Market reaction to FDA Announcements in the context of Patent Cliff

Author: Andrei ARMENEAN

Supervisor: Dr. Christian SCHMALTZ

December 2012
Acknowledgments:

I would like to thank Dr. Christian Schmaltz, Associate Professor in the Department of Economics and Business Studies at the Aarhus University, for supervising my thesis and for his continued support and guidance throughout the period of this research. To Dr. Anders Grosen for being immensely patient and for his inspiring session in the preparation of this topic.
Market reaction to FDA Announcements in the context of Patent Cliff

Andrei Armenean
Business and Social Sciences,
Aarhus University
November 28, 2012

Abstract

This study examine the approval decision of the Food and Drug Administration (FDA) and exposes implications of Patent Cliff in this process. We show that investors adjust expectations towards the final approval event, and their perspective changes depending the product and company type. While top pharmaceutical firms benefit from the approval of NMEs (new molecular entities), the effect of generic approvals changes by the end of the period studied (2000-2012). Approvals of niche therapeutic class like diabetes treatments do not register any effect in the financial markets. Generic competitors tend to overtake new patent expiration with increase strategic synergies towards big pharmaceuticals.

Keywords: Food and Drug Administration, Approval process, Pharmaceutical Industry, Event Study, Financial Markets, Product announcement, Market reaction,
JEL classification: E22; L15; L65
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Introduction</strong></td>
<td>1</td>
</tr>
<tr>
<td>1.1 Background</td>
<td>1</td>
</tr>
<tr>
<td>1.2 The Decreased R&amp;D Efficiency within the pharmaceutical industry</td>
<td>2</td>
</tr>
<tr>
<td>1.3 Expectations of the current study</td>
<td>4</td>
</tr>
<tr>
<td>1.4 Study Outline</td>
<td>4</td>
</tr>
<tr>
<td><strong>2 Literature Review</strong></td>
<td>6</td>
</tr>
<tr>
<td>2.1 The Pharmaceutical Industry</td>
<td>6</td>
</tr>
<tr>
<td>2.2 Industry Structure</td>
<td>6</td>
</tr>
<tr>
<td>2.3 FDA Regulations</td>
<td>13</td>
</tr>
<tr>
<td>2.4 New Drug development and approval process</td>
<td>18</td>
</tr>
<tr>
<td>2.5 Efficient Market Hypothesis Theoretical Framework</td>
<td>21</td>
</tr>
<tr>
<td>2.6 Event Study Overview</td>
<td>21</td>
</tr>
<tr>
<td>2.7 An Event Study Model</td>
<td>22</td>
</tr>
<tr>
<td>2.8 New Product approval and Firm-value Effect</td>
<td>25</td>
</tr>
<tr>
<td><strong>3 Methodology</strong></td>
<td>28</td>
</tr>
<tr>
<td><strong>4 Data and Sources</strong></td>
<td>32</td>
</tr>
<tr>
<td>4.1 FDA Data</td>
<td>33</td>
</tr>
<tr>
<td><strong>5 Empirical Results and Analysis</strong></td>
<td>37</td>
</tr>
<tr>
<td>5.1 Hypothesis testing results</td>
<td>38</td>
</tr>
<tr>
<td>5.2 Concluding remarks</td>
<td>42</td>
</tr>
</tbody>
</table>
List of Figures

1  Top Global Largest Pharmaceuticals  
   
2  Consolidation of today’s biggest pharmaceuticals  
   
3  Intense R&D Industries and Internationalization  
   
4  Effective Patent life  
   
5  NMEs Approvals vs Research and Development Spending  
   
6  Pharmaceutical industry Research and Development expenditure Ranking  
   
7  Approval Process for a New Molecular Entity (NMEs).  
   
8  New Drug Application (NDA) Review Process  
   
9  Overview of New Drug Application (NDA) Review Process, Source: 
   www.fda.org  
   
10 Time line for an event study, based on MacKinley (1997).  
   
11 Top 20 Pharmaceuticals by R&D Spending  
   
12 Sample 1 Summary Pharma Sample Part 1  
   
13 Sample 1 Summary Pharma Sample Continued  
   
14 Generic Samples Description Table  
   
15 Average Abnormal Returns - All samples overview  
   
16 Pharma Sample AAR  
   
17 Generic 2001-2002 AAR
1 Introduction

The pharmaceutical industry has enjoyed a prolonged success line in which it has scored a decade of tremendous growth and profits on the back of novel and important innovative medicines. The big question of the moment is *where the growth will come from for the next decade?*. The pharmaceutical industry has entered a period of substantial uncertainty and transition, as showed by R&D costs and scarcer new treatment against a set of calls for price and governmental controls.

Pharmaceutical industry finds itself under increasing pressure to maintain its high margins by a society that reached the limits to pay for pharmaceutical innovation. Three important trends affecting the industry systematically: 1) microeconomics conditions and slow down of western markets but strong growth in emerging countries, 2) raising pressure on health care costs (EU &US) and 3) aggressive generic competition and increasing costs of pharmaceutical innovation.

1.1 Background

Considering a 20 years investment horizon for research-based pharmaceuticals and U.S. presidential elections in which the industry is often under pressure, there is a message that is more and more repeated within the industry: *the outdated pharmaceutical R&D business model*(PhaRMA 2009) *will not be able to generate sufficient returns on a today basis expenditure to discover, develop and marketing the next wave of decade of new medicines to market.* Many experts confirm that the new model has to be an evolved one, a reduced expenditures and focus on areas of sustainable returns or in most real case a mixture of both.

While the industry more than doubled from 1995 to 2005 from $280 to $600 bill (DeMasi 2003) it switched shifts and many investors *shorted* the pharmaceutical industry the past few years. Furthermore it underperformed S&P and consumers goods industry by more than 2% points during the first half of past decade(BCG 2010).

The investors did the math deciding to *shorter* the industry due to declining productivity and surging R&D costs for new drug developments e.i. new molecular
entities (NMEs). Their perspective is that there is an overcapacity and today’s returns are unlikely to match the past decade returns. The numbers do not sum up anymore and regarding what mathematical models advisers use to project investments returns, based on the past decade golden period, the success stories were a mater of brilliance and fortune. If taken out the governmental demand and the declining costs preclinical modules, the success rate reduce the internal rate of return (IRR) to nothing but 11% and that is something not many investors consider worth taking the risk [13] for. It is starting to look more like a consumer goods industry, with the inclusion of branding rather than patent powered portfolio in line with low growth rates.

The common denominator of these changes described above, is called The Patent Cliff and market evolution. It is nothing else than a massive expiration of exclusivity rights for a range of products owned by the top 20 big pharmaceuticals that concentrates on more than half of the industry and profit R&D pipeline productivity loses against generic competitors that are challenging every patent-expiring blockbuster drug. According to (Thomson 2011 report) these products that weight heavily in their owner’s portfolio are about to leave big wholes that will shrink their sales and ignite changes within the dynamics of the industry shifting the perspective of patents and efficiency of R&D. The pharmaceutical companies are facing a number of challenges:

◊ changes in R&D pipeline igniting unexpected increase activity in M&A and other kind of alliances.

◊ sharing resources and knowledge, finding new revenues/value segments i.e. developing markets

1.2 The Decreased R&D Efficiency within the pharmaceutical industry

The topic of the pharmaceutical industry as research context was chosen because the outcomes of drug development efforts are clearly evident. The FDA is a crucial
gatekeeper that has the final word in whether a NME (New Molecular Entity) can be approved for marketing to end-user. Each FDA decision is a clearly marked event that can be studied to evaluate the effect of a new drug on firm performance. The outcome allows the application of Event Study methodology to evaluate the link between product approval as R&D efficiency and element of firm financial performance.

The purpose of our study is to observe how the approval announcement of NMEs affect the stock price of the firm at the approval moment. Considering this event to affect in different way a diversified (top pharmaceuticals) and therapy-segment focused pharmaceuticals (diabetes), and that the patent cliff has a spillover effect for the generic companies approximating these affects towards 2011-2012, peak for the patent cliff (OptumRx 2011). The majority of event studies in this field of research date back to the 1990s. Most of this research is focused on long-time periods to study the relations between R&D expenditures and the profits of the pharmaceuticals. These studies are good to understand the pattern of the industry but not for trying to explain the current changes and their long term effects. On the other hand these studies update old ones back to 70s or 80s when the pharmaceutical industry was sampled as part of the chemical industry. We feel this issue needs to be investigated more intense over separated industry key sectors that tend to converge to each other and that will fight for the future $1.1 trillions in sales of the global market by 2015 [24].

The purpose of this paper is to fill the gap in the study of R&D efficiency of the pharmaceutical industry focusing on new market segmentation and updating results for a long outdated time horizons and put it into the perspective of the patent cliff. Using a segmentation criteria we study the abnormal returns from the overall pharmaceutical industry perspective down to one of its niche, diabetes. The second segmentation is time related and focuses on generic industry in early 2000 and later 2012 and evaluate changes in abnormal returns. What is the role of the generic market also affected by these changes in the industry or these may present an opportunity.
Therefore we intend answering next research questions:

→ Are there abnormal returns at the FDA announcement date?

→ In what measure are these findings different from other research findings?

→ What changes in FDA approval impact can be explained by the patent cliff?

1.3 Expectations of the current study

The attempt of this study is to identify the existence of these abnormal return in the stock price of FDA announcement, and measuring differences if any, in the way financial markets react to FDA announcements, across our segments of study. I believe that measuring these differences will help us understand better the way the patent cliff affects systematically the pharmaceutical industry. We measure these abnormal returns for firms during a specific period around the announcement date of an approval of a new drug by the Food and Drug Administration (FDA).

Preview literature focused on the trend of these abnormal returns over time, at different stages of the approval or rejection decision. On the other hand these studies focus mainly in long time horizon, unlike our study that focuses mainly on the latest possible available data.

Ignited by the adjustments the patent cliff is causes into the industry, the present study is a examination of the current changes. This study also asses the link between product innovation and financial performance of the sponsor company. A particular study that is being used as reference is Market Response to FDA announcements (De Jong & Sarkar 2006). To test the announcement effect into the financial markets, the well known event study methodology is being used in current study, using MacKynaley 1997 as reference methodology [19].

1.4 Study Outline

Following the first section, the rest of this study is organized as follow: Section II is dedicated to Literature review and other theoretical frameworks, discussions about the pharmaceutical industry and the recent developments related to the patent cliff.
The theoretical framework contains a review of the efficient market hypothesis as ground for the existence of abnormal returns. Section III describes the applied methodology of Event Study and details of implementation. Section IV presents detail descriptions of the nature of the data and its sources. Segmentation methods and selection processes. Section V include the presentation of our findings and results to our three main research questions. Section VI summarizes concluding remarks of this research, and suggests alternative topics for future research.
2 Literature Review

In this section we discuss past findings related to the FDA approval impact in the financial markets together with regulation and approval process of NMEs (New Molecular Entity) of the pharmaceutical industry. Detail information about the current trends and R&D performance as well as industry dynamics will be included in the subsection Pharmaceutical industry. In the next subsection we will analyze different aspects of new product development and different characteristics that have new implications in today’s R&D. We dedicate another subsection to Regulatory implications and bring to light the political courses that affect R&D and new product development in the sector. The last section is dedicated to the event studies and some basic aspects that need to be discussed about challenges at conducting an event study.

2.1 The Pharmaceutical Industry

About Food and Drug Administration

Most known as Food and Drug Administration (FDA). It is a regulatory institutions (European Medicines Agency, EMEA in Europe) with the role of assuring the safety of the pharmaceutical products and regulate the pharmaceutical industry. Every new drug has to pass a series of clinical trials where is tested for safety, efficiency and side effects. The FDA regulates more than $1 trillion worth of consumer goods, about 25% of consumer expenditures in the United States. The FDA is responsible for protecting and promoting public health through the regulation and supervision of pharmaceutical products and consumers goods.

2.2 Industry Structure

The demand for products can be separated between products that end consumers can by directly, over the counter, and those that must be prescribed by doctor. The last kind of segment that is currently the most important sector and that makes this market more special in terms of regulations and market structure. The demand for prescribed drugs at its turn can be separated in intramural market (hospital) and
the extramural market (domestic, home consumption) Craig and Malek (1995).

The pharmaceutical sector is a high-technology and knowledge-intensive industry. The structure of the industry is a two-tier structure. The largest companies account for the majority of the R&D investment in the industry holding the majority of patents. The second tier is formed by a large number of smaller firms manufacture off-patent products or under license to a patent-holder. The pharmaceutical industry is deeply regulated. Few aspects of the industry are unaffected by regulatory controls (OECD 2000 Regulatory in the Pharmaceutical industry). Patent protection is designed to enable innovators to recover the fixed costs caused by the development of the new drug, thus fostering incentives for innovation. The optimal length of patent life can be regarded as the outcome of a non-cooperative game between regulator and innovator [1]. The price quality relationship is characterized by the countries regulation system. As concluded in their study [11] (Frutos, Ornaghi, Siotis 2010) the doctor patient relationship stimulus the price elasticity and therefore the effect new generic competitors might have [10].

Price competition on markets for pharmaceuticals is limited not only because of market closure due to patent protection but also because of low price sensitivity of patients due to health insurance. However, three types of price competition cause the prices of innovative drugs to converge towards those of existing preparations own innovation drugs, generic alternatives, and generics among themselves. In a recent report of Congressional budget office (CBO) it was mentioned that the pharmaceutical industry is one of the most research-intensive industries in the United States. Pharmaceutical firms invest as much as five times more in research and development, relative to their sales, than average U.S. manufacturing firm (CBO Study, 2006, pp: 19). CBO report on the R&D in Pharmaceutical Industry also mentioned that over past 25 years, R&D intensity has grown by about 50 percent. Although in the past decade evidences have been found that sometimes companies spend more on marketing strategies and compensations compared to the actual R&D costs. Most of that growth occurred in the 1980s and since then, the R&D intensity of the pharmaceutical industry remained around 19% of Sales according to the pharmaceutical industry’s trade association, Pharmaceutical Research and Manufacturers of Amer-
The product development is also driven by demographic factors and life expectancy that are highly correlated and affect market size. In this study (Endogenous innovations in the pharmaceutical industry by Rodrigo A. Cerda), Rodrigo founds the market size very close linked to new drug developments. In its study, increase of population is close linked to new drug products into the market that expend the life expectancy, which at its turn retro aliment the population drug consumption and the direction the new R&D efforts are going towards. Demand for therapeutic medicines in developed countries is pointing to diabetes, Alzheimer or cancer targeting high income aging population. Strategic decision respecting the

![Table](https://example.com/table.png)

**Table 1:** Top Global Largest Pharmaceuticals

*Source - IMS Health Midas, December 2010*
flow of innovation that are linked to the realization of abnormal profits from the market. This observation revealed the fact that the continuous stream of product innovations gives competitive advantages to the firms to face the competitors and keep its existence in the market intact. However, the flow of innovation requires allocation of R&D resources, innovation that is prerequisite part of introducing new products into the market (ASHLEE B. MEHL 2006). Eventually, at the end of this process the R&D pipeline a final approval or rejection decision by the Food and Drug Administration. This will allow the company to commercialize its product. The newly introduced product faces limited direct competition study of (Sharma & Lacey, 2004). About 20% of all submissions of New Molecular Entities (NMEs) are approved in the final stage of the process (See www.fda.gov for more details).

Has the Drug Industry's Innovative Performance Declined?

We notice that the number of new drugs introduces each year has not kept pace with research and development spending in the drug industry. A conventional measure of R&D performance, the number of new molecular entities (NMEs) per annual research spending has declined significantly over the past three decades. These misleading measures, if incomplete, affected by structural changes like M&A (Figure 2) or increase technological complexity have hurt the real productivity of the industry. Major advances in some therapeutic areas foothold-growing costs per innovation. The period 1970 to 1990 indicates steady growth in NMEs approved by the FDA with R&D expenditures increasing more gradually then accelerating. The important shift happened after 1990 when NMEs approvals dropped sharply although R&D continued to rise (See Figure 6).

Can be misleading to drag conclusions regarding the performance of the drug industry based on these observations. The benefits and quality of these drugs to the society are not straightforward observable and many advances in the period 2000 including important, pioneering, or more effective drug therapies, the industry’s actual R&D productivity would not necessarily be lower.

Another factor influencing the productivity in the drug industry is the consolidation process (M&A). Like in the decade of 1990 we live another wave of consolidations and we can see intense consolidation activities in the industry. Currently, eight of
Figure 2: Consolidation of today’s biggest pharmaceuticals

Source: Congressional Budget Office based on information from IMS Health and the companies listed above

the top 10 firms are the products of horizontal mergers between two or more large drug companies, all of which occurred since 1989 (Figure 2).

The pharmaceutical industry being a science-driven environment, is inexorably global. Considering small pharmaceutical companies that originate in their local small country markets, where high R&D costs can only be recovered by targeting the resulting drug product to a worldwide market. International trade statistics by the WTO (2002) illustrate the tremendous increase in international business over the past twenty years. Characterized by a high R&D to sales ratio, pharmaceutical companies are highly R&D intensity. Many of the these companies included in (Figure 3) have their R&D increase even further with the internationalization and boost their R&D to Sales ratio up to a 20%. Most of the pharmaceutical companies are found in the top right of the graph (See Figure 3, next page) and are one of the global biggest in their industry [1].

This internationalization of R&D not as much driven by science & technology-related factors but by sales to output efficiency like mentioned in the study. Direct cost advantages (such as the often publicized labor costs) rarely influence the in-
ternationalization of R&D, but other efficiency factors such as costs of coordination and transfer, and critical laboratory size do have an even bigger impact on international R&D organization. Direct costs may become more important in the coming years as the other factors improve in low labor cost countries [1].

The Generic and the Diabetes Segments

A small number of NMEs receive marketing approval from FDA and of those approved, only a few are successful. The profitability of a new best-selling drug can be substantial and pharmaceutical companies spend substantial amounts of money promoting their branded drug. Despite the research-intensiveness of this sector, pharmaceutical companies began spending more on marketing than on R&D (OCDE 2000). Although there are a large number of drug manufacturers, the level of concentration for drugs to treat a given medical condition (known as the therapeutic class) can be very high.
Diabetes is the syndrome of having excess blood sugar due to low levels of insulin or insulin resistance. Approximately 21 million individuals in the U.S. have diabetes, and this number is growing at 10% a year, or over 1.5 million new cases annually. Age and obesity are both risk factors, and contributes to this number. There are two types of diabetes affections:

- **Type I Diabetes**: can occur at any age, but it is most often diagnosed in children, teens, or young adults. In this disease, the body makes little or no insulin. Daily injections of insulin are needed.

- **Type II diabetes**: makes up most diabetes cases. It most often occurs in adulthood. However, because of high obesity rates, teens and young adults are now being diagnosed with it. Many people with type 2 diabetes do not know they have it.

The Global Market for Diabetes Management accounted for USD 40 billion in 2010 and is expected to attain a market size of around USD 114 billion following a growth rate of 13.5% CAGR. The major products in this market consists of glucose meters, test strips, lancets, continuous blood glucose meters, syringes, insulin pumps, insulin and other insulin delivery devices and anti-diabetic drugs. However, insulin, test strips and anti-diabetic drugs are the most revenue generating products. Diabetes often cannot be cured; many drug manufacturers and biotechnology companies make glucose monitors, insulin delivery devices, and drug products to help manage the condition. It is estimated that the total market for diabetes products and related care is worth $92 billions in the (Datamonitor 2007) U.S. Diabetes is especially important to Amylin, Novo Nordisk, Insulet, and DexCom, which focus on this market. Future of insulin market is closely monitored by FDA to increase its safety on heart affections side effects as disclosed during this year a panel meeting between the leaders manufacturers and FDA [3].

In Europe, with high level of national fragmented regulation, many countries also have explicit policies to encourage consumption of lower-cost generic medications. These policies can affect any of the different actors of the drug industry doctors,
pharmacists, wholesalers or customers. Economic incentives for the doctors to prescribe certain level of drug price for a specific therapeutic class to pharmacists that are obliged by law to ask if the customer wants a branded or a generic one.

'The strong headwinds facing big pharmaceutical groups are due in part to pressure from the rise of generic rivals. But many of these off-patent counterparts are having an equally tough time as they feel the squeeze from a harsh economic climate’ writes Andrew Jack in Financial Times.

2.3 FDA Regulations

Starting with Kefauver committee investigation, that evaluated the private R&D in the pharmaceutical industry in 1962 the R&D, role in the industry has not always kept balance between annual number of new NDAs and the correspondent investments. The claims of the Kefauver committee were that although the industry is one of the heaviest in R&D expenditure at that time it did not brought much social benefits because large part of the most important discoveries were derived from work outside the industry e.i. publicly founded (U.S. Senate Report 1961, pp. 115-41), and the commercial laboratories in the industry were concerned largely with molecule manipulations which implies the new drugs were therapeutically similar to those already in the market. The industry rejected the claims in support of deregulation [9]. This debate led, in subsequent years, to a considerable effort to explore the determinants and effects of the research and development in the pharmaceutical industry (Comanor, 1986).

Other source analyzing role of the R&D in the industry is the Congressional Budget Office (CBO) reports. A study of CBO (2006) found that the R&D can reach as five times more than in the average U.S. manufacturing firm (CBO Study, 2006, pp: 19). The pending on drug R&D has grown between threefold and sixfold over the past 25 years and that rise has been closely matched by growth in drug sales. Despite those increases, there has been little change in the number of innovative new drugs approved for use each year (Figure 4), even though the federal government has streamlined its drug-approval process (CBO Study, 2006, pp: 7).
In 1980, U.S. top companies spent a total of $5.5 billion (in 2005 dollars) on research and development, by the year 2005 hat figure had grown to more than $17 billion (National Science Foundation (NSF). The real growth of these investments in real terms has decreased from a 9% till 2003 to a 5% annually increase in 2008. The costs of developing a new molecular entity vs. the average R&D spending on it crossed direction in early 90s (Figure 5).

Between 1996 and 2006 the number of blockbuster drugs with annual sales of $1 billion or more (in 2000 dollars) increased from 6 to more than 50. These blockbuster drugs that are key for rising drug expenditures account for 50 percent of annual sales comparing to 10 percent in 1996. Since then, patent expiration and the arrival of competition from generic drugs have apparently reduced the revenue for brand-name drugs more quickly than it is being replaced by revenue from the introduction of new drugs (CBO Study, 2006, pp: 7). For the pharmaceutical industry as a whole, slower revenue growth could continue until sales of new drugs once again outpace revenue losses from expiring patents. Real R&D spending per successful new drug has been rising for many years [17], largely because of growth in the size and length of clinical trials and an increased rate of failure. Those changes mostly reflect drug compa-
Figure 5: NMEs Approvals vs Research and Development Spending

Source: Congressional Budget Office based on Pharmaceutical Research and Manufacturers of America, Pharmaceutical Industry Profile 2006 (PhRMA, March 2006).

Companies strategic choices about which kinds of drugs to pursue choices that depend on anticipated demand and scientific opportunities. In particular, drug companies are devoting more resources to developing drugs for chronic illnesses. Because those drugs require prolonged use, although they also have longer clinical trials are comply.

Development times vary by type of drug but have been averaging about 12 years from discovery through clinical trials all the way to approval by the FDA. Although private drug companies have been pursuing increasingly costly R&D projects, they would not do so if they did not expect to recoup their investment through sales of the resulting drug products. With this scenario of high R&D intensity and, relatively, the lower rate of new drugs introduced in the market grew the interest of stakeholders of the pharmaceutical industry and the New Drug Approval by FDA has become one of the highly watched and sensitive issue in the stock and the securities markets.

A study from Price Waterhouse Coopers (2011 Patent Litigation Report) shows that significant increase in lawsuits compensations due to misconduct, patent violations over the past 25 years from $1 bill in 1995 to $15 bill in 2011. More precisely, a different study (Public Citizens) estimates that over the past two decades, es-
especially during the past 10 years, there has been a marked increase in both the number of government settlements with pharmaceutical companies and the size of the accompanying financial penalties. Other regulatory implication is linked to the number of NMEs approved by FDA. During the second half of the 20th century, Rodrigo A. Cerda (2007) estimates regulation has deep effect on and founds evidences that number of NMEs drops every time increase regulatory shifts, increasing Time To Market process [7].

In a paper about incentives in the industry, (Wesley Yin 2007) (Market Incentives and Pharmaceutical Innovation) shows that tax credits can stimulate R&D; yet because they leave revenue margins unchanged, tax credits appear to have a smaller impact on private innovation in markets with smaller revenue potential [28]. Although innovation in R&D intensive industries has been shown to respond to market incentives (Newell 1999; Acemoglu and Linn 2004; Finkelstein 2004) We know that the costs of developing new drug entity rised till $800 mill Sharma and
Lacey, (2004); Grabowski (2002). On the other side, since FDA imposed more control and regulation the aggregate amount the pharmaceuticals settle to pay their infringements has also increased during the years. Therefore positive correlation might indicate that these costs are passed further on to the consumers indirectly. Referring to (DiMasi, 2003), the average cost is 802 million US$ for developing a new drug [13], which has a 21% chance of getting through the process and takes 11.9 years to develop. Patents last for 20 years and are normally filed after the discovery of the drug. As 12 years are spent on developing it, only 8 to 10 years of effective market monopoly are left.

As the costs for development a NMEs surged in the last decade, is understandable that maintaining the same level of profitability and expenditure is not sustainable. Studies that considered a new approach to these soaring costs have in focus the Time to Market element. Increase effort to reduce Time To Market (TTM) that implies a tradeoff between negotiating for a higher subsidy versus negotiating for a faster market introduction (Klaus-Challenges in Shortening New Product Introduction in the Pharmaceutical Industry). In a study about the pharma valuations (Jack Kloeber Ch:13) identifies five pillars that need to be considered adding value to a portfolio by considering four aspects of investment decisions: timing, risk, costs and value of opportunity. We already showed timing is a fundamental variable but very rigid and affected by regulations.
2.4 New Drug development and approval process

New molecular entities (NMEs) are drugs that contain an active substance not previously approved for marketing in the United States. Priority NMEs are ones that receive accelerated reviews by the Food and Drug Administration because of their potentially significant therapeutic value for rare health affections. The Food and Drug Administration department, Center for Drug Evaluation and Research (CDER) is responsible for carrying out the review process for all drugs including NMEs. The next self-explanatory illustration based on (pharma.org) shows the track of development of a NME:

![Table of New Drug Application (NDA) Review Process](fda.gov, 2007)

**Figure 7:** Approval Process for a New Molecular Entity (NMEs).
Source: Self illustrated from Pharmaceutical Research and Manufacturers of America [www.Pharma.org](www.Pharma.org)

To look more closely to the decision timing and the steps of the approval process we also include the FDA approval track illustration (or visit [www.FDA.gov](www.FDA.gov)). There are FDA announcements published at every step since one applicant files its IND (Investigation New Drug) application at FDA throughout NDA (New Drug Application) till they receive the verdict.

Bellow New Drug Application (NDA) Review Process (self-explanatory) Chart ([fda.gov](fda.gov), 2007) provides a general overview of CDER’s new drug application review process, including how CDER determines the benefit/risk profile of a drug product prior to approval for marketing. The regulation and control of new drugs in the United States has been based on the New Drug Application (NDA) since 1938.
Every new drug has been the subject of an approved NDA before commercialization in the U.S. drug market. All the information gathered during the IND will become part of the NDA application. The objective of this documentation regarding the clinical trials is to provide sufficient information to permit FDA reviewer to reach the following key decisions:

- If the drug meets the safety and efficiency requirements in its proposed use(s), and whether the benefits of the drug outweigh the risks.

- If the drug’s proposed labeling (package insert) is meets the regulatory framework and matched the use(s) the drug was approved for.

- If the methods used in manufacturing meet the requirements for its quality,
The required documentation for an NDA is designed in such a way that is providing the drug life-data from start of the research, ingredients throughout the testing on animals studies and how the drug effect on body, side effects etc. manufacturing process, quality label information and quality controls. Summary of the NDA content, format and classification of the NDA review process can be found in The New Drug Development section of the Center for Drug Evaluation and Research (CDER) Handbook.
2.5 Efficient Market Hypothesis Theoretical Framework

The efficient-market hypothesis (EMH) stats that in an efficient market, prices reflect all available information and one cannot achieve excess returns on risk-adjusted bases since securities are fairly priced. Based on EMH a security prices react efficiently to new relevant information and this is instantly reflected in the price, therefore investors cannot achieve abnormal returns based on this assumption on rational markets.

The ground of EMH start in 1933 but was consolidated by Eugene Fama at University of Chicago in the 70s and widely accepted and debated during 90s. According to the theory three conditions must be met for efficient markets. First, the market is free of transaction costs or taxes. Second, all investors have simultaneously access to information. And third all investors agree on the information’s impact on the security’s price. In reality, frictionless markets that fulfill all these conditions do hardly exist. Nevertheless, a market can still be efficient as long as an adequate number of market participants have free access to available information and the majority is able to interpret their implications rationally [15].

In 1970 Eugene B. Fama classified three types of market efficiency in order to test for the fairly general term market efficiency: week form, semi-strong form and strong form. All these forms vary in how historical information and predictable events and news are incorporated in the security price at different level of assimilation. Overall investors cannot apply technical analysis to predict future price movements since historical patterns cannot predict this changes [14].

2.6 Event Study Overview

An event study measures the effect of an economic event in the value of a firm using data of financial markets. Implemented widely over a range of disciplines such as Accounting, Marketing, Finance this method has become almost ubiquitous nowadays. At its core, event study methodology asses the impact of a particular event: earnings announcements, M&A, issues of debt or announcements of macro-economic variables.
In the late 1960s seminal studies by Ray Ball and Philip Brown (1968) and Eugene Fama (1969) introduced the methodology that is essentially the same as that which is in use today. Their contribution helped deal with 'complications arising from violations of the statistical assumptions used in the early work and relate to adjustments in the design to accommodate more specific hypotheses' (MacKinlay 1997).

Chaney (1991, pp: 580) describes the event study methodology as 'a natural outgrowth of the rational expectations/efficient markets tradition in the financial economics'. The Efficient Market Hypothesis (EMH) has been the ground of the theoretical background when researchers conducted the empirical studies to understand the way the financial market responded efficiently (and quickly) in publicly traded firms. This change in valuation of firm happens through the changes in stock price that is a reflection of assimilation of all publicly available information (Sharma & Lacey, 2004, pp: 299).

Given a certain event the change in security prices is regarded as an unbiased reflection of changes in the expected future cash flows of the firm, because the securities prices reflect all available information about the firm and also any new information received by the market is supposed to be incorporated instantaneously into the stock price in an efficient market. So, the event study methodology allows the researchers to investigate the price behavior of the firm's stock price around the time when a new information is received in the market about an event that affects the firm's cash flow [8] and that, essentially and explicitly, is a test of the underlying change in the unbiased market forecast of the firm's future income (Chaney et al., 1991, pp: 581).

2.7 An Event Study Model

A simple screening of the events studied in the wide literature, lists them by: good news (positive impact), bad news (negative impact) and no news (zero or no impact). The methodology studies the behaviors for firms/industries experiencing a common type of event such as: public announcements, performance data or more closed linked
to our study, approval of new products that could be marketed by the sponsoring firms only after the approval. The events can be spread over the period studied or clustered in a certain time such as regulatory events affecting the sample of firms. Although in the case of a clustering, statistical challenges may arise treating this clustering incidence [18]. (Khotari & Warner, 2006).

**Estimation period and Event Window**

After choosing the event we want to study we need to establish the estimation period and the event window. The event study methodology compare realized returns with expected returns equals the stock performance in the absence of the event. The event window is the time frame that can record this abnormal stock return in the presence of the event. In the event study literature, researchers use to define the size of this event window as number of days before and after the announcements to make sure that any leaks can be recorded or to see the duration of these excess returns.

![Figure 10: Time line for an event study, based on MacKinley (1997).](image)

The announcement day is defined as day \( t = 0 \). The period from \( T_0 \) to \( T_1 \) represents the estimation period and the period from \( T_1 \) to \( T_2 \) the event window.

Normal returns are estimated using the period prior to the event window, the 'estimation period'. (MacKinley, 1997; Petersen, 1989). Historical information of the estimation period is used to estimate the expected returns for a certain security. The size of the estimation period vary from study to study, but following the common practice in short term horizon event study we use as estimation period 250 days before the event window i.e. 260 days before the event.

The standard model (Khotari & Warner, 2006, pp: 09) suggests the time of the event is notated \( t = 0 \) e.g. for each security from the sample \( i \), the return for period \( t \) relative to the event is given by:
\[ R_{it} = X_{it} + e_{it} \] \hspace{1cm} (1)

Where:

- \( R_{it} \) - is the return on stock \( i \) on day \( t \)
- \( X_{it} \) is the normal (i.e., expected or predicted return given a particular model of expected returns), and \( e_{it} \) is the component of return that is abnormal or unexpected. In consequence the abnormal return is the difference between the observed return and the expected return:

\[ e_{it} = R_{it} + X_{it} \] \hspace{1cm} (2)

In event study methodology, the abnormal return is measured as the difference between the return conditioned by the event and the return unconditioned by the event. So abnormal returns is a direct measure of the unexpected change in security-holder’s wealth associated with the event. Typically, a security is a common stock unless is defined otherwise by the research. To be able to calculate the abnormal returns for a particular sample of firms, a model for predicted returns, i.e., expected returns unconditional on the event must be specified (Khotari & Warner, 2006, pp: 10). A survey of event study methodology literature identifies three common used models to estimate the expected returns (MacKynlay 1997, pp:17):

- **Constant Mean Return Model:** perhaps the simplest model, it can have similar results of more sophisticated models. It calculated the predicted return for a security equal to a constant is estimated by averaging a series of past returns (Brown and Warner (1980, 1985).

- **Market-adjusted Return Model:** the market-adjusted return model can be viewed as a restricted market model with \( \alpha_i \) constrained to be zero and \( \beta_i \) constrained to be one given the model \( R_{it} = \alpha_i + \beta_i + e_{it} \). Here estimation period is not required to obtain parameter estimates (MacKynlay 1997, pp:19).
• Market Model: statistical model based on a standard linear relationship between the market return and the security return.

The efficiency of these three models to estimate precisely the existence of abnormal performance are similar on a broad term, there are some preferences for the Market Model are found in the literature (Dyckman et al., 1984, pp: 29). Regarding the model used for expected returns the calculation of the abnormal returns (AR) is:

\[ AR_{it} = R_{it} - \alpha_i - \beta R_{mt} \]  

(3)

for each firm using the estimation period, in our case -260 to -11 days to the event day. \( R_{mt} \) being the market return during the estimation period.

The average abnormal return for each day \( t \) in event window is computed, and then the cumulative abnormal returns (CARs) were computed by cumulative daily average returns over different intervals using the following formula:

\[ CAR_{t,t+k} = \sum_{k=1}^{t+k} AR_k \]  

(4)

2.8 New Product approval and Firm-value Effect

Over the research literature studying the effect of innovation and R&D in the value of the firm was Mansfield (1964) investigated the number of significant innovations by the firm. Mansfield concluded that the expected rates of return from R&D projects determined the R&D expenditures. A subsequent study by Chaney, Devinney, and Winer (1991) found that new product announcement CARs (+1, 1) were highest for the most technologically dependent industries [8]. They mentioned that the use of monthly were 'not precise enough to reflect the impact of new products on security prices'. Although in their study, the pharmaceutical industry was grouped together with other chemical firms.

Desai and Jain (1997) found that wealth effect of stock split announcements is higher in smaller firms than in large ones [12]. Atiase (1985) described this difference between large and small firms as a surprise content for smaller firms and supported
the founding that the dissemination of publicly available information is a increase function of firm size in capitalization [2].

Woolridge and Snow (1990) studied the introduction of new products and stock market reaction as part of their research in Stock Market Reaction to Strategic Investment Decisions. Their sample composed of 767 announcements made by 248 companies in 102 industries using Marker-Adjusted return model of event study methodology. Their founding consistent with the EMH indicated the abnormal returns disappeared from -1 to +10 days window (Woolridge & Snow 1990 and Sharma & Lacey, 2004, pp 299). The lack of a statistically significant effect is a reflection of efficient market because the no significant price reaction may indicate, 'investors anticipated such moves and stock price already reflected this information' [27] (Woolridge & Snow 1990, pp: 359).

Another study, by Bosch and Lee (1994) investigated the market reaction to FDA announcement and found that average abnormal returns were statistically significant on the day before the announcement t= -1 to 0 day. Their sample based on Wall Street Journal publications of announcements from 1962 to 1989 for FDA decisions [4].

Exploring the changes in the stock market valuation of firms whether they are influenced by the outcomes of efforts to develop new products (Sharma & Lacey, 2004) explore the approval and the rejection FDA decision impact in the financial markets [23]. Using event study methodology and the market model to project the expected returns they construct a sample based on previous studies of Skowronsiki and Carlston (1989). Their sample analyses a total of 344 approvals and 41 outright rejections by the FDA. On a three-day cumulative abnormal returns they found on positive (1.56%) versus negative (-21.03%) news regarding rejections by the FDA were compared [25]. They conclude that information about new products is assimilated efficiently quickly and cleanly in the valuation of the sponsoring firm and that the markets compensate successful approvals by an increase in firm valuation, but they punish to a greater extent failure outcomes by a sharp decreasing valuation.

Valuating portfolios of products in the pharmaceutical industries studied by Terwiesch and Ulrich (2006). They examine the effect of the portfolio level project
interactions over the approval or rejection decision by FDA at phase III of the clinical trials. The probability of failure at this stage is about 20 per cent [26]. The existences of similar projects that utilize the same development resources as the fail project mitigate the impact of failure estimated at $405mill.

Studying the Market response to FDA announcements by Sarkar and Jong (2005), they study these decisions at four points in time and review process and explore conditions that may impact final approval. Based on FDA database they construct a sample of 189 firms from 1990 till 2001. They found positive abnormal returns on the day of the announcement and the day after of 0.35% and 2.2%, although with none of the CAAR (cumulative average abnormal returns) values are statistically significant [22]. The size of their abnormal returns in case of product approval or failure at the final stage while smaller than Bosch and Lee (1994) or Terwiesch and Ulrich (2006) explained that investors had already adjusted their portfolios and most of this announcement effect may already be factored into the price. Another interesting aspect is that between the two studies, 10 years difference, the cumulative abnormal return over the rejected decisions captured by 5 days period negative 4.76% is in their study only seen in one day, $t = 0$ but about the same size -4.04%.
3 Methodology

To evaluate the effect of the FDA approval of new drug and identify if these new flows of information reflect a change in the value of the companies we will use event study methodology. Based on standard financial theory we in previous section, we assume markets are efficient i.e., stock prices reflect all available relevant information (Fama, 1970). Therefore only uncertain, or unanticipated events will cause a change in the firm’s stock price. The public announcement of an official approval of a New Drug is considered as a information release event (IRE) in the stock market. We will consider different event windows to assess the size and length or leaking of this IRE in the firm stock price. For example the three-day window is formulated as the day of the event and the day before and the day after the event.

We will describe here only the market model as the market since Constant Mean Return Model and market-adjusted return model are straightforward and further disclosed in the appendix. Based on market model (Fama, Fisher, Jensen, and Roll, 1969, MacKanlay 1997) the expression for abnormal returns as:

\[ AR_{it} = R_{it} - E(R_{it}|X_t) \]  \hspace{1cm} (5)

where \( AR_{it}, R_{it} \) and \( E(R_{it}|X_t) \) are the abnormal return, actual return and predicted return respectively for the time t. \( X_t \) is the conditional information for the normal return model. Calculating the coefficients for the market model over the estimation period of -260 to -11 days prior the event. This will allow us to predict the stock behavior around the event date:

\[ R_{it} = \alpha_{it} + \beta_{it} R_{mt} + e_{it} \]  \hspace{1cm} (6)

Where \( R_{it} \) is the return on stock i on day t, for the period -260 to -11 day window. Here \( t = o \) would mean the event date. \( R_{mt} \) is the return on market index m on day t. \( \alpha_j \) and \( \beta_i \) are the regression intercept and coefficient. And \( e_{it} \) is the error
term of the regression model respectively.

Therefore the abnormal returns using market model as expected return model:

\[ AR_{it} = R_{it} - \alpha_i - \beta R_{mt} \]  \hspace{1cm} (7)

The abnormal returns is the disturbance term of the market model calculated on past performance bases (MacKinlay 1997). In addition to the estimation of the coefficients of the abnormal return, the coefficients of cumulative abnormal returns (\(CAR\)) have been estimated with different combinations of windows of the event-dates. Given \(N\) events, the sample aggregated abnormal returns for period \(t\) is:

\[ \overline{CAR_t} = \frac{1}{N} \sum_{i=1}^{N} AR_{it} \]  \hspace{1cm} (8)

Having the variance as following:

\[ var(AR_t) = \frac{1}{N^2} \sum_{i=1}^{N} \sigma_{it}^2 \]  \hspace{1cm} (9)

The coefficient estimate of the cumulative abnormal return may capture the information leakage about the NDAs before the event-date and it also may take into account of the information that how long the effect of the event sustained in the stock market. The hypothesis of this event study i.e., the presence of non-zero average abnormal return \(H_1\) could be tested against the null hypothesis \(H_0\):

\[ H_0 : \theta = 0 \]
\[ H_1 : \theta \neq 0 \]

\textbf{Abnormal Performance Testing}

Parametric tests embedded in the t-tests which are used to assess abnormal performance, are based on a number of strong assumptions: security prices must be
normal distributed (Brown, Warner, 1980). The non-parametric tests, sign test and rank test are based on less restrictive assumptions [5]. The analysis of cumulative abnormal returns \((CAR)\) lays on the assumption that the event windows of the included securities do not overlap in calendar time. This assumption allows us to calculate the variance of the aggregated sample CAR without concern about the covariance across securities because is almost 0. For instance, if the assumption of event windows does overlap, and the would have a non-zero covariance the CAR would no longer be representative for the information event we try to analyze.

The parametric tests proposed in the literature rely on the important assumption that individual firms abnormal returns are normally distributed. The standard statistic is:

\[
t = \frac{AR_0}{S(AR_0)}
\]

Where \((AR)\) is the average residuals and \(S(AR)\) is s an estimate of standard deviation of the average abnormal returns \(\sigma (AR)\).

- Cross-sectional interdependence: Considering cross-sectional independence, i.e., that the residuals are not correlated across securities. These assumptions are very restrictive and relaxed in the next tests (Brown, Warner, 1980; De Jong, 2007; Serra, 2002).

- Cross-sectional dependence: to account for the dependence across firms’ average residuals, in event time, Brown and Warner (1980) suggest that the standard deviation of average residuals should be estimated from the time series of the average abnormal returns over the estimation period. A reason for cross-sectional dependence might be event clustering, meaning that several events occur in the same period (Brown, Warner, 1980; De Jong, 2007; Serra, 2002).

- Cross-sectional interdependence with standardized abnormal returns: Standardized abnormal returns are calculated to account for differences in variances. Some stocks have a higher volatility than others. Abnormal returns are
standardized to ensure that abnormal returns have the same variance. Less weight is put on stocks with a high variance (Brown, Warner, 1980; De Jong, 2007; Serra, 2002).

The Non-parametric tests: Previous studies have shown that abnormal returns distributions show fat tails and are right skewed. Parametric tests reject too often when testing for positive abnormal performance and too seldom when testing for negative abnormal performance. When the assumption of normality of abnormal returns is violated, parametric tests are not well specified. Non-parametric tests are well-specified and more powerful at detecting a false null hypothesis of no abnormal returns.

- Rank test: this test accounts for the magnitude of abnormal returns. Abnormal returns of each firm are ranked over the entire period (estimation and event period). The ranks in the event period are then compared to expected average ranks that would occur under the null hypothesis of no abnormal returns (Corrado, 1989; De Jong, 2007; Serra, 2002).

- Sign test: this test focuses on the sign of abnormal returns. The sign test is a simple binomial test of whether the frequency of positive abnormal residuals equals 50%. To implement this test, we first need to determine the proportion of stocks in the sample that should have non-negative abnormal returns under the null hypothesis of no abnormal performance. The null hypothesis states that the proportions of positive and negative abnormal returns are equal, meaning that there are no abnormal returns (De Jong, 2007; MacKinley, 1997).

All details regarding the calculations of the parametric and non-parametric tests can be found in the Appendix.
4 Data and Sources

We use the FDA database to select our sample of IRE (Information release events) Drugs@FDA. Announcements of New Drug Approvals (NDAs) are ranged from January 2000 to December 2012 focused on the top twenty pharmaceutical companies (based on annual sales revenue and the R&D expenditures in 2012).

<table>
<thead>
<tr>
<th>Rank 2011</th>
<th>Company</th>
<th>Sales 2010 $ bill.</th>
<th>% Change 2009</th>
<th>R&amp;D spend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pfizer</td>
<td>58.5</td>
<td>28.90%</td>
<td>9.413</td>
</tr>
<tr>
<td>2</td>
<td>Novartis</td>
<td>42</td>
<td>9.20%</td>
<td>7.100</td>
</tr>
<tr>
<td>3</td>
<td>Sanofi-Aventis</td>
<td>40.3</td>
<td>-4.10%</td>
<td>5.147</td>
</tr>
<tr>
<td>4</td>
<td>Merck</td>
<td>39.8</td>
<td>58%</td>
<td>11.000</td>
</tr>
<tr>
<td>5</td>
<td>Roche</td>
<td>39.1</td>
<td>4.10%</td>
<td>8.612</td>
</tr>
<tr>
<td>6</td>
<td>GlaxoSmithKline</td>
<td>36.2</td>
<td>-4.20%</td>
<td>6.126</td>
</tr>
<tr>
<td>7</td>
<td>AstraZeneca</td>
<td>33.3</td>
<td>1.40%</td>
<td>4.200</td>
</tr>
<tr>
<td>8</td>
<td>Johnson&amp;Johnson</td>
<td>22.3</td>
<td>-0.40%</td>
<td>4.432</td>
</tr>
<tr>
<td>9</td>
<td>Eli Lilly</td>
<td>21.1</td>
<td>5.40%</td>
<td>4.880</td>
</tr>
<tr>
<td>10</td>
<td>Abbott</td>
<td>19.9</td>
<td>27.70%</td>
<td>3.724</td>
</tr>
<tr>
<td>11</td>
<td>Bristol-Myers Squibb</td>
<td>19.5</td>
<td>3.60%</td>
<td>3.566</td>
</tr>
<tr>
<td>12</td>
<td>Teva</td>
<td>16.1</td>
<td>16%</td>
<td>933</td>
</tr>
<tr>
<td>13</td>
<td>Amgen</td>
<td>14.1</td>
<td>1.80%</td>
<td>2.894</td>
</tr>
<tr>
<td>14</td>
<td>Bayer</td>
<td>14.5</td>
<td>-3.60%</td>
<td>2.320</td>
</tr>
<tr>
<td>15</td>
<td>Takeda</td>
<td>14.2</td>
<td>-0.10%</td>
<td>3.198</td>
</tr>
<tr>
<td>16</td>
<td>Boehringer Ingelheim</td>
<td>12.9</td>
<td>-10.80%</td>
<td>3.056</td>
</tr>
<tr>
<td>17</td>
<td>Novo Nordisk</td>
<td>10.8</td>
<td>9.90%</td>
<td>1.709</td>
</tr>
<tr>
<td>18</td>
<td>Astellas</td>
<td>10.8</td>
<td>6%</td>
<td>2.109</td>
</tr>
<tr>
<td>19</td>
<td>Daiichi Sankyo</td>
<td>9.8</td>
<td>20%</td>
<td>2.124</td>
</tr>
<tr>
<td>20</td>
<td>Eisai</td>
<td>8.4</td>
<td>8%</td>
<td>1.932</td>
</tr>
</tbody>
</table>

Figure 11: Top 20 Pharmaceuticals by R&D Spending
Illustration Source: 12th Annual Pharm Exec 50 of 2012
http://www.pharmexec.com

To include an event in our dataset, the company has to fulfill several conditions: to be listed on Center for Research in Security Prices (CRSP)/WRDS, information must be available on several levels, including drug classification and drug specification, dates of FDA final approval and applicant ID. The company who’s approval event would be included in the sample, needs to have stock price data available for the over the estimated period 2000 to 2012. With these filters we build our samples:

- Pharmaceutical industry: out of 232 NMEs filtered between 2000 and 2012 we
create a sample of 82 NMEs of top 20 largest companies.

- Diabetes industry: filter database per product type and select the ones that fall within this therapeutic class, not all of the approvals are NMEs class.

To construct our generic sample we use the FDA Orange Book database: Approved Drug Products with Therapeutic Equivalence Evaluations. It is available on the FDA website in the same csv archive file format like the Drugs@FDA data.

- Generic firms 2001-2002 - Sample 1
- Generic firms 2011-2012 - Sample 2

Having the events and the companies selected we look for the stock prices for the companies in our sample in the WRDS (Wharton Research Data Services) - Center for Research in Security Prices (CRSP)/Compustat. The reason of building the generic sample at these two moments in time is to see whether the patent cliff inflicted any changes in which the financial markets assimilate new information release events from the generic markets and review these changes. The companies on which we focus our sample building are top 20 of the global pharmaceuticals based on global sales.

### 4.1 FDA Data

The Generic data sample has been selected using the database available online on the Food and Drug Administration web-page. From the optional ways to collect the information, we download the file Drug@FDA to sample the events. The Drugs@FD is a compressed folder that contains seven CSV files of all kinds of drug approvals which, in addition to NDAs, include Abbreviated New Drug approvals (ANDAs) and Biologic License Application (BLAs). After filtering the Drugs@FDA for the selected 20 firms, 82 NDAs were found for the time span mentioned above for the Pharma sample and other 34 for the Diabetes sample.

For the drugs that have multiples approvals for different dosage and uses, these are cases of multiples approvals at a single date and are included as a single event. We can find supplementary approval for other drugs but with no relevant effect in
the stock market. These are complementary approval parts of the application process. In conclusion, the original approval dates have been filtered using historical information of the approval process for each of the drugs.

The NDAs approval dates have been merged with the CRSP data of the stock market of the formal sponsor company that produces 82 exclusive event dates and 34 for the diabetes market.

<table>
<thead>
<tr>
<th>App ID</th>
<th>Company</th>
<th>Period</th>
<th>Nr of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>21688</td>
<td>AMGEN</td>
<td>2004</td>
<td>1</td>
</tr>
<tr>
<td>21332</td>
<td>AMYLIN</td>
<td>2005</td>
<td>2</td>
</tr>
<tr>
<td>22161</td>
<td>ASTELLAS</td>
<td>2004-2008</td>
<td>4</td>
</tr>
<tr>
<td>21344</td>
<td>ASTRazeneca</td>
<td>2002-2003</td>
<td>2</td>
</tr>
<tr>
<td>21321</td>
<td>BAXTER</td>
<td>2002</td>
<td>1</td>
</tr>
<tr>
<td>21400</td>
<td>BAYER</td>
<td>2003-2005</td>
<td>3</td>
</tr>
<tr>
<td>21567</td>
<td>BRISTOL MYERS SQUIBB</td>
<td>2005-2009</td>
<td>4</td>
</tr>
<tr>
<td>21286</td>
<td>DAIICHI SANKYO</td>
<td>2000-2002</td>
<td>3</td>
</tr>
<tr>
<td>20789</td>
<td>EISAI INC</td>
<td>2000-2008</td>
<td>4</td>
</tr>
<tr>
<td>22307</td>
<td>ELI LILLY AND CO</td>
<td>2009</td>
<td>1</td>
</tr>
<tr>
<td>21431</td>
<td>FOREST LABS</td>
<td>2003-2011</td>
<td>3</td>
</tr>
<tr>
<td>22311</td>
<td>GENZYME</td>
<td>2000-2012</td>
<td>2</td>
</tr>
<tr>
<td>20941</td>
<td>GLAXOSMITHKLINE</td>
<td>2008-2009</td>
<td>2</td>
</tr>
<tr>
<td>21368</td>
<td>LILLY</td>
<td>2003</td>
<td>1</td>
</tr>
<tr>
<td>20427</td>
<td>LUNDBECK LLC</td>
<td>2009-2011</td>
<td>2</td>
</tr>
<tr>
<td>21995</td>
<td>MERCK</td>
<td>2001-2006</td>
<td>6</td>
</tr>
<tr>
<td>21204</td>
<td>NOVARTIS</td>
<td>2000-2011</td>
<td>14</td>
</tr>
</tbody>
</table>

Figure 12: Sample 1 Summary Pharma Sample Part 1

App ID is the identifier number for the dataset Drug@FDA we used to screen down the relevant application through the database files. To access the CRSP database has been access it throughout the Wharton Research Data Services (WRDS). Using every companies number International Securities Identification Number (ISIN) uniquely identifies a security.

When forming the generic sample we looked for the biggest players of the generic market, mainly the Top 10 companies.
Requirements for a company to be included in the sample:

- Publicly traded between the periods 2000-2012
- If acquired by another we used it acquirer peer (see Sandoz/Novartis)
- Be one of the top 10 Generic companies by revenue.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NOVO NORDISK INC</td>
<td>2</td>
<td>8</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>PFIZER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROCHE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SANOFI AVENTIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAKEDA GLOBAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEVA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VALEANT INTL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WATSON LABS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WYETH PHARMS INC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Grand Total 82

Figure 13: Sample 1 Summary Pharma Sample Continued

Figure 14: Generic Samples Description Table

We excluded the companies that had only one or two observations, because it did not balance the sample. The main purpose was to create a balanced sample with of top 10 companies of the generic industry.

When building a sample of two years timeframe we had to avoid the clustering issue of the observations. Therefore we deleted the observations with the date within
the 21 days frame of another observations. The diabetes data was screened by
the human insulin ingredient between 2000 and 2012. Having in count the high
probability of event clustering in the generic sample of 2001 and 2012 we looked to
segregate the observations when another event is find in between the 10 days after
and before the main event date.
5 Empirical Results and Analysis

According to the methodology described in Section III, Figure 15 exposes the results of the AAR calculated for the 21 days event window over the four samples. Figure 15 resumes the four sample average abnormal returns based on the Market model to estimated the expected returns. The approval has a statistically significant impact on the same day and of the announcement in the case of the Pharma Sample and on the second day but negative impact on the generic product approval for the events Generic 2001-2002 Sample. The reactions of the stock prices for the generic products approval at the end of the decade (sample 2011-2012) is positive nonetheless not statistically significant compared to the sample of the generic products from the beginning of the decade. The abnormal returns for the Top Pharma are comparable and equivalent with previous findings of Sharma & Lancey (2004) e.g. De Jong (2005).

Figure 15: Average Abnormal Returns - All samples overview

The size of the average abnormal returns for the NMEs in the pharmaceutical industry (Pharma Sample) is lower than the previous studies of De Jong (2005). Comparing their results with Bosch and Lee (1994) who found significant FDA final
approval returns for days 0 and 1. De Jong (2005) found a final approval significance reaction in days 0 and +1 of 0.4% at 5% significance level. In our case we find similar findings of 0.4% abnormal returns at 10% significance level only on the day of the event (based on FDA approval date). The implementation of more simple models to calculate the expected returns, Constant mean return model and Market adjusted return model has showed not to be sufficient enough to spot any significant abnormal return in the stock price.

5.1 Hypothesis testing results

We will discuss below how our conclusions and findings regarding our tree main research questions:

I. Are there abnormal returns at the moment of the approval date? We fin statistically significant abnormal returns that confirm preview foundlings of De Jong (2005), Bosch and Lee (1994), Sharma and Lacey (2004). The difference and similarities between these studies is the data collection period. While their study is focused on large periods of time 1980 to 1999 we see that our findings back the effect of the approval product in the stock price. Although the most important difference can be found in the size of the abnormal returns registered on average. We can detect excess return on the day of the event release (day 0 Pharma Sample) in contrast with preview findings that detect abnormal returns for 3 days event window date.

The average CAR (cumulative abnormal returns) statistically significant for 5 and 10 days before and after the event comparing to (0.5% [-1,+1]) with CAR of 1.56 at 1% level of significance by (Sharma and Lacey 2004). The CAR of De Jong (2005) are not statistically significant.

Having in count the countless alliances between big pharma like Pfizer and top generic manufacturer (The Economist, Clifhanger December 3, 2011) the big pharma can gain up to 70% of future revenues from authorized copies of their out of patent blockbuster drugs. This aspect as the loophole exploitation in 1984 law can allow them to mitigate these losses. Although predicted, is in the past decade these
agreements have raised to the media headlines, regarding ways big drug manufacturer developing their new strategies. Analysts argue that in the future this kind of agreements will turn into fusing the generic and intense R&D pharma into develop farther these alliances discouraging the generic manufacturer in challenging the patents in the first place. There are also evidence that suggest that absence of the abnormal returns, can be explained in most cases because markets anticipated the approval and already adjusted the stock price (Woolridge & Snow 1990, Sharma & Lacey, 2004) or because the event in question was simply ignored. This indirect information perceived by the market, probable approval is that the New Molecu-

![Daily Average Abnormal Returns](image-url)

Figure 16: Pharma Sample AAR
lar Entity (NME) or the New Chemical Entity (NCE) gets patented, long before the actual drug receives approval by FDA (Di Masi 2003). If the Efficient Market Hypothesis (EMH) is in effect, the market assimilates the available information of these forthcoming drug approvals and the securities and stock market prices of the sponsoring companies become adjusted smoothly before the actual approval of a specific drug by the FDA.

***Significant at 1% level **Significant at 5% level *Significant at 10% level

### Daily Average Abnormal Returns

<table>
<thead>
<tr>
<th>Day</th>
<th>AAR</th>
<th>t-test</th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
<th>Test 4</th>
<th>Test 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 5</td>
<td>-0.01%</td>
<td>-0.03</td>
<td>-0.02</td>
<td>-0.77</td>
<td>-0.78</td>
<td>-1.80</td>
<td>-1.71 *</td>
</tr>
<tr>
<td>Day 4</td>
<td>-0.07%</td>
<td>-0.15</td>
<td>-0.02</td>
<td>-1.12</td>
<td>-1.13</td>
<td>-1.55</td>
<td>-1.45</td>
</tr>
<tr>
<td>Day 3</td>
<td>-0.21%</td>
<td>-0.46</td>
<td>-0.01</td>
<td>-0.27</td>
<td>-0.09</td>
<td>-0.77</td>
<td>-0.68</td>
</tr>
<tr>
<td>Day 2</td>
<td>0.09%</td>
<td>0.19</td>
<td>0.00</td>
<td>0.11</td>
<td>-0.03</td>
<td>-0.52</td>
<td>-0.42</td>
</tr>
<tr>
<td>Day 1</td>
<td>0.12%</td>
<td>0.25</td>
<td>0.00</td>
<td>0.13</td>
<td>0.04</td>
<td>0.52</td>
<td>0.60</td>
</tr>
<tr>
<td>Day 0</td>
<td>0.10%</td>
<td>0.22</td>
<td>0.02</td>
<td>1.15</td>
<td>1.09</td>
<td>1.29</td>
<td>1.37</td>
</tr>
<tr>
<td>Day +1</td>
<td>0.03%</td>
<td>0.07</td>
<td>-0.01</td>
<td>-0.32</td>
<td>-0.65</td>
<td>0.25</td>
<td>0.35</td>
</tr>
<tr>
<td>Day +2</td>
<td><strong>-0.88%</strong></td>
<td><strong>-1.91</strong></td>
<td>-0.05</td>
<td><strong>-2.64</strong></td>
<td><strong>0.09</strong></td>
<td>0.52</td>
<td>0.60</td>
</tr>
<tr>
<td>Day +3</td>
<td>-0.06%</td>
<td>-0.14</td>
<td>0.00</td>
<td>0.01</td>
<td>-0.14</td>
<td>-0.25</td>
<td>-0.17</td>
</tr>
<tr>
<td>Day +4</td>
<td>0.08%</td>
<td>0.18</td>
<td>0.02</td>
<td>1.00</td>
<td>1.07</td>
<td>0.52</td>
<td>0.60</td>
</tr>
<tr>
<td>Day +5</td>
<td>-0.03%</td>
<td>-0.06</td>
<td>-0.01</td>
<td>-0.73</td>
<td>-1.00</td>
<td>-1.55</td>
<td>-1.45</td>
</tr>
<tr>
<td>Day +6</td>
<td>-0.08%</td>
<td>-0.17</td>
<td>-0.02</td>
<td>-0.83</td>
<td>-1.30</td>
<td>-1.03</td>
<td>-0.94</td>
</tr>
<tr>
<td>Day +7</td>
<td>0.10%</td>
<td>0.21</td>
<td>0.02</td>
<td>1.09</td>
<td>1.95 *</td>
<td><strong>2.06</strong></td>
<td><strong>2.14</strong> **</td>
</tr>
</tbody>
</table>

### Cumulative Average Abnormal Returns

| CAAR [0:1] | -0.85% | -2.29 ** | 0.01 | 0.59 | 0.31 | 1.09 | 1.22 |
| CAAR [-1:1] | -0.75% | -2.02 ** | 0.01 | 0.56 | 0.27 | 1.19 | 1.34 |
| CAAR [+5:5] | -0.91% | -2.45 ** | -0.02 | -1.04 | -0.46 | -1.01 | -0.70 |
| CAAR [-10:10] | -1.20% | -3.24 ** | -0.07 | -3.36 ** | -0.48 | -1.29 | -0.87 |
| CAAR [-10:1] | -0.43% | -1.17 | -0.03 | -1.51 | -0.96 | -2.61 ** | -2.31 ** |

Figure 17: Generic 2001-2002 AAR

II. In what measure are these findings different from other research findings?

Previous research context has focused over the impact of the approval at different stages over the clinical trials and approval process (De Jong 2005), other studies focus on the wealth impact of approvals or failure products in the value of the
sponsors (Sharma & Lancey 2004). Other studies centered in the intensive R&D industries valuate the impact of firm product portfolio as a measure of its value. These studies found that financial market asymmetric response to success or failure of NMEs and product development efforts (Lancey 2004), on the other hand the financial market reaction to stage three of the clinical trials is much larger than the final approval effect (De Jong 2005).

The approval event in the case of the diabetes market doesn’t have any reaction from the financial markets which indicates that the efficiency of the financial markets is in place and this information is already incorporated in the stock price or the event is ignored. Although many of the companies from the diabetes market are focused into particular therapeutic class, they seem to indicate higher signaling power and assumption of approved product way before the announcement date.

We work on the same direction we find differences in the way the new product approval are understood by the financial markets. Although a generic product approval does not equal a NMEs (New Molecular Entity) approval in terms of R&D expenditure but the two events are comparable in terms of market share and comparative loose of sales for the patent holder e.i. ways that the cliff affects this nexus of blockbuster drug patent holder and generic competitors. We find negative statistically significant market reaction on the second day after the product approval date for the generic company (Sample Generic 2001-2002). Although by the end of the decade (Sample 20011-2012) we cannot reject our null hypothesis of zero abnormal returns. This can be interpreted as a direct measure of decrease in some way the competition between these two segments and supported by an increase in number of alliances [16] with the pharmaceuticals. This difference can be explained by the ferrous competition in the generic market and by the fact that generic competition to be particularly intense for blockbuster drugs, which experience significantly more generic entrants, price erosion, and generic penetration than other drugs [21]. The negative reaction of the financial markets are found to be larger in size comparing to positive reactions, this in the case of the pharmaceutical industry (De Jong 2005). Generalizing the conclusions of (Lancey 2004) ‘the effect on firm value is severe when expectations about an anticipated new product are not fulfilled’ this fact can reflect the competition in the generic market as the negative market response in
the second day after the approval, mainly because every generic manufacturer can challenge the expiration date of a patent.

III. What changes can be explained by the patent cliff?

Our results indicate investors react positively to FDA approvals of NMEs. The effect of these estimates is registered in smaller number of days than for previous studies which considered larger periods of time. Estimating the patent cliff effect in the sector we see this fact as increase anticipation of the investors in terms of approval effect for the sponsor company. This is consistent with increasing costs of R&D implying that a NME approval to have a smaller wealth effect. De Jong (2005) suggested this final approval solves only a small degree of the uncertainty, most of it is assimilated by the investors perspective during the approval process. The low power of parametric and non-parametric tests suggest that sample selection could be improved. We don’t find any indications of information leaking in the markets, fact that withholds with our investor anticipations. Although we expected statistically positive reaction in the case of our diabetes sample we suggest future research should contain a wider collection of niche dedicated companies to a certain treatment in the health industry. This assumption is based on findings (De Jong 2005) which finds larger market reaction when NMEs are approved for medium size pioneer companies.

5.2 Concluding remarks

The valuation of a pharmaceutical company is very closely linked to it product portfolio and efficiency of R&D innovation. Considering the amount of resource that the risk of developing the next blockbuster drug, consolidation and acquisitions is well accepted by the financial markets as way to overstep the deficit of eroded R&D pipeline. Overall, managers should be very careful at considering the signals they send to the markets before final approvals since negative surprises are heavenly sanctioned by financial markets (Lancey 2004).

Although patent cliff is just one side of the coin, the other side is the direction the new R&D efforts are going towards. Demand for therapeutic medicines in developed
countries is pointing to diabetes, Alzheimer or cancer leaving the already expired therapeutic remedies for generic competitors to share the leftovers. In developing countries, with high growth for generic products and increase spending in healthcare [6], this is where the growth will come in the future and where the big pharma are targeting.

Cliffhanger strategies and increase number of alliances between generic players and big pharmaceuticals seams to be the fundamentals increase in positive market reaction for generic players. From a negative market response in 2001-2002 sample we find that by the 2011 and 2012 new generic approvals market doesn’t react in a negative way. This anticipation of increase importance of generic markets alliances for big pharma shows investors are aware of these deals and can anticipate the effects in the stock prices, deals where both generic and patent holders benefit.

Future studies could target these agreements and look over company valuation basis and the way financial markets value them. Regarding the studies who target direct efficiency of R&D innovation future studies can target whether pharmaceuticals can reduce their R&D costs by internationalization of their operations.
References


\textsc{LaTeX}