA approvals and generics are ANDA approvals.

Productivity was measured by the ratio of total NDA approvals to industry R&D spending. We used the National Science Foundation (NSF) to compile data on the industry's R&D expenditure[1]. For the period 1956-1998, we used data on *Total (company, federal, and other) funds for industrial R&D performance, by industry and by industry size of company*. In this data, pharmaceutical R&D spending is referred to as Drugs and Medicines. Missing data in this period was replaced by data from *company and other (except federal) funds for industrial R&D performance, by industry and by size of company* in the period 1956-1998. Comparing these two data sources, we only found negligible differences in the period where data on R&D spending are available in both datasets. Data from 1999-2002 was compiled from the *Industry R&D Series* that reviews trends in R&D performed by industries in the U.S.[2] Note that R&D spending data provided by NSF does not include research conducted outside the U.S. Compared to PHRMA estimates, NSF's figure is much lower. Consequently, NSF's data on R&D spending is an underestimation of the actual R&D spending. Therefore, our measure of productivity is more likely to overestimate

[1] www.nsf.gov/statistics/iris/search_hist.cfm?indx=1
[2] www.nsf.gov/statistics/industry/

productivity.

We used market value as a measure for profitability, which offers superior advantages compared the standard accounting measure. This is due to, among others, its forward looking characteristics. Market value data was obtained from COMPUSTAT, which was calculated by multiplying the (closing) price with the number of common share outstanding. We compared market value of brand-name pharmaceutical companies with the rest of the companies in the COMPUSTAT database. Data on pharmaceutical companies were obtained based on the North American Industry Classification System (NAICS), which is coded 325412 (pharmaceutical preparation manufacturing). The data on the rest of the industries was compiled by using the universe of active companies from the COMPUSTAT minus the pharmaceutical companies.

We constructed pharmaceutical firm return by dividing companies' market value by the total number of NDA approvals. The annual number of NDA approvals was defined as the annual number of total drug approvals minus the annual number of ANDA approvals. In constructing companies' return, we used a sample of pharmaceutical companies. We refer to appendix B for detailed information on how we selected the sample.

APPENDIX D: REPLACING MISSING VALUES FOR ADVERTISING

In this appendix we describe the procedure of how we replaced missing values of advertising and how we came up with the final dataset used in the analysis of chapter 4 and chapter 5. Financial data of companies in our data that was obtained from Compustat database had a considerable gap, especially in advertising data. We applied the following procedure to replace missing values of advertising. First, although Compustat contains financial data back in 1950, we only used observations after 1970. The main reason is that advertising data is not available for all companies prior to 1970. Moreover, advertising data is not available for all companies, even after 1970. Many companies in our dataset do not have consecutive financial data, including advertising, prior to 1980. Some companies do not even have data prior to 1990. By taking this into account, our final dataset is an unbalanced panel data, where few of the big players have data since 1971, while many others start much later.

This final dataset, however, still contains considerable gaps in advertising data; 32% of our final observations do not have advertising expenditure. This gap in advertising especially exists in the period 1993-2005. The staff of COMPUSTAT whom we contacted on this matter informed us that these companies did not provide the information on advertising data in this period.

To get more information, we consulted the companies' annual report via internet. Especially, we looked at the cost of selling or marketing at the financial statement of companies with considerable gaps in advertising expenditure. Because company usually only report the most recent annual reports, i.e. the last 5 years, we can only gather information after 1997. Financial statement reports the so called marketing and administration expenses and sometimes they also call it selling and distribution expenses. Indeed, we found different variations on the name of this account, such as: marketing & administrative; selling, administrative & general; marketing and selling; and marketing and distribution. We acknowledge that this account consists not only of advertising, but also other purposes such as

administration, distribution and selling cost in general. Therefore, we use a proxy of this account to estimate the advertising expenditure. After replacing most recent missing values using information from companies' financial statement, approximately 18% of advertising data is missing. We replace the missing values left by linear extrapolation. Extrapolation is performed in STATA by using the ipolate command.

We used a trial and error procedure to determine the size of the proxy by comparing two figures; (1) the annual average of advertising values from original Compustat data that contains missing values and (2) the annual average of advertising values after replacing missing values with information from annual report and with extrapolation. Figure Appendix D.1 to Figure Appendix D.4 show the comparison between the annual average of advertising from the original dataset and the annual average of advertising in the final dataset. The latter is obtained, as has been mentioned above, by using various percentages of marketing and administration (proxies), which is obtained from the annual report of companies. The solid line in each figure represents the annual average of available advertising expenditure of all companies in each year based on the Compustat data. The dashed line shows the average advertising data of all companies for each year, after (1) replacing the missing advertising data with various proxies (1 or 100%, 50%, 20%, and 10%) of marketing & administration from the annual report and, thereafter, (2) we replaced the missing values left by linear extrapolation.

As the above figure shows, advertising as a 20% of total cost of marketing & administration seems to be a reasonable proxy. We also consulted some information from companies that do provide advertising data. For example, in its notes to financial statements, Pfizer declares advertising expenditure in 2004 and 2005, which is approximately 19% of total marketing and administration cost in that years[1]. We found a similar figure for Bristol Myers Squibb as well, one of few companies that reported advertising expenditure. Nevertheless, we acknowledge that companies such as Abbott and GlaxoSmithKline have lower actual proxies than 20% in the same years. Nevertheless, we think that 20% as is a reasonable proxy.

[1] http://www.pfizer.com/pfizer/annualreport/2005/financial/financial2005.pdf

Our final financial dataset consists of 599 firm-year observations, ranging in the period 1971-2005 and consisting of 27 companies. Minimal firm-year observation for each firm is six years, and maximal is 35 years. This dataset is, therefore, an unbalanced panel data. In chapter 4, we use less than 599 observations, namely 596 observations for the regression analysis due to the use of sales in the previous year to calculate growth of log sales.

Figure D.1 The Original Versus the Final Advertising (Proxy=1)

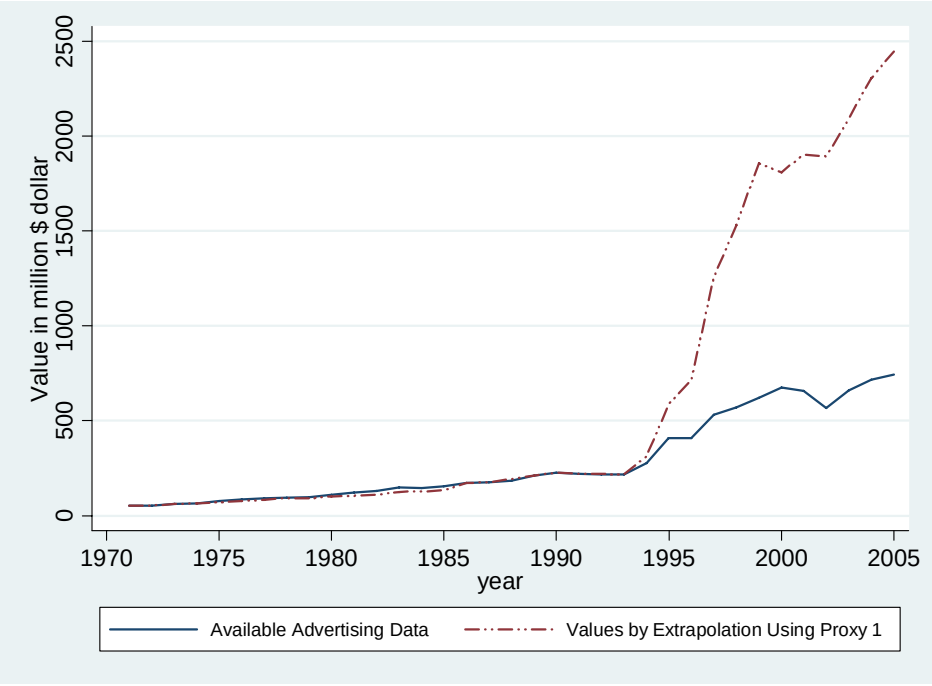


Figure D.2 The Original Versus the Final Advertising (Proxy=0.5)

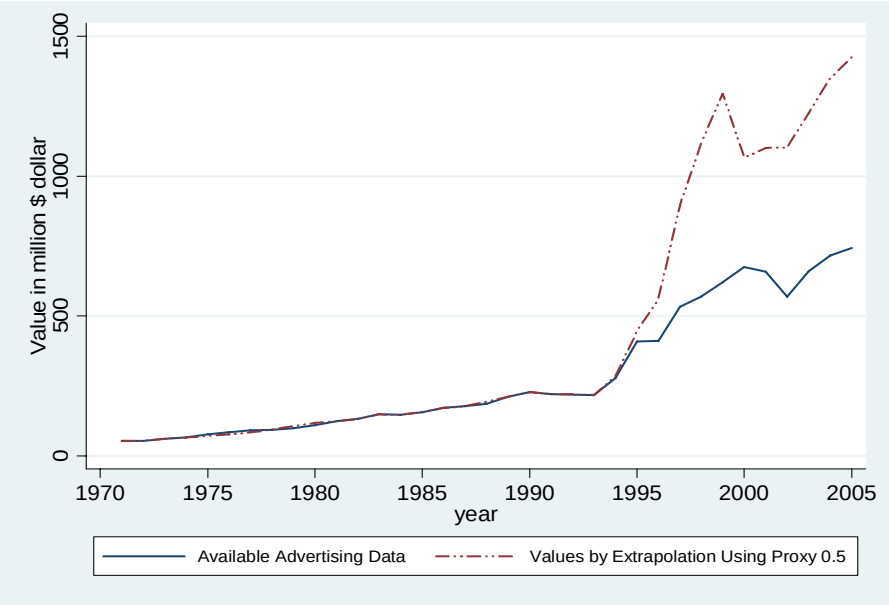


Figure D.3 The Original Versus the Final Advertising (Proxy=0.2)

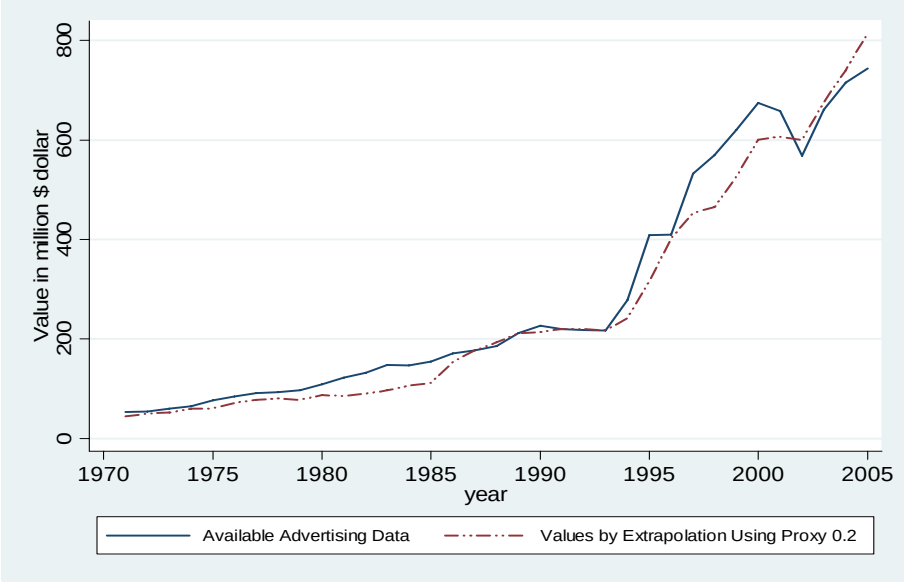
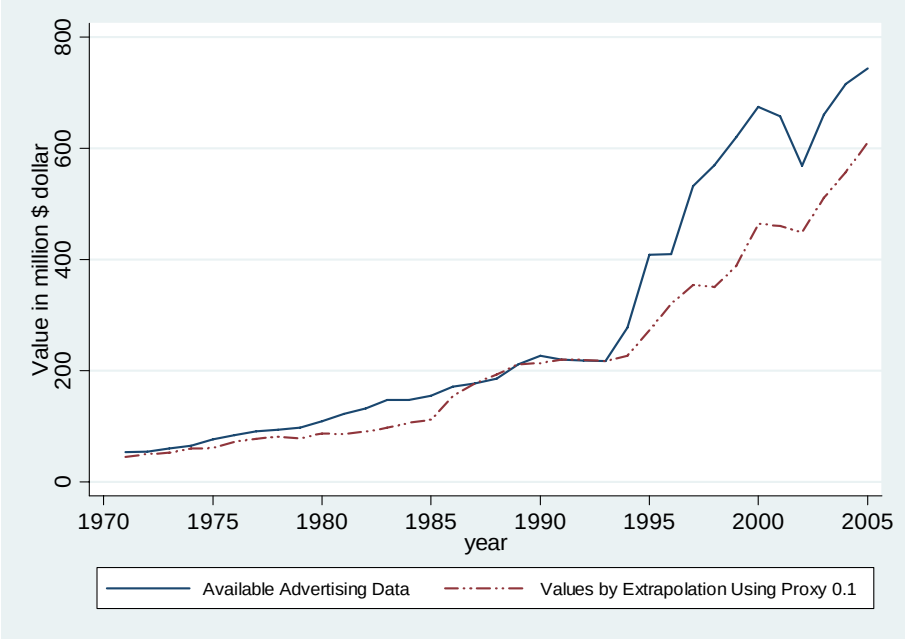


Figure D.4 The Original Versus the Final Advertising (Proxy=0.1)



APPENDIX E: CONSTRUCTION OF VARIABLES IN CHAPTER 5

This appendix provides a more detailed discussion of the construction of variables used in chapter 5. Except for the variables of *competition* and *industry index*, all data is obtained from COMPUSTAT. All time *t* variables are end of fiscal year values.

Research and Development (R&D) : Research & Development expenses.

Growth of Research and Development (*grR&D*): is defined as follows:

$grR\&D_{it} = \ln (R\&D)_{it} - \ln(R\&D)_{it-1}$ (i) [1].

Advertising (Adv): Advertising expenses.

Cash flow (CF): is defined as the sum of *income before extraordinary items*, *depreciation and amortization.*

Leverage (De): is defined as debt (D) divided by equity (E) where D refers to the book value of long term debt plus current liabilities and E is the common equity (market value) plus the preferred equity (liquidating value).

Competition (C): competition for firm *i* is defined as the total number of NCEs launched in the industry minus the number of NCEs launched by firm *i*.

Volatility Variables[2]

Daily returns are used to generate annual volatility. Total uncertainty is decomposed into industry and firm specific components by estimating a single index model.

$$r_{i\tau} = \alpha_{i\tau} + \beta_{i\tau} r_{I\tau} + \varepsilon_{i\tau} \qquad (ii)$$

where $\varepsilon_{i\tau}$ is assumed to be independently and identically distributed with variance $\sigma^2_{\varepsilon i\tau}$, and $\tau = 1,2, \ldots, t_i$. t_i is the number of trading days in year *t*. $r_{i\tau}$ is the daily return on firm *i*'s equity, which is defined as $r_{i\tau} = (P_{i\tau} - P_{i\tau-1})/P$

[1] Other growth variables in equation 5.1, namely Advertising growth (*grADV*) and Cash flow growth (*grCFA*), are defined in the same way.

[2] The following constructs are based on Bulan (2005)

$_{i\tau-1}$, with $P_{i\tau}$ is the stock price for firm i on day τ. $\beta_{i\tau}$ is the industry beta for firm i in year t, as indicated by the single index model. We estimated $\beta_{i\tau}$ by using ordinary-least-squares. The estimate of the standard deviation of the residuals $\sigma_{\varepsilon i\tau}$ is the measure of firm specific uncertainty. This measure captures the volatility of a firm's return that is orthogonal to the movement of the industry index. Using the estimated beta from equation (*ii*), industry uncertainty is measured as $\hat{\beta}_{i\tau}\hat{\sigma}_{i\tau}$. This is the portion of total industry uncertainty that matters for the firm. Therefore:

Industry specific volatility is defined as:

$$\hat{\sigma}_{It} = \sqrt{\frac{1}{t_i}\sum_{\tau=1}^{t_i}(r_{I\tau} - \bar{r}_{I\tau})^2}$$

Firm specific volatility is defined as:

$$\hat{\sigma}_{\varepsilon it} = \sqrt{\frac{1}{t_i}\sum_{\tau=1}^{t_i}\hat{\varepsilon}_{i\tau}^2}$$

Where $\tau = 1,2, \ldots, t_i$. t_i is the number of trading days in year t, $r_{i\tau}$ is the daily return on firm i's equity, $r_{I\tau}$ is the daily industry index return, $\varepsilon_{i\tau}$ is the residual from equation (*ii*).

APPENDIX F: A META-ANALYSIS OF NEW PRODUCT PERFORMANCE[1]

ABSTRACT

This appendix describes a review on studies on new product performance' study by using a meta-analysis technique. This meta-analysis includes 46 studies and involves 5309 firms. We investigate the relationships between new product performance and 34 variables, as well as the potential moderators of these relationships. Our results indicate that the effects of most of these variables are likely to be moderated by other variables. These include the effects of classical predictors such as product advantage and strategic orientation. Nevertheless, organizational variables such as top management support, communication and information exchange, integration, management skill, resources and marketing synergy possess stable and significant relationships with NPP. The findings also reveal some inconsistencies with previously published meta-analysis on the same subject. We suggest that the differences are due to the method of collecting observations.

INTRODUCTION

The last two decades show an increasing number of studies investigating the phenomenon of new product performance (henceforth NPP). During this period, there have been a growing number of variables that are hypothesized to affect NPP, some of which are gaining popularity in NPP research. To name a few, product advantage, market orientation, firm synergy, and innovativeness. The growing number of empirical studies has opened up the possibility to summarize the findings on NPP in a meaningful way, for example by using a meta-analysis technique. This method of integrating research quantitatively can synthesize studies examining similar research questions in a reliable and valid way, issues that have been argued to lack in non-quantitative reviews (Wolf 1986).

The need for quantitative review on NPP has produced two meta-analyses on this subject (Montoya-Weiss and Calantone 1994; Henard and

[1] This section is based on Pattikawa, Verwaal, & Commandeur (2006)

Szymanski 2001). Montoya-Weiss and Calantone's (1994) meta-analysis provides a framework for classifying the numerous variables that have been hypothesized to be associated with NPP. However, the meta-analysis performed on effect sizes was not corrected for artefacts and did not provide a moderator analysis, two activities that are crucial for meta-analysis (Hall, Tickle-Degnen, Rosenthal and Mosteller 1994). Furthermore, since the publication of the Monotoya-Weiss and Calantone study, numerous studies have been published that could potentially be synthesized in the body of NPP literature as a whole.

A more recent meta-analysis (Henard and Szymanski, 2001) fills this gap by including more research studies, corrects for artifacts, and gives a moderatot analysis. Nevertheless, we note one small problem of this study, namely on their method in arriving at the number of observations. In Henard and Szymanski's study, a single correlation coefficient represents one observation. This can be a problem when one single study consists of multiple correlations. Henard and Szymanski perform an averaging of reported correlations across all models and all studies to arrive at an estimate of the central tendency of the predictor-criterion relationship, such that the number of correlations across all studies are equal to the number of observations. In contrast, our study considers that one correlation can only represent one independent sample. This is done by eventually averaging correlations within our study. The number of observations in our study needs not to be similar with the number of studies, because one study may have more than one independent sample.

Our approach is consistent with Hunter and Schmidt's recommendations (Hunter and Schmidt 1990, p. 452; Matt and Cook 1994, p. 509) and ensures the statistical independence among the effect sizes, whose assumption is needed to formulate the meta-analysis statistics. Furthermore, if a very large number of observations comes from one single study, there can be considerable distortion if statistical significance tests are used (Hunter and Schmidt 1990, p. 452). Also, using Henard and Szymanski (2001)'s approach will yield more observations (correlations) and the statistics resulting from this observation can be biased toward studies that report many correlation coefficients. This is especially true in NPP studies that are included in a meta-analysis, where approximately 40% of construct

variables is represented by more than one measurement and more or less 25 % of them are represented by more than 5 measurements. This current chapter shows that using Hunter and Schmidt (1990)'s method can lead to a quite different conclusion then the previous meta-analysis (Henard and Szymanski, 2001), which is one of the main drivers behind our study on this topic.

Our study attempts to synthesize the existing NPP research in the following way. First we investigate what variables[1] have been associated with NPP in the past. Next, we formulate the statistics of this association (in the form of a correlation coefficient) to arrive at the central tendency and the variance composition. From this, one can infer whether a certain association is robust across the studies or whether it exhibits a potential moderator effect. In the latter case, we perform a moderator analysis.

The paper is organized as follows. First, we discuss a framework in classifying variables that are hypothesized to affect NPP. Second we briefly discuss the methods. Thereafter, results of meta-analysis will be presented, followed by some discussion. Finally, we conclude this chapter by summarizing the main findings, giving some recommendations for future research and providing some limitations of our study.

CONCEPTUAL FRAMEWORK

After correlations are collected, 34 classes of variables are revealed, where each class contains a minimal number of two observations.[2] We propose a framework that enables us to classify these classes of variables in a meaningful way. This framework is based on the study of Montoya-Weiss and Calantone (1994), which uses the following premise: "NPP is determined by the interaction of the market environment with new product strategy and development process execution." This premise can be rephrased as follows. NPP is determined by a set of variables, which begins

[1] Below, we will interchangeably use 'independent variables' or simply 'variables' to refer to these variables.

[2] Although with $n = 2$ we expect a low statistical power, an emission of this variable may discourage future research on this variable. Furthermore, Lipsey & Wilson (2001) states that meta-analysis can be done with $n = 2$.

with the firm's strategic formulation. This strategic view is a result of a proactive interaction with the market environment. Once the strategic formulation is set (this includes firm's strategic orientation, product characteristics, and firm's resources), it has to be implemented in an effective and efficient way, wherein the organizational factors play a key role in facilitating the implementation of the firm's strategic objectives. This includes factors such as interfunctional-coordination, structure and leadership. The unit in the organization that performs new product development is the new product project. In this stage, the process factors are crucial, consisting of variables such as proficiency of predevelopment, marketing, technical and launch activities. This framework is presented in table A.

Although the organizational factor is included in the Monotoya-Weiss and Calantone's framework, it was not stated explicitly. Furthermore, we use concepts such as "strategic orientation," "structure" and "leadership" in the current framework, which is not the case in the Monotoya-Weiss and Calantone's framework. Note also that we categorize top management support as organizational factors representing the leadership concept. Montoya-Weiss and Calantone (1994) included this variable as a process category.

Table F.1 Framework in the Classification of Independent Variables

Category	Sub-Category	Class
1.ENVIRONMENT		Market potential
		Market competitiveness
		Environment uncertainty
		Product homogeneity
2.STRATEGY	1.1Strategic orientation	Market orientation
		Customer orientation
		Competitor orientation
		Technology orientation
	1.2 Product characteristics	Product advantage
		Product newness to the firm
		Degree of radicalness
		Degree of customization
		Cost of innovation
	1.3 Synergy and resources	Marketing synergy
		Technology synergy
		Company resources
		Management skill
3. ORGANIZATIONAL	3.1 Motivation	Top management support
		Project manager competency
		Role of champion
	3.2. Interfunctional coordination	Communication & information exchange
		Degree of interaction
		R&D and marketing integration
	3.3 Structure	Degree of decentralization
		Degree of formalization
	3.4. Other	Project/organization size
		Organization climate
4. PROCESS		(General) proficiency of new product development
		Proficiency of predevelopment activities
		Proficiency of market related activities
		Proficiency of technical activities
		Speed to market
		Proficiency of launch activities
		Financial business analysis

METHODOLOGY

We followed closely meta-analysis method of effect size described by Hunter and Schmidt (1990). A correlation coefficient was used as a metric for synthesizing the studies. The reason for using this metric was that the majority of empirical NPP studies report the correlation coefficient. The mean and the variance of the effects size will be corrected for sample error and error measurement, both in the NPP variable and in the independent variables. This procedure is also called *correction in the reliability variation*[1]. By using the Hunter and Schmidt method, the variances were split into three components: variance due to sampling error, variance due to reliability variation, and the remaining variance. To perform a moderator analysis, we used the 75% rule (Hunter and Schmidt 1990), which suggests that in any given meta-analysis, it is probably the case that the unknown and uncorrected artefacts account for 25% of the variance. Thus, if the real variance estimate is not at least this high, it suggests that there may be no real variance. We also conducted the homogeneity test, which tests the null hypothesis that there is no real variance in unattenuated correlations; that all of the observed variance is due to variation in reliability and also due to sampling error. This is also a way to test whether any potential moderator exists. Hunter and Schmidt argue that the 75% rule had statistical power greater than (or equal to) other methods. This advantage was relatively the greatest when the number of observations was small and the sample size of each study was small.

Moderator Analysis

Moderator analysis is a way to test hypotheses that were not tested, or tested rarely, in primary studies. Moderators are variables that strengthen or attenuate the relationship of the main effects under investigation. By dividing the studies into groups on the basis of several characteristics, one could explain the variations in effect size. In general, moderator analysis in meta-analysis literature can be grouped into two categories. First, moderator analysis can be performed on the differences in the methodology

[1] The reliability measures are infrequently available in studies and therefore we use reliability distribution for correcting the correlations. For a detailed description of this method we refer to Hunter & Schmidt (1990).

used in the primary studies. The second category is by grouping the studies into several characteristics based on the existing theories in the relevant research subject (Sultan, Farley, and Lehman 1990). The former analysis includes analysis on the measurement method, level of aggregation, model-specific variables, variable definition, study quality, etc. The second type of moderator analysis refers to dividing studies into different groups based on what has been hypothesized in the literature to have a different effect size in each group. This second type includes grouping studies into categories such as type of product, environmental differences (such as industry and national setting), and type of organization.

In this study, we perform moderator analysis at the level of the study's quality and the environment. The study's quality can be presented by characteristics such as the measurement method, the study's validity, and the random assignment procedure. In addition, cultural differences and the industry setting are often hypothesized to moderate a relationship between a certain variable and NPP (Hofstede 1980; Hitt and Ireland 1985).

We performed moderator analysis for variables that exhibit a potential moderator. This is done by grouping observations in each class of variables into study characteristics used as moderators and then performing a separate meta-analysis. If the remaining variance is large enough according to the above criteria, the moderator can be accounted for that difference. Because not all studies provide characteristics of study quality such as measurement method, number of respondents, and validity testing, we use the operationalization of reliability measurement to represent this moderator.[1] Moderator analysis at the level of industry could not be conducted due to the unavailability of the relevant information in the primary studies. The environment moderator was represented by whether the study is conducted in eastern or western countries.

[1] Moderator analysis is limited by the fact that not all studies provide the information needed, or the grouping of effect sizes based on a well-known moderator gives no meaningful analysis. In this case, the choice should be based on practical grounds, whose result should be interpreted with caution (Hall et al. 1994).

Sample Selection

Selection was aimed for empirical studies that operationalized NPP as a measured variable. We made a trade off between similarity of the NPP measure used in the studies and the eligibility of the number of studies. Across the studies, various NPP measurements are reported so that one single clear-cut NPP measure will result in very little observation where a meaningful analysis cannot be conducted. We included studies that operationalized NPP in measures such as (perceived) financial- and market performance, whether the project meets the objective (usually on financial base, including budget). We excluded measures such as time, number of ideas generated and productivity as NPP measures. We also excluded NPP measure at the organizational level, such as organizational performance. For most studies, performance measures are based on manager's perspectives that were obtained from questionnaires. A small part of our sample contains also objective measures, such as the level of actual profit earned at a certain year. To ensure similarity, we took only the measures that are frequently used, namely measure that were based on manager's perspective.

The selected studies provide a correlation coefficient between NPP measure and at least one of the variables in the framework. It is not essential whether NPP is operationalized as an independent or dependent variable, because correlation coefficients do not assume a specified direction of the relationship between the variables. Most studies, however, have specified NPP as the dependent variable. The independent variable was included if it has reported a correlation coefficient with NPP. In most instances, the inclusion of a certain variable into a class construct was accomplished by the variable designation employed in a study. However, in certain instances, it was necessary to infer the appropriate variable category on the basis of the terminology of the conceptualization and operationalizations. In less than five cases, we modified the correlations in order to reflect the class construct more appropriately. For example, to measure degree of decentralization, we reversed the sign of correlation that measures centralization.

In comparing results, two statistics were taken for each study, namely the correlation coefficient between NPP measure and the reliabilities of both

the independent variable and the NPP measure. For moderator analysis, we noted the following information from each study: (1) whether they provide reliability measurement for the independent variable in question; and (2) Western versus Eastern culture; with Western culture represented by countries such as the USA, Canada, Europe, Australia and New Zealand; and studies in China representing Eastern culture.

The search for studies was conducted in the following way.[1]
(1) Search in the electronic databank *ABI/Inform Global via Internet* by using key words such as "new product", "new product performance", "new product success", and other keywords such as "empirical" and "models" to detect empirical studies.
(2) Through the electronic databank *ABI/Inform Global via Internet*, search is conducted for each leading academic journal (since 1986) in which studies on NPP are most likely published.[2]
(3) Using study references from earlier meta-analysis (Montoya-Weiss and Calantone 1994; Henard and Szymanski 2001).

As stated in the introductory section, only one correlation coefficient from one independent sample was considered as one observation. A lot of studies provided more than one correlation coefficient representing one class of variables. This is mainly caused by the use of multiple measurements for a single construct. We perform a meta-analysis is in each lass of independent variables.

RESULTS

We found in total 50 studies eligible for meta-analysis. One study (Souder and Song 1997) was removed because observations from this study were so remote from the rest, which is probably due to a non-random selection and a small number of observations used in this study. There are some cases

[1] Compared to Henard & Szimanski (2001), our search criteria are slightly different. First, we did not use unpublished studies. Second, our search included studies from more journals. In searching in the databank, Henard & Szymanski employed also key words such as product innovation and pioneering products. Furthermore, we include more recent studies. Overall, in our opinion, the samples are more or less comparable.
[2] See the end of this chapter for the list of the journals.

where several studies used the same sample. This happens when the same author(s) publish the same study in different journals. We consider that each case represents one observation only.[1] Two studies are considered as having two observations because they used two samples independently form different industries (random assignment for industry) and they provided the correlation coefficient for each sample. At the end, there were 43 independent samples from 46 studies that can be used for observations.

Approximately 25% of the studies come from one single journal (*Journal of Product Innovation Management*) and less than 15% are articles from the *Journal of Marketing Research*. This collection of data does not exhaust all empirical NPP studies and does not represent a random selection of all the studies that have been conducted. This, however, is typical for a meta-analysis (Matt and Cook 1994).

In total, 764 correlations involving NPP and a total of 5,309 firms involving more than 8,448 new product projects[2] were found. There are 243 correlations that cannot be categorized in any of the construct classes, leaving 521 correlations that are eligible for analysis. Table B presents the direction of the relationship generally hypothesized in the NPP literature, the range of the correlation value, the number of observations and the confidence interval of the corrected means.

[1] One correlation coefficient of a certain construct from one independent sample represents one observation.

[2] Some studies were conducted in the firm level, so that the number of projects was not available. In this case, we made a conservative estimate by making the assumption that the number of projects is equal to the number of firms.

Table F.2 Descriptive Statistics of the Confidence Interval of Corrected Mean of Correlation Coefficient

	Hypothesis	# of observations	# of studies	# of Firm	# of project	min.r	max.r	Lower 95%	Upper 95%
Environment									
Market potential	+/-	8	8	1315	2238	0.02	0.54	-0.09	0.75
Market competitiveness	+/-	10	9	1786	2401	-0.63	0.15	-0.47	0.32
Environmental uncertainty	(a)	8	8	937	1248	-0.24	0.11	-0.13	-0.06
Degree of product homogeneity	+	3	3	625	846	-0.28	0.02	-0.46	-0.01
Strategy									
Market orientation	+	7	7	1283	2067	0.03	0.57	0.18	0.77
Customer orientation	+	7	7	1925	2307	-0.09	0.58	-0.09	0.71
Competitor orientation	+	5	5	962	1183	0.02	0.53	0.03	0.75
Technology orientation	+	6	6	1275	1880	0.03	0.491	0.07	0.64
Product advantage	+	16	15	2442	2559	0.19	0.63	0.26	0.84
Product newness to the firm	-	4	4	262	575	-0.1	0.3	-0.21	0.25
Degree of radicalness	(a)	12	10	1428	2024	-0.09	0.421	-0.09	0.52
Degree of customization	+	3	3	241	472	-0.05	0.04	-0.09	0.08
Cost of innovation	+/-	4	4	553	616	-0.27	0.11	-0.46	0.06
Marketing synergy	+	13	12	1693	3082	0.02	0.5	0.23	0.47
Technological synergy	+	11	10	2434	3495	-0.17	0.51	0.08	0.75
Company resources	+	6	6	671	1094	0	0.31	0.1	0.45
Management skill	+	4	4	378	808	0.32	0.46	0.37	0.62
Organizational									
Top management support	+	10	9	1196	2003	0.02	0.45	0.19	0.43
Role of champion	+	4	4	197	399	0.01	0.39	-0.03	0.34

	Hypothesis	Number of observations	Number of studies	Number of firm	Number of project	min.r	max.r	Lower 95%	Upper 95%
Project Manager skill	+	4	4	141	452	0.18	0.5	0.16	0.68
Communication & information exchange	+	15	14	1949	2374	0	0.51	0.09	0.38
Degree of interaction	+	3	3	283	791	0.1	0.56	0.54	0.79
R&D and Marketing integration	+	5	5	533	818	0.39	0.58	0.55	0.62
Degree of decentralization	+	6	5	275	515	0.04	0.51	-0.08	0.47
Degree of formalization	+	5	4	323	431	0	0.2	-0.01	0.26
Organizational culture	+	3	2	152	158	0.08	0.29	0.05	0.38
Organization / project size	[a]	9	8	1467	1838	-0.17	0.22	-0.03	0.15
Process									
General NPD proficiency	+	6	6	536	984	0.02	0.76	0.2	0.95
Proficiency of predevelopment activities	+	8	7	1094	1928	0.03	0.52	0.05	0.6
Proficiency of market related activities	+	11	11	1427	2895	0.28	0.64	0.36	0.64
Proficiency of technical activities	+	10	10	1312	2084	0.17	0.57	0.11	0.29
Proficiency of launch activities	+	10	9	1354	2398	0.08	0.66	0.1	0.73
Financial business analysis	+	4	4	378	8008	0.31	0.69	0.19	0.9
Speed to market	+	7	7	456	601	0	0.62	-0.07	0.85

[a] The literature does not hypothesize this variable to be associated directly with NPP. This variable is usually used as control variable or as moderator.

As a result of having one independent sample representing one observation for each class of construct, the 521 correlations were reduced to the number of 240 (due to averaging), which are spread out into 34 variable classes. The average number of observations per class is seven. Table B reports the descriptive statistics of correlation coefficients between new product success and independent variables described in our framework.

In table C, we report the summary of mean and variance of correlation coefficients between NPP and variables described in our framework. In the last column of the following table, we provide information whether a variable exhibits a potential moderator by using the 75% rule. The last column of table C shows that 19 out of 34 variables exhibit potential moderator effects, which implies that 19 out of 34 cases have remaining variances of more than 25% of the total variance. The result of homogeneity test is significant for 17 of these 19 variables.

The majority of variables have potential moderators, in spite of the fact that they have significant correlation coefficients with NPP. This includes variables such as market orientation, competitor orientation and product advantage. The same applies to process variables, which have in general significant but unstable relationship with NPP. Organization variables, on the other hand, have most of the time both significant and stable relationship with NPP. For example, top management support, R&D and marketing integration, interaction, and project manager's competency have on average positive and significant correlation coefficients of 0.5. These relationships are relatively stable as none of the remaining variance is greater than 25% from the total variance (see the last column of table C for the relevant statistics).

Table F.3 Central Tendency and Variance Statistics of the Effect Size

Construct class	Sample mean[a]	Sample size adjusted mean	Sample size and reliability adjusted mean [b]	Total variance	Variance due to sampling error	Variance due to reliability variation	Remaining variance (% total variance)
Environment							
Market potential	0.321	0.272	0.329	0.036	0.005	0.001	0.030 (84)+
Market competitiveness	-0.058	-0.062	-0.075	0.032	0.006	0.000	0.026 (82)+
Environmental uncertainty	-0.065	-0.079	-0.096*	0.009	0.009	0.000	0.000 (3)
Product Homogeneity	-0.125	-0.196	-0.237*	0.013	0.004	0.000	0.009 (64)+
Strategy							
Market orientation	0.357	0.397	0.480*	0.020	0.004	0.001	0.015 (75)+
Customer orientation	0.301	0.256	0.309	0.031	0.003	0.000	0.027 (88)+
Competitor orientation	0.317	0.322	0.389*	0.027	0.004	0.001	0.022 (82)+
Technology orientation	0.249	0.292	0.353*	0.018	0.004	0.001	0.014 (75)+
Product advantage	0.414	0.453	0.548*	0.020	0.004	0.002	0.014 (71)+
Product newness	0.046	0.016	0.019	0.014	0.014	0.000	0.000 (0)
Degree of radicalness	0.094	0.178	0.216	0.024	0.008	0.000	0.016 (66)+
Degress of customization	-0.021	-0.001	-0.002	0.002	0.002	0.000	0.000 (0)
Cost of innovation	-0.123	-0.164	-0.199	0.017	0.007	0.000	0.010 (59)+
Marketing synergy	0.285	0.289	0.349*	0.010	0.006	0.001	0.002 (26)
Technology synergy	0.282	0.346	0.419*	0.024	0.004	0.001	0.019 (81)+
Company resources	0.156	0.228	0.275*	0.007	0.007	0.000	0.000 (0)

Management skill	0.398	0.411	0.497*	0.004	0.004	0.000	0.000 (0)
Organizational							
Top management support	0.212	0.255	0.308*	0.010	0.007	0.000	0.002 (24)
Role of champion	0.163	0.129	0.157	0.009	0.009	0.000	0.000 (0)
Project manager skill	0.324	0.345	0.418*	0.016	0.016	0.000	0.000 (0)
Communication & information	0.231	0.194	0.235*	0.005	0.005	0.000	0.000 (0)
Degree of interaction	0.307	0.549	0.664*	0.004	0.004	0.000	0.000 (0)
R&D – Marketing integration	0.460	0.487	0.588*	0.007	0.006	0.002	0.000 (3)
Decentralization	0.164	0.161	0.194	0.018	0.018	0.000	0.000 (0)
Formalization	0.097	0.105	0.126	0.005	0.005	0.000	0.000 (0)
Organizational culture/climate	0.185	0.178	0.215*	0.006	0.006	0.000	0.000 (0)
Organization / project size	0.029	0.048	0.058	0.007	0.006	0.000	0.001 (18)
Process							
General NPD proficiency	0.402	0.477	0.577*	0.033	0.007	0.002	0.024 (74)+
Predevelopment activities proficiency	0.266	0.281	0.339*	0.021	0.006	0.001	0.015 (68)+
Marketing activities proficiency	0.428	0.411	0.497*	0.010	0.005	0.001	0.003 (34)+
Technical activities proficiency	0.371	0.417	0.505*	0.014	0.005	0.001	0.008 (54)+
Launch activities proficiency	0.346	0.340	0.412*	0.024	0.006	0.001	0.017 (72)+
Financial/ business analysis	0.426	0.450	0.544*	0.030	0.007	0.001	0.022 (73)+
Speed to market	0.236	0.323	0.390	0.049	0.013	0.001	0.036 (73)+

* Significant beyond p> 0.05; [a] Simple mean is the average correlation across studies unadjusted for sample error and study artifacts.; [b] This statistic is the average correlation across studies adjusted for sample error and reliability variation. Reliability adjustments are based on the distribution of reliability across all constructs; [+] Significant at p> 0.05 for Chi- Square Homogeneity test with *N*-1 degrees of freedom (*N*=number of independent samples).

Moderator Analysis Results

We performed a meta-analysis like in the previous section, except that we conducted a separate meta-analysis for each moderator category in each variable described in our framework.[1] One should note that the numerous meta-analysis conducted at this level can lower the statistical power of the results.[2] Overall, the moderator analysis does not give meaningful results. In only one case out of 15 where the reliability is taken as moderator, we are able to explain the remaining variance from the preliminary meta-analysis. When cultural differences are taken into account, in three out of 10 cases the meta-analysis can explain the remaining variance. Although this number might indicate the importance of the role of cultural differences as a moderator, we note that all studies that were conducted in eastern countries share one common author. This may imply that it is not cultural differences that explain the variation, but the author's characteristics (Eagly and Wood 1994).

Comparison with Henard and Szymanski's Results

More than 50% of the studies used in Henard and Szymanski (2001) are similar to ours. The differences between our study and theirs are likely caused by the following. First, there is disagreement over the inclusion of NPP measurement (for example, we excluded organizational performance as NPP measure). Second, there are NPP studies that do not provide correlation coefficients, which we did not include in the current study. Several of these studies were probably included in Henard and Szymanski's study where the authors have asked for the correlation matrix. Henard and Szymanski used a total 666 observations, which corresponds to number of

[1] We excluded marketing synergy from the moderator analysis because the remaining variance is very close to 25% of the total variance and the homogeneity test cannot be rejected. Furthermore, note that only three artefacts were corrected, i.e., sample size reliability in dependent and independent variables in this study (see also Hunter & Schmidt). Also, the sample size in this class is considerably large, so that the homogeneity test is likely to have more power.

[2] The total number of meta-analysis that should be conducted are: 18 variables * 2 moderators * 2 = 72. So, each variable will produce 4 meta-analyses. In total, we produced only 52 meta-analyses instead, due to the fact that some variables did not contain enough observations ($n \leq 1$).

correlation coefficients. Meanwhile, our study used 43 observations that refer to the number of independent studies.

Our results differ substantially from Henard and Szymanski (2001). Table D gives the summary of the findings and some comparisons with Henard and Szymanski's results. Note that from the 12 variables that are both investigated in the two studies, half of them has different interpretation compared to Henard and Szymanski. For example, we found that top management support and marketing synergy have stable relationships across the studies and their relationships with NPP are significant. On the other hand, Henard and Szymanski's findings indicate that these two relationships are not stable across the studies, although they do have significant relationships. Furthermore, market orientation and technology synergy relationships show to be significant, which are not the case in Henard and Szymanski's study. Similarities of the finding can be found at the process variables, except for speed to market. In contrast to what has been suggested in the literature, our findings do not give enough support for the significance of the relationship between time to market and NPP.

We also found that all relationships in the Henard and Szymanski (2001)'s study exhibit potential moderators, which is not the case in our study. One could suggest that the procedure used by Henard and Szymanki tends to result in a more unstable relationship between variables and the NPP. We argue, however, this is an issue for further empirical testing.

Table F. 4 Summary of the Findings and Comparisons with Henard and Szymanski's Results

	Stable variables (S)	Potential Moderator (M)
Significant (*)	Environment uncertainty	Product homogeneity
	Company resources	**Market orientation (M-)**
	Management skill	Competitor orientation
	Top management support (M*)	Technology orientation
	Project manager competency	**Product advantage**
	Communication & information	**Technology synergy (M-)**
	Interaction	General project proficiency
	R&D-marketing integration	**Predevelopment activities proficiency**
	Culture	**Market related activities proficiency**
	Marketing synergy (M*)	**Technical proficiency**
		Launch activities proficiency
		Financial & business analysis
Insignificant (-)	Product newness	**Market potential (M*)**
	Product customisation	Market competitiveness
	Champion	Radicalness
	Decentralization	Cost of innovation
	Formalization	**Customer orientation**
	Size	**Speed to market (M*)**

Notes: [a] Variables with bold letters correspondence with the variables that were also operationalized in the Henard andSzymanski's study. Symbols in parentheses refer to the H&S findings. [(S*)= stable and significant; (M*)= exhibit potential moderator and significant; (S-) = stable and insignificant; (M-) = exhibit potential moderator and insignificant).
Variables with bold letters and that are not ended with symbols in parentheses resemble the similarities between Henard and Szymanski's and our study.

CONCLUSIONS

Our findings show that in general the variables in our framework have potential moderator effects. This implies that the effects of variables in the NPP literature that are hypothesized to affect new product success are likely to be dependent on other variables. We, however, note some exceptions. Organizational variables such as leadership and interfunctional coordination do show a positive and stable relationship with the success of new products.

Nevertheless, our moderator analysis cannot explain potential moderator effects shown in the majority of variables. In addition to the small sample size problem, the possible cause is likely to be the choice of the moderators. The choice was made on practical grounds, based on what is available in the studies. Other moderator variables that are recommended by the literature are most of the time not available from the sample of studies we used.

The potential existence of potential moderators shows that new product's success is a complicated and uncertain phenomenon. Studies that aim to reveal the secrets of successful new products face a huge challenge to be able to describe and explain its relationship with a list of factors, which include, for example, strategic, organization, process and environmental factors. We recommend future studies to take into account variables recommended in our framework and to explore the interaction effects among these variables. Also, using hard figures such as the actual sales of new products can contribute to the validity of NPP measurement and eventually to understanding of NPP. The dynamic approach that investigates the relationship over time is also a useful endeavor for future studies.

We found quite substantial differences between our findings and a previous meta-analysis (Henard and Szymanski, 2001). We argue that that differences in the method of collecting observations has resulted in the substantial differences between our results and Henard and Szymanski's (2001). This suggests that two meta-analyses on the same subject with comparable samples can show inconsistent findings. Nevertheless, we urge future research to investigate this issue in more details.

This study is not without limitations. Since we used only published studies, our conclusions may indicate publication bias toward significant findings.

Also, despite the fact that our target population is empirical NPP studies that operationalize NPP measure, there are some studies of this kind that cannot yet be included, because they do not provide any correlation. Further limitation of this study is the heterogeneity of measurement taken in NPP measures across the studies. As noted in the previous section, this is a trade-off between having meaningful observations and having a single clear-cut measure of NPP. We chose a moderate approach, where only certain definitions of NPP were included. Future studies on NPP could operationalize NPP in a more clear-cut way. This latter depends, in turn, on the number and quality of future studies on NPP.

LIST OF JOURNALS USED IN THE META-ANALYSIS

Academy of Management Journal, IEEE Transactions on Engineering Management, Industrial Marketing Management, Information Management, Journal of the Academy of Marketing Science, Journal of International Business Study, Journal of Marketing, Journal of Business Venture, Journal of Product Innovation Management, Management Science, Marketing Science, R&D Management, Research Management, Journal of Engineering & Technology Management.

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SUMMARY

In the recent years, innovation in the pharmaceutical industry has been under thorough scrutiny. Intensive marketing activities that go beyond R&D spending, the explosion of me-too drugs in the market, and the spur of high profit in the industry have all contributed to public skepticism toward the industry's innovativeness. These criticisms, however, have been attacked for their simplification. They seem to overlook the fact that developing a new drug is a very risky business that can only be compensated for by an attractive rate of return. In addition, it is argued that the profit rates in the industry tend to exceed the risk-adjusted cost of capital by only a modest amount. Driven by this debate, this dissertation aims to answer the following questions. (1) What is the performance of the pharmaceutical industry in terms of innovativeness and profitability? (2) What is the role of advertising and product differentiation on pharmaceutical firms' profitability over time? (3) What are the drivers behind pharmaceutical companies' motivation to introduce drug extensions? Throughout chapter 3 to chapter 5 of this dissertation, we present three studies to provide answers to these questions. Based on the three studies, chapter 6 provides several implications for firms' strategies and we also provide recommendations for public polices and future research.

As an introduction to the industry analysis in chapter 3, chapter 2 describes three important features that characterize the industry. First, we present several basic conditions for competition in the industry that includes market definition, types of firms, and types of drug products. We also describe a typical product life cycle in the industry. Second, we discuss the Hatch-Waxman Act, which was passed as a response to the growing concern on increasing health care costs and that aims to facilitate the generic entry. Simultaneously, the Act has the objective to keep the incentive of innovative firms intact by giving a variety of exclusivity rights based on patent terms and marketing exclusivity. Doing so, the Act strived for creating the balance between keeping the drug prices down on the one hand and on the other hand giving incentives for research on innovations. Finally, we take a look at several prominent criticisms that are addressed toward the industry and we also present some counterarguments.

Chapter 3 answers the first research question of this thesis by providing an

industry analysis of the U.S. drug sector. Before we discuss the industry's performance, we first present several basic analyses such as the demand and supply conditions of the industry and we discuss several forces that affect pharmaceutical firms' profitability. We also illustrate pharmaceutical firms' strategies to cope with existing regulations in order to sustain profitability, which include, for example, the strategies that exploit the loopholes of the Hatch-Waxman Act. Thereafter, we discuss several indications on innovativeness and profitability of major U.S. pharmaceutical firms over time by using new evidence and an alternative measure. Generally, our findings coincide with the established criticism that the number of most innovative drug products has been declining over time. Incremental innovations have been dominating the industry in the past two decades. With respect to profitability, we show that the stock market valuation of pharmaceutical firms exceeds the average industries. Nevertheless, from a long term perspective, we acknowledge that it is hard to judge whether the industry has underperformed in terms of innovation.

In chapter 4, we investigate the roles that advertising and product differentiation play for the profitability of pharmaceutical firms. Despite the vast increase of advertising expenditure, as well as the high degree of product differentiation, few empirical studies examined their relationship with profitability. Instead, their focus has been on the role of R&D for pharmaceutical firms' profitability. In addition, our study provides an opportunity to test the popular claim that pharmaceutical firms put more emphasis on advertising than on R&D. Our results show that in the recent years, pharmaceutical firms' performance is not only closely linked to their R&D activities but also to advertising activities and product differentiation. In terms of total expenditure, we found no evidence that pharmaceutical firms spend more on advertising than on R&D. However, we do have an indication that advertising has been more effective in promoting firms' performance. Since the 1990's, the return of advertising has become three times larger than that of R&D. This characteristic is perhaps typical for the drug market as past studies usually found much higher R&D returns than that of advertising. In addition, we found that the impact of product differentiation came largely from the introduction of IMDs. The vast expand of the number of IMDs since the 1990s is likely to contribute to this.

Chapter 5 aims to answer the final question of this dissertation regarding the prevalent behavior of pharmaceutical companies in product differentiation strategies. We use a real option framework that assumes that a line extension is a firm's response to uncertainty both within and outside the firm. Using a repeated events duration model, we identify some determinants that affect companies' decision to extend or modify an existing drug product. These include uncertainty regarding the firm's stock volatility, financial constraints, competitive pressure and advertising growth. Our results reveal an important role for advertising and stock price volatility. In contrast to our hypothesis, however, we found that unlike cash flow and leverage, R&D expenditure does not function as a constraint in launching product extensions. The reason might be due to the fact that R&D expenditure is determined to a certain extent within companies' strategic planning. With respect to innovation, we argue that exclusivity rights have contributed to the rise of drug extensions over the years. For example, we show that the introduction of line extensions was the most intensive in the period when a drug product was protected by marketing exclusivities.

In chapter 6, we summarize the key findings of this dissertation, discuss their implications for firm strategies, give recommendations on public policies, and draw our limitations that provide endeavors for future research. Our recommendations for future research direct towards studies on the project level, studies that help to improve the implementations of a rational decision approach in drug prescriptions, and studies that use more accurate weights in assessing the innovation quality of drug products. Additionally, future research can generalize our findings on pharmaceutical firms' behavior in R&D, advertising and product differentiation.

Despite our indications that support the current criticisms, we emphasize that any change in public policy must be carefully considered in order to keep the innovation intact. Nevertheless, we provide several policy recommendations that might improve the current situation. These include the improvement of dissemination of information regarding the value of drug products to the stakeholders. Using better information can provide a more accurate signal about the relative value of different drug treatments that can eventually encourage firms to produce high value drug products.

This information can also be related to patents and marketing exclusivity

grants, as well as to rebate programs in the health insurance scheme. Evaluations and revisions should be made of current policies regarding patents and marketing exclusivity, as well as regarding the rebate programs that provide an indirect incentive for firms to launch modified drugs. This implies a new policy that strongly discriminates between innovative and less innovative drug products. For example, new policy can reward longer market exclusivity to breakthrough drugs and at the same give a shorter exclusivity period for slight modifications than the current regulations do.

Finally, we argue that the disclosure of information on advertising can facilitate future research, which in turn, contributes to a better assessment of industry innovativeness and profitability.

We note several implications for pharmaceutical firms' strategies. First, we believe that incremental innovations complement radical innovations in enhancing firms' profitability in the pharmaceutical industry. Therefore, the emphasis has to be put on lengthening the product life cycle of blockbusters, instead of focusing on each category independently. Second, due to in creasing cost of legal strategies, we argue that marketing strategies can give a good alternative. In the face of patent expiration, combining several strategies with product differentiation has strengthening effects on the revitalization of firms' revenue. These strategies include advertising, product and pricing strategies. Nevertheless, we argue that pharmaceutical firms cannot survive without true innovations.

SUMMARY (IN DUTCH)

De afgelopen jaren is innovatie binnen de farmaceutische industrie kritisch bekeken. Intensieve marketing activiteiten die meer nadruk krijgen dan R&D uitgaven, de explosieve stijging van het aantal me-too medicijnen in de markt en de hoge winsten binnen de industrie hebben allen bijgedragen aan de publieke scepsis over de innovativiteit van de industrie. Deze kritieken zijn echter ook bestreden om hun eenvoud. Ze lijken voorbij te gaan aan het feit dat het ontwikkelen van een nieuw medicijn een riskante onderneming is die slechts kan worden gecompenseerd met aantrekkelijke opbrengsten. Daarnaast wordt er gesteld dat de inkomsten van de industrie de kosten (wanneer deze worden gecorrigeerd voor het aanverwante risico) maar weinig overstijgen.

Vanuit de bovenstaande discussie beoogt dit proefschrift de volgende vragen te beantwoorden: (1) Wat zijn de prestaties van de farmaceutische industrie in termen van innovativiteit en winst? (2) Wat is de invloed van reclame en productdifferentiatie op de winst van farmaceutische bedrijven door de tijd heen? (3) Wat zijn de drijfveren van de farmaceutische industrie om extensies van bestaande medicijnen te introduceren?

In de hoofdstukken 3, 4 en 5 van dit proefschrift bespreken we drie studies die een antwoord geven op de bovenstaande vragen. In hoofdstuk 6 bespreken we de implicaties van deze studies voor de strategieën van bedrijven en doen we aanbevelingen voor overheidsbeleid. We doen eveneens suggesties voor vervolgonderzoek.

Ter introductie van de industrieanalyse in hoofdstuk 3, beschrijft hoofdstuk 2 drie belangrijke kenmerken van de farmaceutische industrie. Ten eerste bespreken we enkele basiscondities voor concurrentie binnen de industrie: de aard van de markt, het type bedrijven dat in die markt opereert en de verschillende soorten medicijnen die er zijn. We beschrijven tevens een productlevenscyclus die typisch is voor de producten in de industrie. Ten tweede bespreken we de Hax-Waxman Act, die is aangenomen als reactie op de toenemende bezorgdheid over stijgende kosten binnen de gezondheidszorg en die tot doel heeft toegang tot de markt voor generieke medicijnen te vereenvoudigen. De Act heeft tevens tot doel om meer innovatieve bedrijven te stimuleren in hun activiteiten door de verlening van rechten voor exclusiviteit middels patenten en marketing exclusiviteit.

Zodoende streeft de Act naar een balans tussen enerzijds lage prijzen voor medicijnen en anderzijds het behoud van innovativiteit. Ten derde bespreken we enkele belangrijke kritieken op de industrie en komen hun tegenargumenten aan bod.

Hoofdstuk 3 beantwoordt de eerste onderzoeksvraag van het proefschrift op basis van een analyse van de farmaceutische industrie in de VS. Voordat we ingaan op de prestaties van de industrie doen we eerst enkele basisanalyses betreffende de vraag en aanbod condities van de industrie en de verschillende krachten die de winsten van farmaceutische bedrijven beïnvloeden. We beschrijven tevens de manieren waarop farmaceutische bedrijven omgaan met de bestaande regelgeving teneinde winstgevend te blijven, zoals de strategieën waarmee ze de mazen in de Hatch-Waxman Act benutten. Vervolgens bespreken we een aantal indicatoren van de innovativiteit en winstgevendheid van de grotere farmaceutische bedrijven in de VS voor een langere tijdsperiode. We maken hierbij gebruik van nieuwe gegevens en een alternatieve maat. Over het algemeen vallen onze bevindingen samen met de gevestigde kritiek dat het aantal van de meest innovatieve medicijnen door de tijd heen is afgenomen. Incrementele innovaties hebben de industrie de afgelopen twee decennia gedomineerd. Wat betreft de winstgevendheid tonen we aan dat de waardering van de farmaceutische industrie door de effectenbeurs groter is dan die van andere industrieën en dat de opbrengsten in de afgelopen 50 jaar niet hoger zijn geweest. Desondanks erkennen we dat het moeilijk is om vanuit een langere termijn perspectief te beoordelen of de prestaties van de industrie in termen van innovatie achterblijven.

In hoofdstuk 4 onderzoeken we de invloed van reclame en productdifferentiatie op de winstgevendheid van farmaceutische bedrijven. Ondanks de enorme toename van reclame uitgaven en de hoge mate van productdifferentiatie onderzochten maar weinig empirische studies deze relaties en is de aandacht vooral uitgegaan naar de invloed van R&D op winstgevendheid. Onze studie biedt daarnaast de mogelijkheid om de veelgehoorde bewering te toetsen dat farmaceutische bedrijven meer nadruk leggen op reclame dan op R&D. De resultaten laten zien dat de prestaties van hedendaagse farmaceutische bedrijven niet alleen sterk gerelateerd zijn aan hun R&D activiteiten, maar ook aan reclame uitgaven en productdifferentiatie. In termen van totale uitgaven vinden we geen

bewijs voor de stelling dat farmaceutische bedrijven meer uitgeven aan reclame dan aan R&D. We hebben echter wel een indicatie dat reclame een grotere bijdrage levert aan de prestaties van bedrijven. Sinds 1990 zijn de opbrengsten van reclame drie keer zo groot geworden als die van R&D. Dit is wellicht een typisch kenmerk van de farmaceutische industrie daar voorgaande studies gewoonlijk grotere opbrengsten uit R&D dan uit reclame vonden. Daarnaast vinden we dat de invloed van productdifferentiatie voornamelijk voortkomt uit de introductie van incrementele innovaties. De sterke stijging van het aantal incrementele innovaties sinds 1990 draagt hier waarschijnlijk aan bij.

Hoofdstuk 5 tracht de laatste vraag van dit proefschrift over het gedrag van farmaceutische bedrijven betreffende productdifferentiatiestrategieën te beantwoorden. We gebruiken een real option raamwerk dat aanneemt dat een uitbreiding van de productlijn de reactie is van een bedrijf op onzekerheid binnen en buiten de organisatie. Middels een repeated events duration model identificeren we enkele determinanten van de beslissing van bedrijven om een bestaand medicijn uit te breiden of aan te passen. Deze determinanten zijn onder meer onzekerheid over de veranderlijkheid van de waarde van aandelen van een bedrijf, financiële beperkingen, concurrentiedruk en de groei van reclame uitgaven. Onze resultaten wijzen op een relatief grote invloed van reclame uitgaven en onzekerheid met betrekking tot de aandelenwaarde. Tegengesteld aan onze verwachtingen, echter, vonden we dat, in tegenstelling tot cashflow en financiële beperkingen, R&D uitgaven niet functioneren als een beperking op het lanceren van lijnextensies. De verklaring hiervoor kan zijn dat R&D uitgaven voor een deel bepaald worden door de strategische planning van een bedrijf. Wat betreft innovatie zijn we van mening dat rechten op exclusiviteit hebben bijgedragen aan de toename van incrementeel innovatieve medicijnen door de jaren heen. We laten bijvoorbeeld zien dat de introductie van lijnextensies het meest voorkwam in de periode waarin het medicijn werd beschermd door marketing exclusiviteit.

In hoofdstuk 6 vatten we de belangrijkste bevindingen van het proefschrift samen en bespreken we de implicaties ervan voor bedrijfsstrategieën. We doen tevens aanbevelingen voor beleidsmakers en wijzen op de beperkingen van het onderzoek die om vervolgonderzoek vragen. Onze aanbevelingen voor toekomstig onderzoek betreffen het doen van

onderzoek op projectniveau, het doen van studies die van dienst kunnen zijn bij het verbeteren van de invoering van een rationele beslissingsbenadering bij het voorschrijven van medicijnen en studies die kwaliteit meewegen bij het beoordelen van de innovativiteit van medicijnen. Daarnaast kan toekomstig onderzoek zich richten op de generaliseerbaarheid van onze bevindingen betreffende het gedrag van farmaceutische bedrijven voor wat betreft R&D uitgaven, reclame uitgaven en productdifferentiatie.

Ondanks onze aanwijzingen die de huidige kritieken op de farmaceutische industrie ondersteunen, benadrukken we dat iedere verandering in overheidsbeleid zorgvuldig dient te worden afgewogen zodat de innovativiteit van de industrie intact blijft. Desalniettemin doen we enkele aanbevelingen voor beleid die de huidige situatie zouden kunnen verbeteren. Deze betreffen onder meer de verbetering van de beschikbaarheid van informatie over de waarde van medicijnen voor alle belanghebbenden. De beschikbaarheid van betere informatie geeft een nauwkeuriger beeld van de relatieve waarde van verschillende medicinale behandelingen en dit kan bedrijven uiteindelijk aanmoedigen om hoogwaardige farmaceutische producten te ontwikkelen.

Deze informatie kan ook worden gerelateerd aan patenten, de rechten op marketing exclusiviteit en kortingsprogramma's binnen het gezondheidszorgstelsel. Het huidige beleid dat daar betrekking op heeft moet worden geëvalueerd en herzien, omdat het indirect een prikkel vormt voor bedrijven om voornamelijk gemodificeerde medicijnen op de markt te brengen. Dit vraagt om nieuw beleid dat een duidelijk onderscheid maakt tussen innovatieve en minder innovatieve medicijnen. Zulk beleid zou bijvoorbeeld langduriger rechten op marketing exclusiviteit kunnen verlenen voor revolutionair nieuwe medicijnen en tegelijkertijd een kortere periode van exclusiviteit kunnen verlenen voor minder innovatieve medicijnen.

Als laatste stellen we dat het openbaar maken van informatie over marketing uitgaven het inzicht in de innovativiteit van de industrie zou kunnen verbeteren. Dit draagt op zijn beurt bij aan een betere beoordeling van de innovativiteit en winstgevendheid van de industrie.

We geven tot slot enkele implicaties voor de strategieën van farmaceutische

bedrijven. Allereerst zijn we van mening dat incrementele innovaties een aanvullende rol kunnen vervullen naast radicale innovaties bij het verhogen van de winst van farmaceutische bedrijven. De nadruk dient daarom te liggen op het verlengen van de levenscyclus van blockbuster medicijnen in plaats van op de discussie over welke innovaties beter zijn dan andere. Ten tweede, met het oog op het verloop van patenten, heeft een combinatie van verschillende strategieën in combinatie met productdifferentiatie een versterkende werking bij het vergroten van de inkomsten van bedrijven. Deze strategieën betreffen onder meer reclame, prijszetting en ook juridische strategieën. Desondanks wijzen wij erop dat farmaceutische bedrijven niet kunnen overleven zonder werkelijke innovatie.

CURRICULUM VITAE

After studying technical metallurgy for one semester at Universitas Indonesia, Jakarta, Lenny Pattikawa (1973) decided to pursue a master's degree in economics at the Erasmus University Rotterdam. She specialized in economics and business economics and graduated in May 2000. In September 2000, she became a research assistant at the same university in which she carried out a study on the determinants of new product performance. In October 2002, she joined ERIM as a PhD candidate and started research on the pharmaceutical industry. Lenny has published her work in the *European Journal of Marketing*, ERIM working paper series, and in several international proceedings. She also presented her research at national and international conferences, including those of *Prebem*, *Marketing Science*, the *Academy of Management*, and the *American Marketing Association*.

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Innovation in the Pharmaceutical Industry

Evidence from Drug Introductions in the U.S.

Society benefits the most when pharmaceutical industries supply drug products at competitive prices and when they simultaneously maintain optimal innovation rates. Nowadays, however, the U.S. pharmaceutical industry has been under thorough scrutiny. The increasing cost of healthcare, intensive marketing activities, the strong rise of me-too drugs, and, despite all, the high industry profitability have contributed to public skepticism. On the other hand, developing a new drug is a high-risk activity that can only be compensated by attractive rates of returns that are secured by patent systems. High profitability is needed to fund R&D that can, in turn, advance innovation. Against this background we present three studies on the U.S. pharmaceutical industry.

The first part performs an industry analysis by using theoretical frameworks from economics. We describe several forces that have shaped the industry, including supply and demand conditions, market structure, and government regulations. We show how firms respond to these by implementing various conducts such as legal and marketing strategies. Thereafter, we assess performance of the industry in terms of profitability, productivity, and innovativeness. The second part explains the industry's profitability over time as a function of their intangible assets by using a market valuation model. Our results show that firms have successfully utilized their intangible resources to sustain high market performance. Additionally, we found an increasing contribution of advertising on firms' performance. Part three focuses on product differentiation strategies. We use a real option framework that perceives a line extension as a firm's response to uncertainty. Using a repeated events duration model, we identify several determinants that affect firm decisions concerning line extensions. These include uncertainty regarding stock volatility, financial constraints, competitive pressure, and advertising growth. We conclude with implications for public policies, firms' strategies, and future research.

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