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THE IMPACTS OF REGULATION ACTIVITIES ON THE SUPPLY OF NEW PRODUCTS IN PHARMACEUTICAL INDUSTRY

SEHER DEMİRBAŞ

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“İLAÇ ENDÜSTRİSİNDEKİ DÜZENLEYİCİ FAALİYETLERİN YENİ ÜRÜN ARZI ÜZERİNDEKİ ETKİLERİ”

SEHER DEMİRBAŞ

ÖZ

Teknolojik ilerlemeler ve ilaca ulaşım sorunsalı düşünüldüğünde devletin ilaç pazarında uyguladığı yaptırımlar bu iki kavramı bir paydada toplayan konuların başında gelir. Daha önce bu alanda yapılan çalışmaların azımsanamayacak oranında, ilaç üzerine uygulanan yaptırımların firmaların AR-GE çalışmaları üzerinde negatif etkileri olduğu sonucuna varılmıştır. Bu çalışmada ilaç pazarında uygulanan yaptırımların ilaç firmalarının AR-GE kararlarını nasıl etkilediği üzerinde durulmuş olup, ilaç sektörüne ilişkin dinamikler, yatırım ve AR-GE süreçleri işlenmiş ve ağırlıklı olarak uygulanan yaptırım çeşitleri anlatılmıştır. Ayrıca, çalışmada iki farklı denklem kullanılarak regresyon analizine başvurulmuş ve firmaların AR-GE kararlarında etkili olan faktörlerin yaptırım uygulayan ve uygulamayan ülkelerde ne derece değiştiği anlaşılmaya çalışılmıştır. Yaptırımların etkisini göstermeyi amaçlayan bu çalışma sonucunda, daha önceki çalışmaları destekleyici sonuçlara ulaşılamamış olmakla beraber, değişkenler arasındaki ilişki yönüne ve korelasyon oranlarına dayanarak örneklem sayısının artırılması ve farklı değişkenlerin eklenmesi sonucu daha önceki çalışmalarla benzer sonuçlara ulaşılabileceğinin muhtemel olduğu kanısına varılmıştır.

Anahtar Kelimeler: İlaç endüstrisi, yaptırım, araştırma ve geliştirme, fiyatlandırma.

“THE IMPACTS OF REGULATION ACTIVITIES ON THE SUPPLY OF NEW PRODUCTS IN PHARMACEUTICAL INDUSTRY”

SEHER DEMİRBAŞ

ABSTRACT

When the technological improvements and the problem of access to medicine are thought, the regulations applied on the pharmaceutical markets by the government is one of the leading subjects which comes to one’s mind as link combining these two concepts under one common common ground. A considerable amount of the previous works conducted in this field has come to the conclusion that the regulations applied on the pharmaceuticals have negative effects on the R&D activities of the firms. In this current study, it is focused on how the R&D decisions of the firms are affected by the regulations on the pharmaceuticals and mentioned the dynamics regarding the pharmaceutical industry, investment and R&D processes along with the commonly used regulation types. Moreover, it is applied to regression analysis by using two different models in order to understand how the factors effecting the R&D decisions of the firms are differing from one country which applies regulations on pharmaceuticals to the other which do not. At the end of this study which aims to indicate the impact of the regulations, we could not reach to a conclusion supporting the previous studies, however by depending on the direction of relationship between the variables and the correlation strengths it can be deduced that in case of an enlargement in the sample size and additional variables, it might be possible to reach to the same conclusion with the previous works.

Keywords: Pharmaceutical industry, regulation, research and development, pricing.

PREFACE

Lots of studies have been done previously in order to discuss the possible effects of the regulations on the R&D activities of the pharmaceutical firms. In this current paper, two different models are tested by using SPSS 15.0 for Windows Evaluation version for 12 countries. One of the models includes the data regarding some of the major countries with high pharmaceutical market volume and value as grouped together and behaved as if they all were one single country. For the second model, on the other hand, only the US data is used as it is known to be the only country in the world which does not apply any kind of regulations on the pharmaceuticals. By doing so, it is aimed to identify the differences in behaviour for the variables that are influential in deciding on R&D investment between the countries which apply regulations and which do not apply regulations.

Due to the lack of data and the multicollinearity and autocorrelation issues for the existing data, even if the models are statistically significant the coefficients of the explanatory variables are not found significant in statistical terms. However, the direction of the relationship between the variables and the correlation among them are supporting the fact that those variables that used in these models are valid for explaining the change in the spending on R&D investment partially.

Notwithstanding, no statistically significant difference in the behaviour of the explanatory variables are found between two models which suggests that the regulations of pharmaceuticals do not cause any kind of negative or positive impact on firms' decision on spending on R&D investment. But again, if the model is enhanced with a larger sample size and some more additional variables, the results might be identical with the previous works.

I would like to express my special thanks to my advisor Ass. Prof. Dr. Haluk Zülfikar for his support to my work. I also thank to Ass. Prof. Dr. Türkan Turan for her moral support.

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AIFD : Association of Research- Based Pharmaceutical Companies
BMI : Business Monitor International
DTC : Direct to Consumer
DTCA : Direct to Consumer Advertising
DTPP : Direct to Physician Promotion
EFPIA : European Federation of Pharmaceutical Industries and Associations
EMA : European Medicine Agency
EMEA : European Medicines Evaluation Agency
EU : European Union
FDA : U.S. Food and Drug Administration
GATT : General Agreement on Tariffs and Trade
IEIS : Pharmaceutical Manufacturers Association of Turkey
IMS : Intercontinental Medical Statistics
ITA : International Trade Administration
MCC : Marginal Cost of Capital
MRR : Marginal Rate of Return
OECD : Organisation for Economic Co-operation and Development
OTC : Over-the-Counter Medicine
PPRS : Pharmaceutical Price Regulation Scheme
R&D : Research and Development
RMOs : References Médicales Opposables
RX : Prescription Medicine
SSI : Social Security Institute
TITCK : Türkiye İlaç ve Tıbbi Cihaz Kurumu
TSI : Turkish Statistical Institute
UK : United Kingdom
US : United States
VAT : Value Added Tax
WTO : World Trade Organization

INTRODUCTION

Due to the extensive medical insurances, the consumers are only supposed to pay a small amount of the cost so that they are not concerned about the prices of the medicines. Hence, pharmaceutical markets have a highly price inelastic demand. It can easily be deduced that as the consumers do not have the option of choosing not to consume drugs or they are not the ones who are making the selection between several drugs (as they are not the decision-maker), prices have only a limited effect on their demand.

The pharmaceutical sector is the one which has the highest amount of expenditure on research and development (R&D) in the world. The R&D process and innovation are among the uppermost costs of the pharmaceutical firms and they have only a given limited time period under the patent protection to recover the sunk costs resulted from R&D and to be encouraged for further innovation. This situation forces them to take precautions in order to recover the whole cost and start earning profits before the patent expiration date after which the competition will be so fierce with the entrance of the generic drugs to the market. Thus, the firms tend to charge high prices by exploiting from their market power in the course of patent protection.

The problem for the payer (government in most cases) occurs when these two aspects of the pharmaceutical markets, one from demand side and one from supply side, combined. The differences in the medicine prices in the world can be explained to some extent by the various regulations applied by each government in order to solve the problem mentioned above and to control the public pharmaceutical expenditure.

The decision for investment, specifically the R&D decision for this paper, depends mostly on the expected rate of return from it. The firms will not choose to invest on innovation as long as they expect no/low profit from it under the strict market controls. That is why there is a very thin line between keeping the public expenditures low and preventing the firms losing courage for innovation at the same time. The role of the government is to find a method that will create a balanced point.

There are several methods of intervention/regulation to the pharmaceutical markets used in the world. Thus, it is crucial for a country to choose the method which is most suitable to its own conditions in order to retain from discouraging the firms. The aim of this study is to explain these methods of regulations and to discuss their effects on R&D investment by introducing a theoretical model.

The study starts with a general view of the structure of pharmaceutical industry in which we mention the size of the global pharmaceutical market and the share of the global players in the market. By doing so, we set a framework for the countries that we will be focusing on this paper. The application of the patent protection along with its benefits to the firms and the trends in the public pharmaceutical spending in different countries are disclosed. The dynamics of the generic drug industry and the post-patent competition caused by the entrance of them to the market are also addressed in this chapter.

The concept of investment is discussed broadly as well as the investment in pharmaceutical sector specifically throughout the second chapter. All types of investments are explained in order to put forward the reason for the differentiation of R&D investment from others. A theoretical model is introduced so as to assert the possible variables that might be influential in firms' R&D decisions and the feasible reasons for their potential impacts are reviewed. This is also the section where we refer to one of the fundamental investment models, Modigliani-Miller Theorem and explain why it may not be applicable in today's investment environment where the companies have different options for financing their investment each of which has various costs. A brief explanation about the process of bringing a new drug to the market is also given in order to put forward a base for how a costly work realising R&D in pharmaceutical industry is.

In the third chapter, we mainly focus on the regulations in pharmaceutical markets. The regulations that can either be addressed to the supplier of the pharmaceuticals or to the demanders are examined. We study the different methods of the regulations in detail mainly under the titles of direct and indirect price and reimbursement controls, delays in marketing and price approvals, limitations on promotion, and prescription

barriers along with the application of them by the countries. The differences in medicine prices between the countries that apply regulations and that do not apply any regulations are put forward by a comparison of U.S. and Europe.

In the fourth chapter, the structure of the pharmaceutical sector in Turkey is mentioned as an additional information, as the main aim of this study is not focusing on the Turkish market but to examine the situation in the whole pharmaceutical industry on global basis via some representative sample countries within the framework. We look into the basic dynamics of the sector such as the market structure, market size in comparison to similar developing countries, production, employment and, external trade which has a large share in the Turkish pharmaceutical market. The topics of reimbursement, price regulation and investment in the Turkish market are examined by referring to the latest updates regarding the insurance rules and goals of the Turkish government for the year 2023 which also comprises the health sector.

In the fifth chapter, we refer to the problem of R&D decision and regulation on price. Two potential channels through which price regulation may have an influence on R&D is evaluated. An empirical model which aims to help in explaining the effect of regulations is introduced and evaluated in this chapter.

We try to reach a conclusion on whether the regulations in pharmaceutical markets done by the governments have a negative effect on the firm's R&D decisions or not. The study is concluded with briefly pointing out the possible implications of the effects on the overall social welfare about the trade-off between access to medicine and innovation.

1. THE FEATURES AND STRUCTURE OF THE PHARMACEUTICAL INDUSTRY

Pharmaceutical sector is an industry branch which provides the production and distribution of active and inactive medicine substances that are synthetic, biologic, vegetal and animal based and used for curative and prophylactic reasons in human and veterinary physics.

"The global pharmaceutical industry is a multinational industry that is highly regulated, capital intensive, and driven by large R&D expenditures. The industry is primarily privately owned and is technologically sophisticated." [1]

As reported by Intercontinental Medical Statistics (IMS), the value of the global pharmaceutical market reached to US$962 billion in 2012 and a 5.3% of growth is projected until 2017.[2] Notwithstanding the rapid growth in pharmaceutical industry in developing countries such as Brazil, China and India in recent years, the irregular distribution of the production of pharmaceuticals around the world is extant considering the fact that developed countries are still the leading producers. The 10 large pharmaceutical companies of which some have sales over US$10 million per year, control approximately one third of the global market. According to the report of European Federation of Pharmaceutical Industries and Associations (EFPIA), the pharmaceutical production in European Union (EU) has grown from 63.010 million € in 1990 to 210.000 million € in 2012. Likewise, the pharmaceutical market value increased almost 5 times and reached to 238.500 million € in the same period. As stated in IMS data, 41% of the world's pharmaceutical sales have been realized by North America (US & Canada), the largest pharmaceutical market in the world, in

[1] Mahdu Agrawal, **Global Competitiveness in the Pharmaceutical Industry: The Effect of National Regulatory, Economic, and Market Factors**, NY, Pharmaceutical Products Press, 1999, p.1.

[2] IMS, "Total Unaudited and Audited Global Pharmaceutical Market By Region/2012 – 2017", **IMS Health Market Diagnosis,** June 2013, (Online) http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/Press%20Room/Total_World_Pharma_Market_Topline_metrics_2012-17_regions.pdf, 15 January 2014.

2012 whereas the share of Europe was 26.7%. As the other country which has high market volume, Japan got 11.7% of the global pharmaceutical market share. [3]

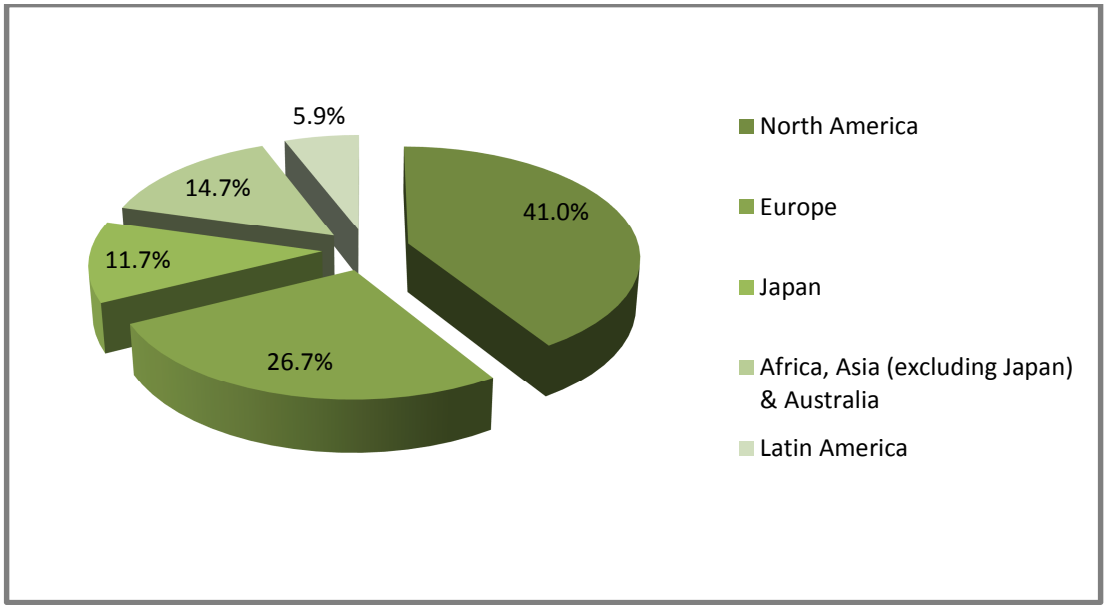

Figure 1. Pharmaceutical Market Shares – 2012 Sales
Source: IMS Health, **IMS MIDAS**, September 2013.

France (27.491), Germany (26.122), Italy (20.272), Spain (13.941), and United Kingdom (UK) (13.801) are considered to be the most valuable pharmaceutical markets in Europe with the values given as million € in the brackets at ex-factory prices. Japan's pharmaceutical market which is the second largest pharmaceutical market in the world at the country level after United States (US), worth $112.1 billion (in 2012). The figure in the same period for North America region shows that Canada and especially US still holds the first rank with $348.7 billion. In addition to these countries, Switzerland is also one of the leading markets in terms of pharmaceutical R&D with a figure of 4.972 million € in 2012.[4] As we have seen above; some of the European countries, North America, and Japan constitute the major players of the global pharmaceutical industry. Those countries mentioned above are also classified as "High-income OECD countries" according to World Bank's Atlas method in 2012 which considers the countries that have more than $12.616 GNI per capita in high income group. To this extent, we will be mainly

[3] EFPIA, "The Pharmaceutical Industry in Figures", **Key Data 2013**, Belgium, 2013, pp. 2-25.
[4] **Ibid.**

concentrating on the leading countries in terms of economic and social welfare levels in these regions throughout this thesis as well as addressing some smaller players when explaining some specific concepts from time to time.

Even if there are some pharmaceutical companies which also provide medical devices and equipment to the market, the main scope of the industry is to mass produce medicines formulated with single or combined specific active substances which are efficient to protect, diagnose and cure living creatures. The medicines in the pharmaceutical markets are classified into two segments as "prescription medicine (RX)" and "over the counter (OTC) medicine" regarding their sales methods. The former segment includes only the products which can be purchased with a prescription by a physician whereas the other segment consists of the products which do not require a prescription to be purchased as they are mostly for minor diseases where safety and the ability to self-diagnose are no concern.[5]

In most of the countries, medicines are divided into two categories as branded and generic regarding the fact that its active substance is patented or not. The pharmaceutical firms can apply for a patent protection as long as the new product that they have developed is a new kind of treatment of an existing illness comprised of a distinctive active substance which is the primary material of the medicine that contains the curative feature or a treatment for a completely new illness. The medicines which qualify this criterion are called as "branded medicine" as they can only be sold by the company that carries out the R&D activity to develop that medicine under the specific brand name for a limited period of time determined by the related country legislation. The substitute products can enter the market only after the patent protection period of the "branded medicine" is over. These kinds of products are called as "generic medicine" which is used for the treatment of the same illness and composed of the same active substances with the original one but sold under a different brand name.

[5] John McGuire et al., "Pharmaceuticals, General Survey", **Ullmann's Encyclopaedia of Industrial Chemistry**, Vol.XXVI, Weinheim, Wiley-VCH, 2012, pp. 453-494.

There are diversified competition types in the pharmaceutical markets. The minor manufacturer pharmaceutical companies which, often produce generic medicine in the regional markets as R&D processes are too costly for them, are competing with the other minor companies. The scope of this competition can mostly be explained as price, cost-effectiveness and quality. On the other hand, even if patent protection causes a weaker competition in on-patent pharmaceutical markets, the perfect substitute generics of the original brand can enter the market to compete for market share after the patent barrier has been removed. Admitting that there might be some loyalty to the original brand, this is still not an impeding condition for off-patent competition.[6] Ultimately, the leading global (mostly) companies get in a fierce competition with the minor companies which produce the generic of their branded product after the patent expiration date.

Besides, the leading global companies which have considerable number of patented products are in a strong competition with the other global firms in terms of R&D to get more shares from the global pharmaceutical market. The reason that the leading pharmaceutical companies focus on R&D activities, is expectation for covering their high expenses with the advantage of monopoly power that they will acquire from launching a new medicine to the market. The regular fix expenditures such as energy or raw material which are valid in the other sectors do not constitute the significant expenses in the pharmaceutical sector. Instead, high marketing and R&D expenditures are taking more shares out of the expenditure sources. In the second chapter of this paper; we will explain the processes of R&D in pharmaceutical industry and demonstrate how exhausting and costly it is for the firms. We will also note the amount of R&D expenditures realized by the countries in question.

Furthermore; throughout this chapter; we will look more closely to the scope of the patent protection and the dynamics of this post-patent competition with the generic medicine entry to the market as well as the strategies that companies apply in order to ease the effects of this competition. The overall expenditures in global

[6] Monique Mrazek, Richard Frank, "The Off-patent Pharmaceutical Market", **Regulating Pharmaceuticals in Europe: Striving for Efficiency, Equity and Quality**, Ed. by. Elias Mossialos, Monique Mrazek, Tom Walley, England, Open University Press, 2004, p.245.

pharmaceutical markets and labour market in the pharmaceutical industry will also be evaluated in the third and fourth sections of this chapter.

1.1. Patent Protection in Pharmaceutical Sector

One of the distinctive features of the pharmaceutical industry is that its knowledge intensive character may change the market shares instantly. For instance, a medicine which breaks a new ground in its own therapeutic branch may put the firm that develops it, to the top of the market in a short period of time. For this reason, the companies that want to protect their competitive power in the market has to carry out studies continuously in order to develop new products and increase the efficiency of their existing products.

The pharmaceutical industry is growing constantly with the considerable contributions of the leading firms based on their highly R&D oriented structure. "Its very success of generating a stream of new drugs with important therapeutic benefits has involved the industry in intense public policy debates over the financing of the cost of its research...and the socially optimal degree of patent protection."[7]

"…a patent is a right to exclude others; it is a right to a temporary monopoly, permitting a higher price to be charged for the product, which turn is supposed to stimulate innovation."[8] Even if there are controversies about the monopoly power that patent ownership provides to the pharmaceutical companies which would possibly cause higher prices for consumers, almost every country applies patent protection systems in order to encourage innovation because without a patent system, the tendency for R&D by a firm would be so low as there will be no opportunity to

[7] Richard E. Caves et.al., "Patent Expiration, Entry, and Competition in the U.S. Pharmaceutical Industry", **Brookings Papers on Economic Activity: Microeconomics**, Vol.MCMXCI, w. Place, Brookings Institution Press, 1991, p. 1.
[8] John H. Barton, Ezekiel J. Emanuel, "The Patents-Based Pharmaceutical Development Process: Rationale, Problems, and Potential Reforms", **The Journal of American Medical Association**, Vol.CCXCIV, No.16, October 2005, p. 2076.

recover their fixed costs in the short time. As a theoretical example, in a market where there is no patent protection, a company will make a substantial investment for R&D so as to produce a new medicine. However, just after the launch of the new medicine, another firm will copy its product and put it to the market with a lower price as its cost, lacking the major cost of R&D, will be less compared to the original firm. This would lead the original company to get into competition in the market so early that there will be no time for it to be able to recover its cost. As Plumb states in one of his works "Once the patent protection has been lost it is possible to lose up to 90% of their market share, to generic manufacturers, within 12 months."[9]

The Agreement on Trade Related Intellectual Property rights (TRIPS) is an international document that includes the patent rules in all industries including the pharmaceutical markets. It sets minimum standards in the field of intellectual property protection that all World Trade Organization (WTO) member countries have to respect. Before the TRIPS initiation in the Uruguay Round of the General Agreement on Tariffs and Trade (GATT) in 1986, the pharmaceutical patents were predominantly under protection in major developed countries (except for Spain and Portugal) by law whereas they were not secure in most of the developing countries. Besides that, the durations of the patent protection were changing from one country to the other ranging from 7-20 years. With the TRIPS, the duration of the patent protection is fixed to 20 years and it is determined that this rule has to be implemented to the patent law of each member country.[10]

In general, the agreement has five main objectives which can be summed up under the headings of technological innovation, transfer and dissemination of technology, production and use of technological knowledge, development of a balance of rights and obligations and keeping the account of the social and economic welfare stable.[11]

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[9] Keith Plumb, "Continuous Progressing in the Pharmaceutical Industry: Changing the Mind Set", **Chemical Engineering Research and Design**, Vol.LXXXIII, Issue 6, June 2005, p. 732.
[10] WTO, "Intellectual Property: Protection and Enforcement", **Basic Information to the WTO's Intellectual Property (TRIPS) Agreement**, (Online) http://www.wto.org/english/thewto_e/whatis_e/tif_e/agrm7_e.htm, 12 February 2014.
[11] Peter K. Yu, "The Objectives and Principles of the TRIPs Agreement", **Houston Law Review**, Vol.XLVI, 2009, pp. 797-1046.

The last two objectives suggest that instead of some approaches about the negative effects of the agreement on the least developed countries' welfare due to a possible increase in prices, the aim of the agreement is to find a balanced point where both the rights of the technology providers and the welfare of the society are protected. The Doha Declaration on TRIPS and Public Health (2001) which gave primacy to public health over private intellectual property also reaffirmed that the aim of TRIPS has to be interpreted and implemented in a supportive manner for all WTO Members' right to protect the public health and to promote the equal access to medicines by all. The Declaration stressed the point that the member countries are free to choose the path they will follow in order to apply the rules of the agreement so that, they can put additional counter rules so as to keep the balance. For instance, one of these rules that is applied by the developing member countries can be compulsory licences which give authorization to third parties to produce, use or sell the patented product for a fixed period of time during the life of the patent upon the payment of a reasonable remuneration.[12]

Existence of patent protection is judged to be fundamental for the development or introduction a high percentage of the inventions in the pharmaceutical industry. According to the results of an empirical study, carried out among 100 firms from twelve industries in US, by Mansfield; if there was no patent protection, 65% of the pharmaceutical products would not have been commercially introduced and 60% of them would not have been developed. [13] In the next section, we will see how the shares of the branded medicines and the firms that produce them are affected after the patent expiration.

[12] Jayashree Watal, "Pharmaceutical Patents, Prices and Welfare Losses: Policy Options for India under the WTO TRIPS Agreement", **The World Economy**, Vol.XXIII, Issue 5, Oxford, Blackwell Publishers Ltd, May 2000, p. 742.

[13] Edwin Mansfield, "Patents and Innovation: An empirical Study", **Management Science**, Vol.XXXII, No.2, USA, Informs, February 1986, pp. 173-181.

1.2. Generic Drug Industry Dynamics and Post-Patent Competition

As the simple economic theory of competition implies, the original firms' profits decrease with the entry of the rival firms providing the same products to the market. Many empirical studies supports that the profits of pharmaceutical firms selling a branded medicine are reduced when the generic versions of the branded product enters the market.

"All Organisation for Economic Co-operation and Development (OECD) countries see the development of generic markets as a good opportunity to increase efficiency in pharmaceutical spending, by offering cheaper products than on-patent drugs for an equivalent health outcome."[14]

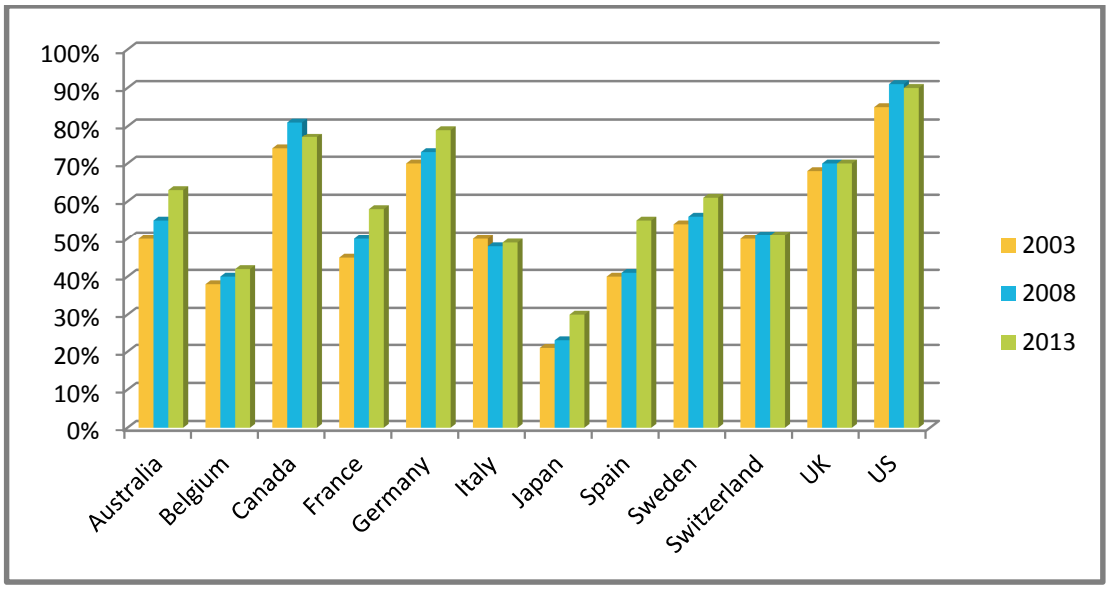

Figure 2. Generic Volume Shares by Country – 2003, 2008, 2013
Source: IMS Institute for Healthcare Informatics, **Global Use of Medicines: Outlook Through 2017**, November 2013.

[14] OECD, "Pharmaceutical Generic Market Share", **Health at a Glance 2013: OECD Indicators**, w. Place, OECD Publishing, 2013, p. 104, (Online) http://dx.doi.org/10.1787/health_glance-2013-42-en, 03 February 2014.

The increasing shares of generic products in prominent pharmaceutical markets are shown in Figure 2. A part of the differences in the share of generic market across countries might be interpreted by market structures, the number of medicines with expired patents, the subjective preferences of the physicians and policies implemented by the governments in order to encourage the generic entry.

It can be deduced from the figure that even if the number of patent holder pharmaceutical companies are abundant in US, there is a high generic volume as well. A key event causes the development of generic industry in US is considered to be the Drug Price Competition and Patent Term Restoration Act of 1984, also known as Hatch-Waxman which has changed the criteria of U.S. Food and Drug administration (FDA) for the approval of generics by reducing the costs and the amount of time for the approval.[15]

On the other hand, the volume of generic shares is quite low in Japan, compared to its market size. There are a couple of reasons for the low volume of generic shares in Japan. One of these was the difficulty of generic substitution in pharmacies. The pharmacies were not allowed to substitutes generics for the branded medicines until April, 2008. After the implementation of a new rule, they have begun to be able to make substitutions as long as the contrary is not implied by the physician. Almost 10% increase in the volume share of generics in Japan from 2008 to 2013 might be explained to some extent with this new rule which encouraged more generic firms to enter the market. In order to make a comparison, it is crucial to keep in mind that many states in US allow generic substitution by pharmacies. Another reason can be the very influential subjective thoughts of the physicians. The low prescription numbers due to the common belief that the generics are not as good as the branded medicines in quality and lack of confidence about sustainability of the production of the generic medicines, the market is not that attractive for generic producers.[16]

[15] Henry Grabowski, "Competition between Generic and Branded Drugs", **Pharmaceutical Innovation: Incentives, Competition, and Cost-Benefit Analysis in International Perspective**, Ed. by Frank A. Sloan, Chee-Ruey Hsieh, w. Place, Cambridge University Press, 2007, pp. 153-288.
[16] Toshiaki Iizuka, "Generic Entry in a Regulated Pharmaceutical Market", **The Japanese Economic Review**, Vol.LX, No.1, March 2009, p.66.

It is seen that the highest volume shares for generics in European countries belong to Germany with an approximate value of 79% which is followed by UK (70%). Even if the volume shares of generics are lower in other European countries, there are radical increases in some of them such as France and Spain in recent years. The volume of generics has increased almost 15% in Spain from 2003 to 2013 as well as in France. On the other hand, the increase of generic share is very low in some of the European countries such as Italy and Switzerland.

There are some incentives taken by some of the European countries to increase the share of generics in the market. For example, the generic volume increase in Sweden can be associated with the mandatory generic substitution law which has been implemented in 2002. Additionally; even in most of the countries where there is no mandatory law, physicians are free to prescribe medicines with their generic names. However, while British physicians write 80% of their prescriptions in generic names, only 12% of French physicians do so. [17] This may partially explain the reason of difference in volume between UK and France. On the contrary, the pay-for-performance act, started to be applied in 2009 in France, might have a positive influence on the increasing rate of generic volumes. Likewise; there is no doubt that the considerable increase in generic volume in Switzerland between the years 2003 to 2008, is mostly caused by the increase in co-payment rates for branded medicine in 2006. Switzerland applies a positive incentive for pharmacists to increase the generic substitution, as well. According to this incentive, pharmacists receive a fee for every generic substitution.

In US, some of the branded producers apply to a variety of strategies so as to delay or reduce the negative effects of generic competition on their profits. One of which is to introduce and promote a new form of its branded medicine to the market. Under the provisions of the Waxman-Hatch Act; if the firm develops a new form of the medicine with longer-lasting effects, fewer side effects and etc., the firm can apply for a patent extension of additional years.

[17] OECD, "Pharmaceutical Generic Market Share", **Health at a Glance 2013: OECD Indicators**, w. Place, OECD Publishing, 2013, p.104, (Online) http://dx.doi.org/10.1787/health_glance-2013-42-en, 03 February 2014.

Another way applied to protect branded medicine's profit gains from a decline is to raise the equilibrium price of the generic medicine. In this context, the branded producers are introducing a generic version of their own product, called "branded generic", just before the patent expiration. This may lead to higher prices in the long-run through a crowd-out effect on generic firms. Reiffen and Ward explains this condition with a metaphor in one of their articles by asserting that "Generic firms can be thought of as entering a sort of lottery in which first approval is the first prize, second approval is second prize and so on".[18]

On an environment where there is an uncertainty about the duration of the approval process by FDA, a branded generic guarantees the first prize, which is the highest share of the generic market, with its already taken FDA approval. As the first entrant, the firm will get 19-27% of the total generic share for that medicine. Hence, this strategy will be quite profitable for the branded producer as its cost will be less than the other generic producers because of the learning effect. When the entry of the branded generic to the market is anticipated, fewer independent generic firms will enter the market as the considerable portion of the profit will be taken by the branded generic firm. This will lead to fewer firms competing in the long-run so the equilibrium prices will be higher. However, there might be some risks in implementing this strategy. There might be applications for FDA approval by independent generic firms before the anticipation of branded generic's entry so that the generic prices will be lower than the initial point. That can be considered as a reason why this strategy is not adopted by branded firms universally.[19]

[18] David Reiffen, Michael R. Ward, "Branded Generics as a Strategy to Limit Cannibalization of Pharmaceutical Markets", **Managerial and Decision Economics**, Vol.XXVIII, USA, John Wiley & Sons, Ltd, 2007, pp. 251-265.
[19] **Ibid.**

1.3. Fluctuations in Pharmaceutical Spending in Time Intervals

Even if the entrance of generic medicines to the market is supposed to have positive effects on pharmaceutical expenditures, spending on pharmaceuticals still accounts for a significant proportion of health spending in the world at an increasing trend with the exception of a downward movement during the global economic crisis of 2009. The possible reasons for this increase might be the increasing life expectancy in most of the countries, increase in the amount of medicine consumed, increase in the price of the medicines, and new technological advancements in medicine for special illnesses which are more expensive compared to the regular products.

Table 1.1. Pharmaceutical Spending per Capita, 2005-2011 *(At current prices and PPPs – US dollars)*

Countries	2005	2006	2007	2008	2009	2010	2011
Australia	426	453	481	506	550	587	625[e]
Belgium	540	545	567	610	633	641	631
Canada	593	638	663	679	731	739	752
France	545	568	595	613	634	637	641
Germany	505	525	559	596	622	640	633
Italy	493	527	522	538	530	510	487
Japan	492	507	546	569	627	652	685[e]
Spain	456	487	509	541	560	556	536
Sweden	396	427	449	472	472	464	474
Switzerland	427	442	471	500	523	513	531
UK	350	368	371	375	N/A*	N/A*	N/A*
US	819	881	919	937	972	973	995

Source: OECD, "Pharmaceutical Expenditure per Capita", **Health: Key Tables from OECD**, No. 8, (Online), 10.1787/pharmexpcap-table-2013-2-en, 15 March 2014.
** The value is not applicable.*

The overall pharmaceutical spending across the OECD countries in 2011 was around $800 billion accounted for 17% of total health spending. There are different

variations in pharmaceutical spending per capita from country to country ranging from $995 in US to $197 in Czech Republic in 2011.[20]

As we acquire from Table 1.1 above, there is a steady increase in pharmaceutical expenditures per capita in all of the countries until 2009 after which either the expenditures has started to fall or the rate of increase has decreased that formed a stable trend because of the economic crisis. The reduction in expenditure is steep in those countries that are hit hardest by the recession. For example, for Greece which is not included in this list has experienced decreases in pharmaceutical per capita by 10% in both 2010 and 2011 following high growth rates in previous years.

Some countries have introduced a variety of measures in order to decrease spending on pharmaceuticals such as price cuts, centralized public procurement of pharmaceuticals, encouraging the use of generics, cutback in the rate of coverage, and increase in co-payments by households. For instance; Spain has applied a compulsory price reduction for generics which also explains the increased volume shares of generics in that country as we mentioned before. In Germany, rebates for manufacturers have been raised and the prices are fixed until 2013. [21]

Furthermore; across OECD countries, pharmaceutical spending is around 1.5% of GDP on average out of which 0.8% is publicly financed.[22] In Figure 3, we can see the shares of public and private pharmaceutical expenditures as a percentage of GDP for some major countries. It can be acquired from the figure that in US where the share of total pharmaceutical expenditures is higher than the other countries, most of the burden is taken by private sector while it is the opposite in Japan which is the country with the second highest amount of pharmaceutical expenditures among the countries studied in this current paper. Canada has a similar pattern with US, yet the overall amount is lower than what US has. France has the highest percentage of GDP dedicated for pharmaceutical expenditure among the European countries within our study's framework. It is also deduced that the pharmaceutical expenditures mostly

[20] OECD, "Health Expenditure and Financing", **Health at a Glance 2013: OECD Indicators**, w. Place, OECD Publishing, 2013, p.160, (Online) http://dx.doi.org/10.1787/health_glance-2013-42-en, 08 February 2014.
[21] **Ibid.**, p.161.
[22] **Ibid.**

comprised of public expenditures in the European countries in general even if the difference between public and private is not much in some.

Moreover, most of the expenditures on pharmaceuticals consist of RX rather than OTC in all the OECD countries. Belgium, which has the highest rate of OTC expenditures among OECD countries, is followed by Australia and Iceland.[23]

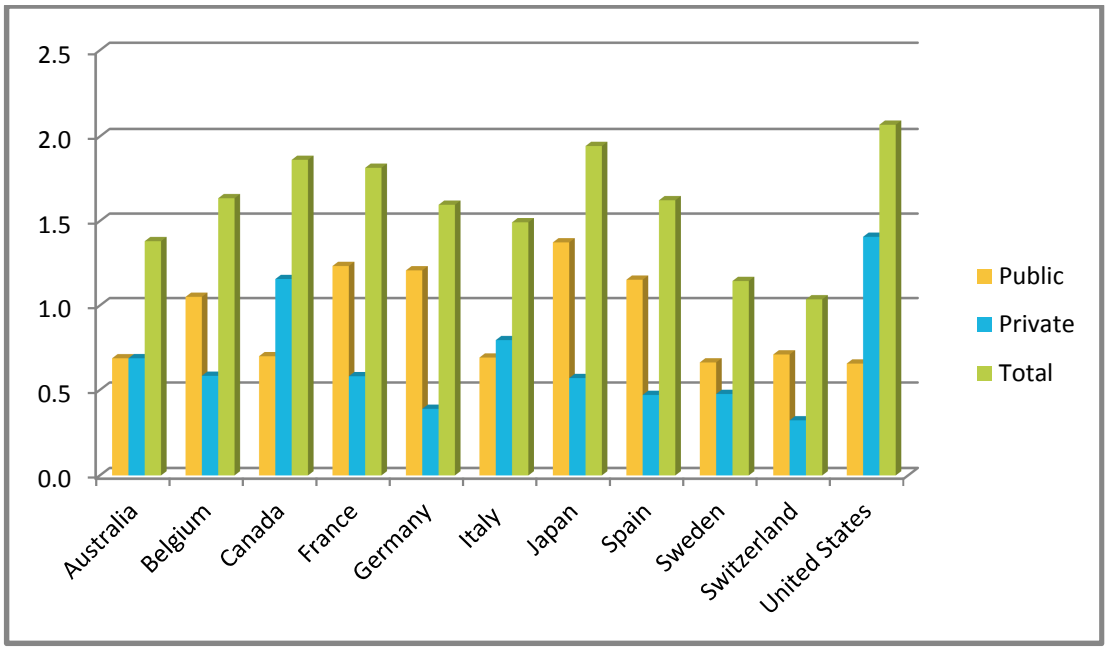

Figure 3. Pharmaceutical Expenditure as a Percentage of GDP, 2011 (or nearest year)
Source: OECD, **OECD Health Statistics**, 2013.

1.4. Employment in Pharmaceutical Markets

Pharmaceutical industry has a very sensitive and high-tech structure which makes the hiring of highly educated people an obligation for the firms. The overall employment level in European pharmaceutical markets is about 700.000 people in 2012 among which approximately 116.000 people are working for pharmaceutical research and

[23] OECD, "Health Expenditure and Financing", **Health at a Glance 2013: OECD Indicators**, w. Place, OECD Publishing, 2013, p.160, (Online) http://dx.doi.org/10.1787/health_glance-2013-42-en, 08 February 2014.

development.[24] We can see some figures related to the number of people employed in pharmaceutical industry in Table 1.2. Even if the years that the data belong to are various due to the fact that availability of the most up-to-date data are different for each country, they are still shown in this paper as the differences in time intervals are minor and the data is still useful for giving an overall opinion about the employment in the industry.

Table 1.2. Number of Employees in Pharmaceutical Industry in Units

Country	Year	# of Employees in Units
Australia	2009	14970
Belgium	2009	18614
Canada	2010	18452
France	2009	78745
Germany	2009	115141
Italy	2009	65117
Japan	2010	90469
Spain	2009	38983
Sweden	2009	16883
Switzerland	2011	38561e*
UK	2009	39910
US	2008	245900

Source: United Nations Industrial Development Organization, **UNIDO Database**, (Online) http://www.unido.org/en/resources/statistics/statistical-databases.html, 19 January 2014.
* *Figure for Switzerland is taken from EFPIA Key Data 2013 and it is an estimate.*

Due to its highly dynamic and innovative structure of the industry, the number of people who are working in the research and development section of the pharmaceutical industry has increased by 52% from 1990 to 2012. Most of the employees in this field are scientists who have higher education degrees like chemists, pharmacists, biologists, physicians and chemical engineers. Later in this paper; we will see how important the employment for research and development is for pharmaceutical firms not only because of the discovery of the new products but also for the high R&D costs.

[24] EFPIA, **op. cit**., p. 3.

Throughout this chapter, we mentioned some key figures related to pharmaceutical market structure in the representative countries in terms of market size, spending, patent protection, employment, and generics and competition. In the forthcoming chapter, the importance of patent protection and employment for investment on new pharmaceuticals will be supported by the facts such as the difficulty of R&D and its determinants which are all directly or indirectly affected by the concepts we referred above.

2. EXAMINATION OF INVESTMENT ON RESEARCH AND DEVELOPMENT

Investment, as a term, has a variety of different implications depending on the context in which that is used. However, the reason that lies behind any kind of investment is uniform, which is simply the expectation of gaining more profits. For instance; investment in financial markets can be defined as purchasing a financial asset or any type of item with the hope of generating profits by selling it to a higher price in the future. Likewise; economical investment is defined as acquiring a new good (a machine, an extended place for a facility etc.) in order to produce new products that will eventually increase profits.

Investment in technology, R&D in other terms, is another type of investment which can be explained as developing new products to put on the market. The products can be anything ranging from automobiles, electronic appliances donated with newer technologies, medicines, even a new version of something simple like a pen. Firms invest on R&D for the same reason that they invest on machines or building new facilities: to increase their profits. Notwithstanding, investment on R&D differs from the economical investment in a way, as the most important outcome of the R&D is the new idea behind the product rather than the product itself.

Especially, for the companies operating in high-tech industries R&D investment is necessary to sustain their competitiveness considering that these kinds of industries have ever-changing product portfolios. That's why the cost of investment on R&D constitutes a remarkable amount of the firms' expenditures which will only be covered in the far future only if it is successful eventually. The gross domestic expenditure on R&D in EU-27 is counted as 245.673 million € in 2010. The Lisbon strategy set an objective for EU for devoting 3% of its gross domestic product to R&D investment by 2010 which is not achieved and extended until 2020. In Figure 4, we can see the evolution of R&D expenditures in some prominent countries through years. Among EU-27, Japan and US; the country that has the highest rate of R&D is

Japan with a rate of 3.29% of its GDP in 2010. The R&D expenditure of US accounts for 2.77% of its GDP whereas it is only 2% in EU-27 in the same period. Within the EU-27, the highest rate of R&D expenditure belongs to the three Nordic countries Finland (3.87%), Sweden (3.42%) and Denmark (3.06%) respectively whilst the countries with lowest R&D intensity are generally southern and eastern European countries.[1] On the other hand; the country which devotes highest rate of GDP on R&D is Israel (4.38%) on OECD basis.[2]

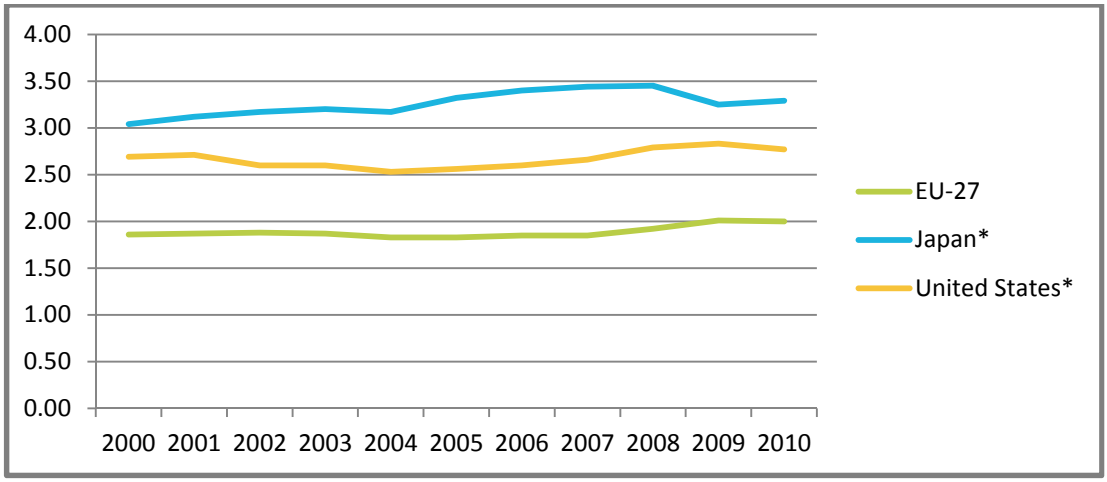

Figure 4. Gross Domestic Expenditure on R&D as a Percentage of GDP, 2000-2010
Source: Eurostat, "R&D Expenditure" – **Statistics Explained** (Online) http://epp.eurostat.ec.europa.eu/statistics_explained/index.php/R_%26_D_expenditure#Further_Eurostat_information, 24 January 2014.
**The values of Japan and United States for 2009 and 2010 are taken from OECD database.*

In almost all of the OECD countries, R&D investments are mostly undertaken by the business enterprises rather than governments. However, this share is considerably higher in Japan and US of which only 15.6% and 27.1% of total gross expenditure on R&D respectively realized by government which might be explained by the fact that these countries have a high volume of technology intensive global companies. [3] However, when the data is evaluated statistically in terms of trends as it is shown Figure 4; there found to be no statistically significant relationship between Japan and

[1] Eurostat, "R&D Expenditure" – **Statistics Explained** (Online) http://epp.eurostat.ec.europa.eu/statistics_explained/index.php/R_%26_D_expenditure#Further_Eurostat_information, 24 January 2014.
[2] OECD, **Main Science and Technology Indicators,** Vol.MMXIII, Issue 1, w. Place, OECD Publishing, June 2013, p.16, (Online) http://dx.doi.org/10.1787/msti-v2013-1-en ,10 February 2014.
[3] **Ibid.**

the others, which suggests that the gross domestic expenditure on R&D in Japan is highly different from US and EU-27. On the other hand; the expenditure behaviour in US and EU-27 shows similar characteristics which has a strong correlation under 99% confidence level.

Table 2.1. Correlation Analysis for Gross Domestic Expenditure on R&D *(EU-27, Japan & US)*

Correlations

		EU27	Japan	US
EU27	Pearson Correlation	1	,098	,844**
	Sig. (2-tailed)		,774	,001
	N	11	11	11
Japan	Pearson Correlation	,098	1	,143
	Sig. (2-tailed)	,774		,675
	N	11	11	11
US	Pearson Correlation	,844**	,143	1
	Sig. (2-tailed)	,001	,675	
	N	11	11	11

**. Correlation is significant at the 0.01 level (2-tailed).

2.1. The Determinants of R&D Investment Decision in Pharmaceutical Industry

Since R&D is firms' key investment for future, it is crucial for them to be able to measure the effectiveness of it at all stages and adjudge to move forward or not. "In accordance with the basic economic theory, the R&D investment decision is determined by the intersection of the marginal rate of return on investment schedule (mrr) and the marginal cost of capital schedule (mcc)."[4] This hypothesis is also supported in the PhD thesis of John A. Vernon where he calculated the optimum

[4]Henry Grabowski, John Vernon, "The Determinants of Pharmaceutical Research and Development Expenditures", **Journal of Evolutionary Economics**, Vol.X, Springer-Verlag, 2000, p. 201.

level of R&D with the equation shown below by utilizing and simplifying the q-model of James Tobin (1969).[5]

$$\frac{MRR}{MCC} = q = 1 \quad (1)$$

As he suggests in Equation (1), firms will choose the most profitable R&D projects which equals its expected marginal returns from investment to the marginal cost that they have to bear in order to realize the project in question and continue to make additional projects as long as the expected rate of return from the projects exceeds its marginal cost of capital.

If we insert the possible principles that may affect R&D through one of these channels as a vector into this equation, the equation can be defined as follows:

$$MRR\ (R\&D, X) = MCC\ (R\&D, Y) \quad (2)$$

X, being the vector of variables that affect the MRR schedule can be considered as the changes in research opportunities or in the industrial or regulatory environments which will both influence the expected rate of return from R&D in a positive or negative way depending on the direction of the change.[6]

[5] John A. Vernon, "Price Regulation, Capital Market Imperfections, and Strategic R&D Investment Behaviour in the Pharmaceutical Industry: Consequences for Innovation", (Unpublished Ph.D. Thesis) University of Pennsylvania, Managerial Science and Applied Economics, US, 2003.
[6] **Ibid.**, p. 24.

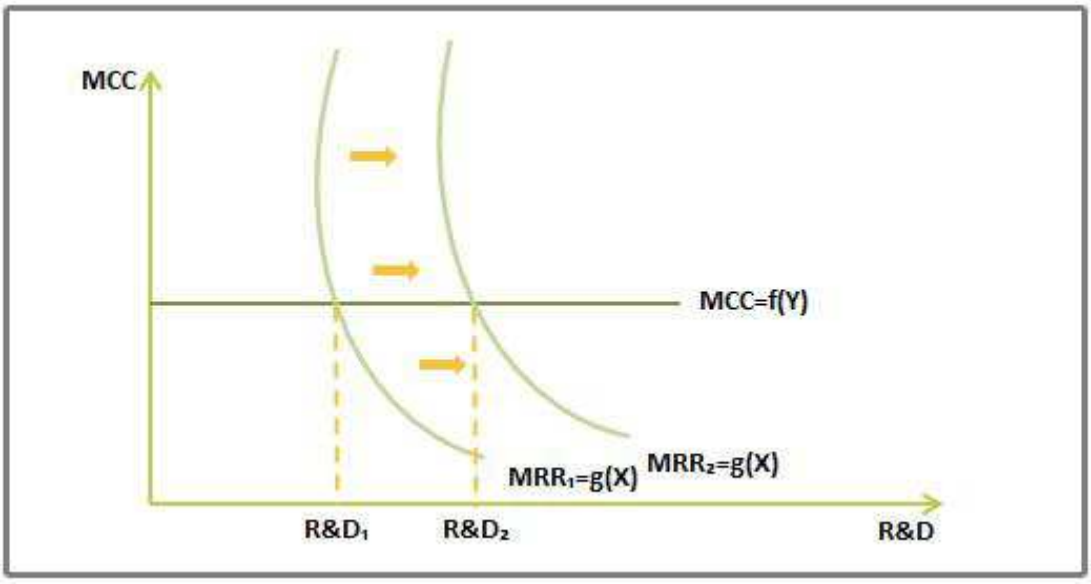

Figure 5. An Increase in the Expected Rate of Returns to R&D

Source: John A. Vernon, "Price Regulation, Capital Market Imperfections, and Strategic R&D Investment Behaviour in the Pharmaceutical Industry: Consequences for Innovation", (Unpublished Ph.D. Thesis) University of Pennsylvania, Managerial Science and Applied Economics, US, 2003.

The graph above visualizes the effect of an increase in MRR on the optimal amount of demand for R&D investment. It is seen that with the influence of higher MRR expectations, the MRR curve will shift to the right and the new optimum will, ceteris paribus, occur at a higher investment level.

Generally; firms cover the cost of R&D either with the internal funds or external equity finance. Mostly, they apply a hierarchy in the order of internal funds, new debt financing and new equity. They begin the R&D by using their internal sources as they are usually more cost efficient and continue to reinforce the investment with external sources when the internal funds wear out. Hence, the vector "Y" on the right hand side of the Equation (2) represents the cost of internal or external funds that influences MCC. In neoclassical investment theory, the cost of internal and external sources will be the same so that, the MCC schedule will be horizontal as shown above. However, because of some imperfections in the markets that we will study later in this paper, this is not the case in practice.

Therefore; considering the difference in costs, the new MCC schedule will be at a higher level than the one we showed in Figure 5 in order to remark the increase in the

cost of changing from the internal to external funds. Vernon displays this change with a graph like the one below.[7]

As we perceive from Figure 6; the R&D investment of the firm rely upon the internal funds at the beginning. With an increase in the expected rate of return, the demand for R&D increases and the optimal amount of R&D occurs at $R\&D_2$. The internal funds of the firm comes to an end in the process so, the firm begins selling bonds, bills or notes to individual and/or institutional investors in order to leverage its capital by borrowing. As the risk that the firm takes is scaling up in parallel to the more and more debt, the cost of borrowing ascends as a result of the debt holders' elevated demand for a higher rate of return to compensate the higher risk. This is indicated with the upward sloping MCC.

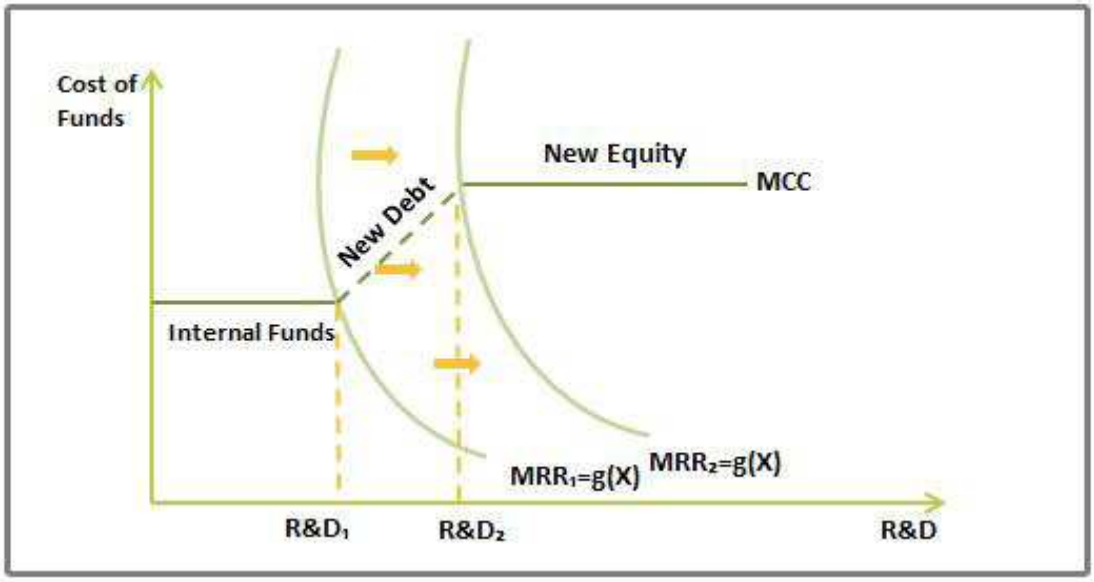

Figure 6. An Increase in the Expected Rate of Returns to R&D in the Presence of Financing Constraints
Source: John A. Vernon, "Price Regulation, Capital Market Imperfections, and Strategic R&D Investment Behaviour in the Pharmaceutical Industry: Consequences for Innovation", (Unpublished Ph.D. Thesis) University of Pennsylvania, Managerial Science and Applied Economics, US, 2003.

Even if the result of an increase in MRR is identical in both in Figure 5 and Figure 6, the firm has to consider the profit-cost trade in the latter due to the increased cost. On the other hand; the two models differ significantly in the case of escalated cash flows.

[7] John A. Vernon, **op. cit.**, p. 28.

Let's assume that the firm is already financing its investment by borrowing. If there is a movement of money inside the business and the firm decides to use this additional source for investment, it will be able to extend its R&D activities, which will cause an increase in demand for R&D at a lower cost. (Figure 7) However, an increase in internal funds will not have an impact on R&D in a market where there are no financial constraints as the internal and external funds already cost the same in these capital markets. Likewise, even if there are financial constraints, the increase in the level of internal funds without any change in the expectations for rate of return, may not affect the amount of R&D investment if the initial MRR is already at the internal funds part of the graph.

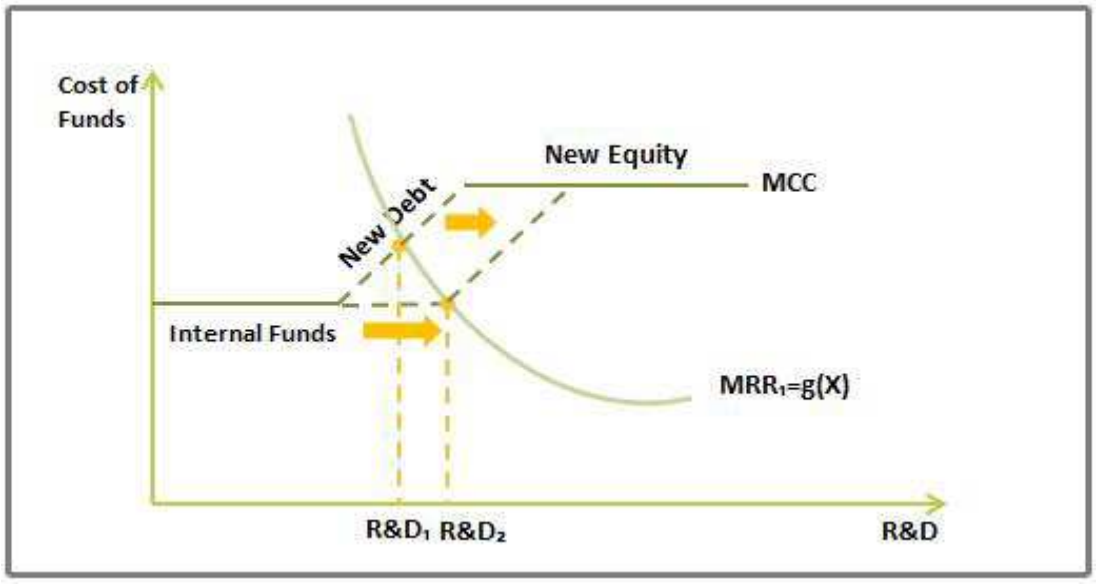

Figure 7. An Increase in the Level of Internal Funds in the Presence of Financing Constraints
Source: John A. Vernon, "Price Regulation, Capital Market Imperfections, and Strategic R&D Investment Behaviour in the Pharmaceutical Industry: Consequences for Innovation", (Unpublished Ph.D. Thesis) University of Pennsylvania, Managerial Science and Applied Economics, US, 2003.

When it is no longer conceiving to issue any more debt, the firms start to issuing equity as the last expedient. Therefore; the firms attempts to raise source of capital by selling company shares to new or existing shareholders in order to finance the rest of the investment. Bharath and his friends, in the article where they analysed the capital structure decisions, explain this situation with the pecking order theory of

Myers (2001). They support the idea that "…companies should use stock issuances to cover financing deficits only as a last resort, after cheaper, less information sensitive alternatives (like internal cash, bank debt, or public debt) have been exhausted." [8]As we see above in the graphs; even though, the part of MCC that signifies the "new equity" does not have an increasing slope as "new debt financing", it is more costly than new debt financing. Predominantly, this stems from the fact that the new debt financing is secured with corporate assets where new equity financing is not.

The Modigliani-Miller theorem (1958, 1961) which is certainly the most outstanding theory on capital structure suggests that a firm is indifferent to the composition of its capital when choosing the optimal level of R&D investment because it would face the same price for both the internal and external funds under the condition of perfectly functioning capital markets. However, as opposed to this theorem, the internal and external funds are not perfect substitutes and the internal funds are more cost efficient compared to the other sources of capital formation due to the imperfections of the capital market caused mostly by the asymmetric information between the inventor and investor, agency costs and moral hazards arising from the separation of ownership and management, transaction costs, and tax advantages.[9] We will examine these topics more closely throughout this chapter.

2.1.1. Asymmetric Information between the Inventor and Investor

As mentioned above; one of the reasons why internal funds is preferred to new debt financing or new external equity for R&D investment is asymmetric information

[8] Sreedhar T. Bharath, Paolo Pasquariello, Guojun Wu, "Does Asymmetric Information Drive Capital Structure Decisions?", **The Review of Financial Studies**, Vol.XXII, No.8, w. Place, Oxford University Press, August 2009, p. 3212.
[9] Bronwyn H. Hall, "The Financing of Research and Development", **Oxford Review of Economic Policy**, Vol.XVIII, No.1, Oxford University Press, 2002, p. 37.

because the R&D projects are not easily understood by the outsiders as much as they are grasped by the entrepreneurs who have better perception of the likelihood of success. Hence, new equity issues for R&D financing in capital markets require a "lemons' premium" as modelled by Akerlof in 1970.[10]

The rationale behind this lemons' premium theory is that the seller has the advantage of knowing more about the quality of his product whereas the buyer knows only as much as the seller is willing to share. So that, the buyer will not be enthusiastic about paying the amount that the seller charges suspecting that he might be over charging. Eventually, the seller will have to decrease his price to a lower rate compared to the one that he might have in a symmetric information environment. This advantage secured by the buyer is named as "lemons' premium". "This premium compensated the investors for their losses- which they incurred by financing the low-quality firms, or "lemons"."[11]

This premium required by the investors may be explained by using the q model, as well. In theoretical terms; it is the difference between the firm's real value and the average value that is given to all the firms in the market. According to this approach, the new shares will be issued only when the new project's value is equal to or higher than the ratio of the real value of the firm to average value given to the all the firms in the market. It is assumed that the outcome of this ratio is equal to "1" if there is no asymmetric information whereas it will be more than "1", if there is asymmetric information in the market between the firms and the investors. This condition is explained with the equations below by Vernon: [12]

$$\frac{Q}{\bar{q}} = 1 \qquad (3) \qquad\qquad \frac{Q}{\bar{q}} > 1 \qquad (4)$$

[10] James R. Brown, Steven M. Fazzari, Bruce C. Petersen, "Financing Innovation and Growth: Cash Flow, External Equity, and the 1990s R&D Boom", **The Journal of Finance**, Vol.LXIV, No.1, February 2009, p. 157.
[11] John A. Vernon, **op. cit.**, p. 49.
[12] **Ibid.**, p. 51.

In the equations above, "Q" signifies the "real value of the firm" and "$\bar{q}$" stands for the "average value for all the firms" given by the market regardless of the fact that they are "lemons" or good firms. Seeing these equations, we can conclude that the difference between Q/$\bar{q}$ and 1 in equation (4) will give us the "lemons' premium" of the investors.

Admitting that this asymmetric information problem might be existent also in economical investments as well as financial investments, the "lemons' premium" for R&D will be higher as the R&D projects are usually long-term investments of which the results are rarely 100% presumable. This is even more salient in pharmaceutical R&D.

Keeping in mind that investment on R&D is based on developing ideas rather than products, the firms will have no heart for articulating their newly created ideas to the public as it will create a substantial cost for them. This restriction on expressing their project explicitly to their investors will push up the cost of external funds to a higher level than the costs of internal funds due to the emerged asymmetric information.

2.1.2. Agency Costs and Moral Hazard Arising from the Separation of Ownership and Management

There are several approaches to the agency costs associated with the financial constraints that firms may face. Some of them explain these costs through internal issues of the firms while some point out its connection with the debt finance. No matter what the emergence point of these costs, they are another cause why there is a gap between the internal and external financial sources for R&D investment.

Nowadays most of the firms have a separation in management which means that the managers and the owners of the firms are not the same people. This differentiation can occur both in the firms owned by shareholders and the ones owned by an individual person by definition.

One of the approaches refers to this cost problem is the internal principal-agent problem caused by the separation of the owner and the management staff hired by the owner as an agent. This binary power that faces to the opposite directions will have a high chance to affect the investment on R&D by causing to invest on projects which are not share-value maximizing or missing the opportunity of a profitable project. Its influence on R&D investment decisions can be realized through several forms among which the most effective and probable ones are explained as follows by Hall[13]:

- The possible inclination of the managers to allocate the sources of the firm on activities that are for their own gain such as growing the firm beyond its efficiency level, moving to larger offices with a nicer atmosphere and etc.
- The unwillingness of the managers who want to play it safe and retain from investing in R&D projects which have ambiguous future.

The first article given above is related with the risks about the probability that the managers will use the firms' resources for their own benefit. The possibility of managers to have ambition and desire for prestige and compensation can be counted on top of these benefits. For instance; managers may have a tendency to increase the size of the firms rather than its profits in exchange for less efficiency and the real value of the firm. According to Hall, this problem can be avoided by limiting the free cash flows available to the managers however this will plausibly make way for using the higher-cost external funds to finance R&D by causing more costs eventually.[14]

The second article addressed previously refers to a more direct effect of agency costs on R&D. Managers are more reluctant about signing in the R&D projects that will increase the precariousness of the firms compared to the owners of the firms. Therefore, the managers will weigh their opportunity cost and the present value of their earnings, and if the opportunity cost is lower than the earnings, they will retain from variance-increasing projects which might be interesting for the owners. This

[13] Bronwyn H. Hall, **op. cit.**, p. 39.
[14] **Ibid.**

condition may appear very often in R&D projects as they are long-term investments which's result that are already totally uncertain, will only be benefited after many years. Thus, Hall suggests providing managers with long term incentives in order to avoid these kinds of missed opportunities which might be highly profitable in terms of maximizing share-value of the firm.[15]

There is a very common contrary approach regarding this second article, which is about debt finance that creates agency problems. According to this approach; managers are behaving in favour of the owners of the firms by taking debt holders against themselves. Managers may choose to ignore some R&D projects with positive present values and obtain some projects with negative present values. On top of everything, the managers can be disposed to issue new debts which will raise the riskiness as we mentioned before while we were explaining the upward slope of the MCC showing the new debt financing. Knowing that their interest will not always be the same with the owners of the firms, the debt holders are applying some rules to restrict the behaviour of the managers.[16] This condition may also cause an agency problem considering that it restrains the financial ability by limiting the management's decisions about investment opportunities. Moreover, it would also a negative effect on the R&D in a straight way which is through the fact that it suppresses the capacity to provide financial sources for R&D projects when the internal funds are not enough.

In the presence of incentive issues and difficulty in monitoring of the managerial behaviours, external providers of financial sources require a higher return to compensate the potential moral hazards related to the managers' supervision of the supplied funds.

[15] Bronwyn H. Hall, **op. cit.**, p. 39.
[16] Gerard Caprio, Jr., Ross Levine, **Corporate Governance in Finance: Concepts and International Observations**. (Online) http://siteresources.worldbank.org/DEC/Resources/corporategover_finance.pdf, 3 January 2014.

2.1.3. Transaction Costs

Transaction costs which arise from exchange of equity are not high price costs but their effect on the firms' decision about the R&D investment in a financial constraint environment may not be insignificant as well. That's why they are one of the other elements that constitute the difference in cost between the internal and external funds, which ultimately may increase the tendency of the firm to finance its R&D with internal funds rather than external.

There are several different ways through which the firms can raise new equity capital as shown below in Figure 8:

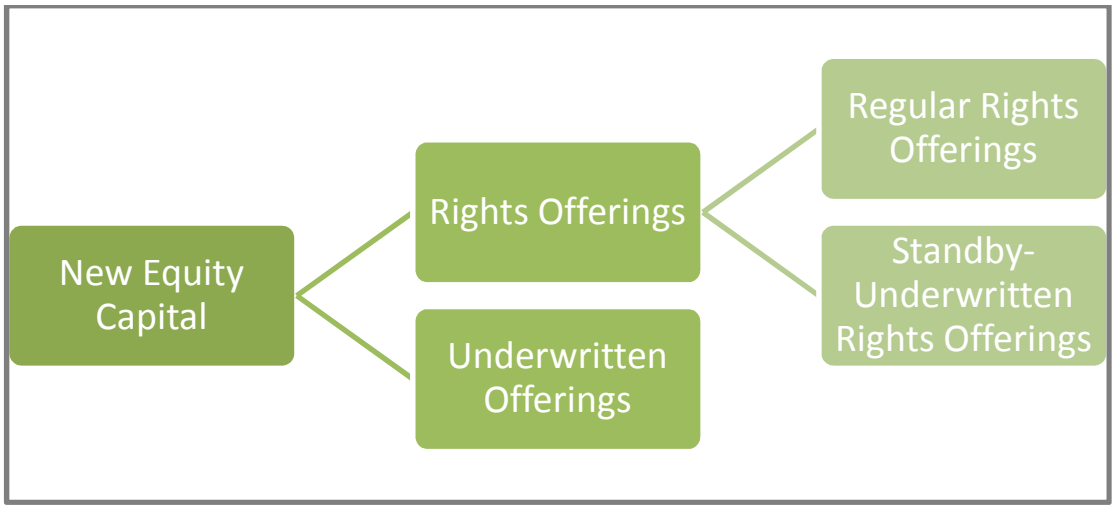

Figure 8. Methods of Raising New Equity Finance
Source: Clifford W. Smith, Jr, "Raising Capital: Theory and Evidence", **Investment Banking Handbook**, Ed. by. J. Peter Williamson, Canada, John Wiley & Sons, 1988, pp. 71-94.

In an underwritten offering; an intermediary firm -usually banks, investment houses, or insurers- purchases equity for its own account and then tries to sell it to another investor in a public offering at a higher price compared to what it paid to the issuing firm. This difference in price, which is mostly called as underwriting spread, forms the earning of the underwriter intermediary firms. If the underwriter firm cannot sell the equity at the price it offers, it sells it to whatever price accepted by the investors.

Seeing that the party which takes the whole risk in this scenario is the underwriter, the issuing firm's gain is stable in any case.

Firms can realize the equity raising through another method called rights offering in which there is no third party involvement. In this type, the firm which wants to raise financial source for its R&D investment offers its existing shareholders the opportunity to purchase additional shares directly from itself in proportion to their current holdings for a certain period of time. This will help the shareholders to be able to purchase additional shares before any other players in the market. The rights offering will also provide convenience of getting a subscription price for the new shares. There will be no expenses such as underwriting fees, legal fees or registration fees in this type of equity offering so, the cost to the issuing firm will be lower than it was in the underwritten offering.

Rights offerings might be underwritten, as well. This method of rights offering is named as standby underwritten rights offering in which there is an intermediary firm, as it was in the underwritten offering. In this sense, this type of equity raising might be defined as the combination of the two methods mentioned before. Initially, the underwriter signs an agreement with the firm accepting that it is the guarantor. If all the shares that the firm wants to sell cannot be sold in the public offering, it is the responsibility of the guarantor to purchase all the remaining shares at the subscription price. Even if, it seems that this is more profitable both for the issuer and purchaser, there is a high risk for the intermediary firm as it has to purchase all the remaining shares after the public offering. Moreover, there is a fee called standby fee that the firms have to pay to the underwriter as a percentage of the capital raised because of the risk that it takes.

In a study by Altinkilic and Hansen; these underwriter spreads which creates a substantial part of the transaction costs are examined. [17] In this study, the total transaction costs of the spreads for underwriting offerings depending on the size of the proceeds are shown through the years 1990-1997. It estimates that up to 85% of

[17] Oya Altinkilic, Robert S. Hansen, "Are There Economies of Scale in Underwriting Fees? Evidence of Rising External Financing Costs", **The Review of Financial Studies**, Vol.XIII, No.1, Oxford University Press, 2000, pp. 191- 218.

the spread costs consist of variable costs rather than fixed costs. Based on 1325 new equity issues ranging in size from $10 million to more than $80 million, the average spread cost is found 5.38% of the total proceeds and fixed costs are no more than 10% of these total spreads. The study suggests that the cost of the spreads seems to be lower at higher amount of capital raised; however this is not related with the economies of scale theory as opposed to many works put forward. For example; for the proceedings more than $80 million the average spread costs falls to 4.37% of the total capital raised. Yet, this is because of the fact that the larger firms which issues larger amount of equity have lower U-shaped cost curves that make the spreads to be smaller as explained by Altinkilic and Hansen.

As we can easily acquire from above; underwritten offerings and standby underwritten rights offerings will be more costly to the firms than the regular rights offering since, the latter does not have any costs such as underwriting spreads. Nonetheless; as the risks of the any underwritten offerings are less to the firms, majority of the firms have a tendency to use these kinds of offerings. Thus, the firms have to bear 5.38% of the total value of a new offering on average as a transaction cost.

2.1.4. Tax Advantages of the Internal Funds

There are many notable works studied the effects of taxes on the capital structure and the preference of the firms between internal funds and external funds. Several types of taxes, one of the causes of the cost differences among the financing sources, are specifically focused in these works as effective elements in the process of financing the R&D investments. These taxes can simply be categorized as corporate taxes, capital gains taxes (also called as retained earning taxes) and personal taxes (also called as dividend taxes or external equity taxes). According to OECD Tax Database, integrated capital tax rates (capital tax combined with corporate tax) range from 21% in Switzerland to 39% in US in 2013 among the countries that we study throughout

this paper. On the dividend tax version of the data; we see that the dividend tax rates are within a wider band of 10% in Japan to 50% in Canada among the same countries. The EU average for integrated capital gains tax rate and dividend tax rates are 24.5% and 27.4% respectively. The same rates are 25.5% and 29.7% for OECD countries.[18]

Hypothetically, firms would be indifferent between internal funds and external equity finance as long as the tax on dividends and internal capital earnings are equal on a ceteris paribus condition. However; as Devereux et al. (1990), Hall (2002) and Vernon (2003) also suggest in their articles related to capital imperfections and financing of R&D, the taxes on the internal capital earnings cost less in most of the countries compared to the taxes on dividends in a majority of the countries, which makes internal finance more attractive for the financing of R&D investments. This proposition can easily be supported by the OECD data shared above which gives a sense for the difference.

Vernon explains this hypothesis with an extension in the q model of investment that he has developed and suggests the following conditions for firms to invest on R&D[19]:

Table 2.2. R&D Investment Project Acceptance Criteria

Source of Finance	Accept Investment Project	Reject Investment Project
Internal Funds	$q \geq \frac{(1-t^d)}{(1-t^c)}$	$q < \frac{(1-t^d)}{(1-t^c)}$
External Funds	$q \geq 1$	$q < 1$

Source: John A. Vernon, "Price Regulation, Capital Market Imperfections, and Strategic R&D Investment Behaviour in the Pharmaceutical Industry: Consequences for Innovation", (Unpublished Ph.D. Thesis) University of Pennsylvania, Managerial Science and Applied Economics, US, 2003.

[18] OECD, **OECD Tax Database** (Online) http://www.oecd.org/tax/tax-policy/tax-database.htm, 7 March 2014.
[19] John A. Vernon, **op. cit.**, p. 54.

q = rate of return

$\mathbf{t^d}$ = tax rate on dividends (personal tax rate)

t = tax rate on capital gains

As it is indicated in the table above; firms are supposed to invest by using their internal funds only when the rate of return is equal to or greater than the ratio of the after-tax yield rated at dividend tax rate to the after-tax yield rated at capital tax rate. If the firms are financially restricted and have no other option than the external funds to finance their R&D investments, they will only accept the investment project with the condition of the rate of return would be equal to unity or higher than it.

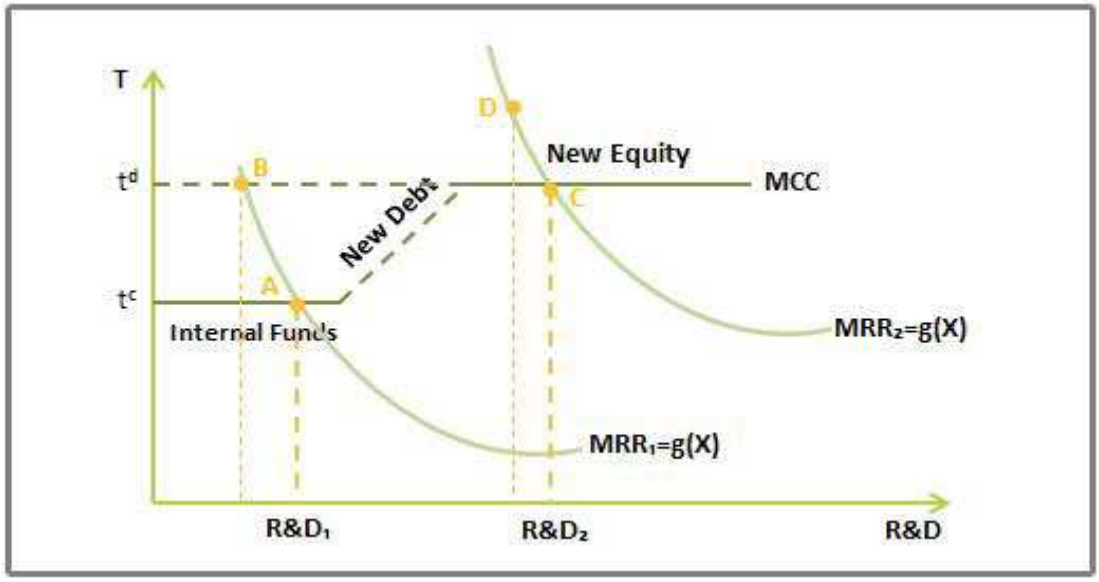

Figure 9. After-Tax Rate of Return for Internal Funds and New Equity Finance, and the Equilibrium Points for R&D Investment

In Figure 9; if we assume that the tax rate on dividends is higher than the tax rate on internal earnings, it is clearly seen that firms will have to bear more tax burden if the investment is realized by new equity sharing.

As long as the capital tax rate is fixed at "t^c" and the firms have enough internal funds to finance the investment, their equilibrium point will occur at point A. Ceteris paribus; if the tax rate increases to a higher amount, to the same level with the new

equity tax rate as an extreme case (B), the firms will consider to apply to another source to finance their investments even if they have enough internal capital for it. Furthermore; the equilibrium point for the new equity financing will occur at point C where the firms bear "t^d" tax rate. If the tax rate increases to more than 1 to point D, investment will no longer be rational for the firms.

On the other hand, in some of the researches made in this subject showed theoretical clues proving that the taxes for debt financing is less than that of retained earnings or new equity issuing (Hall, 2002) (Auerbach, 1984). According to this assumption; as long as the personal income tax rates are not much higher than the sum of corporate and capital gains tax rates, the following order will be valid:

$$(1-\Theta) < \frac{(1-t^d)}{(1-t^c)} < \frac{1}{(1-t^c)} \qquad (5)$$

Where,

Θ = interest for debt deductible at the corporate level

However; there are several other reasons why debt financing would be a disfavoured source of finance for R&D. Top of which is that banks would rather to adopt physical assets to secure loans and are hesitant to lend when the projects involve substantial R&D investments which have uncertain and volatile returns rather than discernable investment in plant or equipment.

Until this point of the chapter; we discussed the financial reasons that the firms would consider while financing an R&D investment and explained the determinants of R&D decision followed by the financial constraints. In the next two sections, we will briefly touch upon the theoretical points that the firms have to bear in mind about the expected fertility of the research itself and the market conditions for R&D in that field when attempting to start an R&D investment project.

2.1.5. Fertility of the Research and Appropriability of Research Results

Prior to checking for the determinants of financing R&D or the ratio of the MRR to MCC for the expected rate of return, firms have to review the feasibility of the targeted project in terms of fertility and appropriability.

If a research is fertile which, means that if spending on R&D has a high chance of leading to new products, the firms will have an active incentive to bear the risk of investing on R&D. At this stage, basic research becomes an important element of the R&D investment decision. "Basic research can be understood as a very early stage research which is defined to build a knowledge base in order to understand fundamental principles."[20] One of the most outstanding features of the basic research is that it is not intended to be used for a specific field of industry. Even if it does not lead to innovation by itself, the decision for the further R&D and its ultimate success depend on basic research. There are three fundamental benefits of the basic research: acquisition of new knowledge, social benefits and economic gains.

According to a study carried out by Toole in which he analyses the possible impact of the basic research on innovation through empirical evidence in pharmaceutical industry; 1% expansion in the amount of public basic research causes a 1.8% increase in the number of new compounds[21].

However; contrary to applied research, basic research activities are predominantly conducted by governmental entities or universities because of the reason that the information attained will be open to public and can be used by any other firms rather than particularly by the firm that develops it. Thus, even if it provides economic benefits, the private firms think that the benefits will not worth for the cost.

[20] Dirk Czarnitzki, Susanne Thorwarth, "Productivity Effects of Basic Research in Low-Tech and High-Tech Industries", **Research Policy: Policy and Management Studies of Science, Technology and Innovation**, Vol.XLI, Amsterdam, 2012, pp. 1555-1564.

[21] Andrew A. Toole, "The Impact of Public Basic Research on Industrial Innovation: Evidence from the Pharmaceutical Industry", **ZEW- Centre for European Economic Research Discussion Paper**, No.11-063, w. Place, December 2011, pp. 1-12.

As we mentioned above; the basic research is not done for a specific area of work, so that it is not possible to dissociate basic research only for pharmaceutical R&D. Unfortunately, even the data regarding the overall basic research is limited. However; just to give a perspective, the total intramural spending on basic research for R&D was 59% of its GDP in France in 2009. In the same year; this figure was 21% and 55% in UK and US respectively. The country which spends the most on basic research is Israel (61% - defence excluded) as parallel to its overall R&D expenditures that we touched upon before.[22]

As it is clear from what is expressed above, the fertility of the research is absolutely an essential parameter for the firms. Nonetheless, the abundance of fertility is also something that makes the firms to look at R&D negatively. Thus, another important point for the motivation of the firm to realize an R&D investment is the degree of expected appropriability of research results. For instance; if the field of a new innovation is extremely fertile, which means that one firm's discovery may lead to an immediate discovery of a higher technology by another firm, the firm will not have an incentive to invest in R&D since its own investment presumably will lead to discovery of even better products by other firms which will offset the original firm's profits.

2.2. R&D Investment Processes in Pharmaceutical Industry

As the behaviour of a new substance in the human body is highly uncertain, there are many questions about the safety, efficacy and quality of it to be answered by a series of various tests within the R&D context. These numerous studies of the R&D project intent to verify the benefit risk ratio of the candidate medicine.

[22] OECD, **Main Science and Technology Indicators,** Vol.MMXI/II, w. Place, OECD Publishing, 2012, p. 29, (Online) http://www.keepeek.com/Digital-Asset-Management/oecd/science-and-technology/main-science-and-technology-indicators/volume-2011/issue-2_msti-v2011-2-en-fr#page11, 18 March 2014.

R&D process in pharmaceutical industry is a tedious and lengthy operation. A new medicine takes almost 10 years until it is ready to enter the market which already consumes half of the patent protection period. The life of a medicine starts with the early discovery period which can be undertaken by a private company, a government facility or a research university. As it is the basic research phase, most of the early discovery attempts do not end up with successful medicine innovations.

Once a discovery is found qualified for further level of research, the company applies for a patent. If the early discovery is done by a research facility, the facility sells the license of it to a private company before the patent application. Only after the application of the patent, the candidate medicine can start to be tested. The testing period starts with pre-clinical development which includes acute toxicity, pharmacology and chronic toxicity, and follows as the way it is shown in Figure 10. Acute toxicity investigates the adverse effect of the core substance of the candidate medicine that results from a single or multiple exposures in a short span of time.

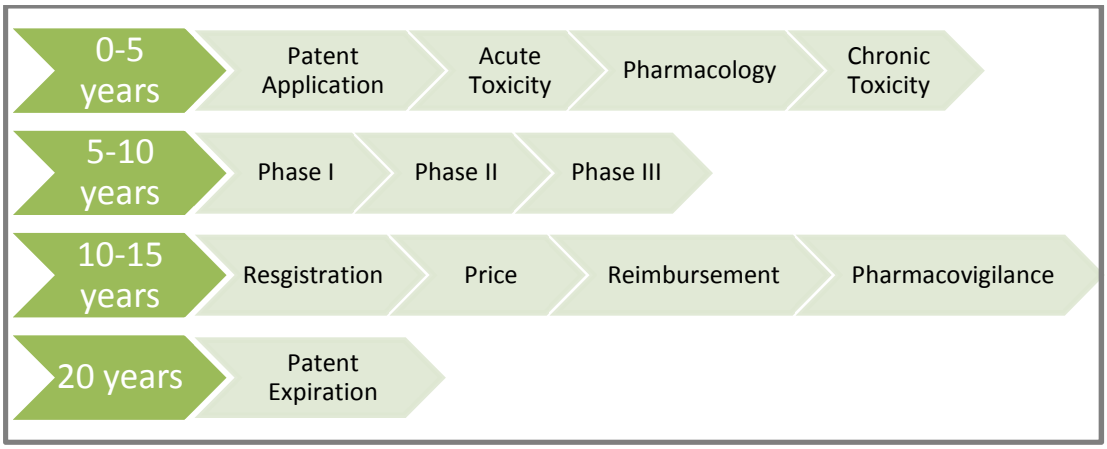

Figure 10. Phases of R&D in Pharmaceuticals
Source: EFPIA, "The Pharmaceutical Industry in Figures", **Key Data 2013**, Belgium, 2013, p. 6.

Pharmacology testing, which starts almost in the third year of the pre- clinical development period, aims to identify the concealed structure of reaction of the substance. In the following year, the chronic toxicity begins in which the adverse effects of the substance are tested on the condition of being exposed repeatedly or continuously. This stage differs from the acute toxicity as the effects of the substance are analysed for months or years.

If the candidate medicine manages complete these tests successfully, the clinical trials that can be defined as biomedical or behavioural research studies, are launched. Unlike the previous stages in which the data comes mostly from animal testing or in vitro studies, clinical trials are conducted on human subjects. In this context, researchers enrol volunteers into different pilot studies and carry on experiments with larger and larger groups to obtain comparable results. The number of subjects is increasing from one phase to the other as positive safety and efficacy data are collected.

Phase I trials are conducted within a group which includes 20-80 subjects who are generally healthy volunteers in order to review the candidate medicine's safety, figure out the safe dosage range, and diagnose the possible adverse effects if there is any. Single-dose and short-term repeated dose studies along with dose escalation experiments are realized in this phase. In addition to the safety studies carried out in phase I, the researchers are launching more comprehensive experiments usually with 100-300 humans to further evaluate the medicine's fundamental efficacy and adverse effects in phase II. The last stage of the R&D process is phase III studies which are large-scale clinical trials on wide range of patient population. Apart from the fact that the experiments in this phase are conducted within 1000-3000 people, the aim of it is fairly the same with the previous ones. With this last phase, the R&D process comes to an end after 10 years of experiments and ready to be registered as a marketable product. Registration is done only after the approval of the ministries of health or similar authorities like FDA in US or European Medicines Evaluation Agency (EMEA) in Europe. The responsible authority has to review all the data and either approve it, send it back for more tests or reject it directly. "On average, only one to two of every 10.000 substances synthesised in laboratories will successfully pass all stages of development required to become a marketable medicine."[23] Moreover, even if the regular process has an estimate of 10 years to finish, this process usually prolong to 12-13 years with the retesting requests of the authorities.

[23]EFPIA, **op. cit**., p. 6.

Most of these phases have considerable cost burdens on the firms however clinical trials are the ones which have the highest rank in terms of cost. These three trial stages (Phase I, Phase II, and Phase III) form 56.9% of the overall R&D investment. Obviously; the reason that the clinical trials have the highest share in the cost is the fact that they have the highest risk as they are carried on human beings. Among these, Phase III studies that are the most comprehensive trials so that, it constitutes the 35.7% of the total investment as expected. Pre-human/Pre-clinical phase comes the second in the list regarding its 21.5% share in the whole cost of investment. It is followed by pharmacovigilance (9.8%) and approval (8.3%) respectively.[24]

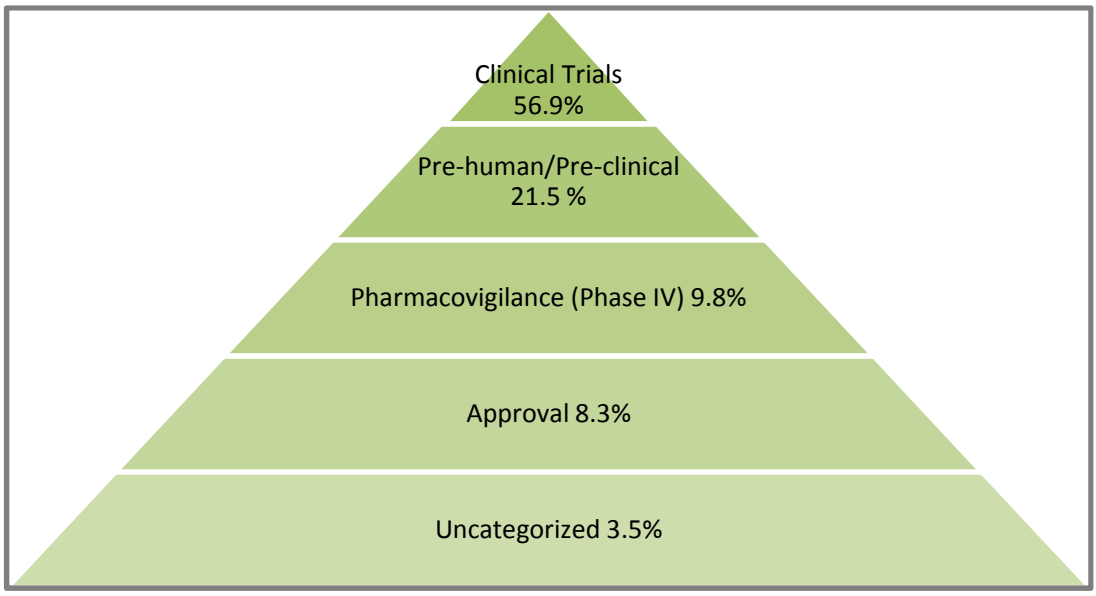

Figure 11. Allocation of R&D Investment in Pharmaceutical Industry
Source: EFPIA, "The Pharmaceutical Industry in Figures", **Key Data 2013**, Belgium, 2013, p. 8.

Before in this paper, we specified some of the distinctive features of R&D investment that differs from the economic or financial investment. As an addition to those characteristics we spoke of, another critical difference is that more than 50% of the R&D expenditures that are indicated above are spent on the wages of highly educated scientists and engineers, especially in pharmaceutical industry. In previous sections, we briefly mentioned the importance of employment for pharmaceutical industry. One of the reasons which make it so essential is hidden within this cost

[24] EFPIA, **op. cit**., p. 8.

framework because part of the resource base of the firm disappears if one of the employees working on the project leaves or is fired during the long trial processes by taking away the learning that they acquired from the project up until that time with them. These kinds of situations make additional R&D costs which are already high enough.[25]

Through this chapter; we explained what R&D investment is and in what way it differs from the other kinds of investment. We demonstrated the options for financing R&D and the streams that are effective in both R&D decision and the decision for allocation of the sources of R&D. Finally, we displayed the process of R&D investment in pharmaceutical industry step by step. As doing all these, we stressed on the cost originated from the investment and the equilibrium point where the firms would be willing to start or continue an R&D investment.

It is expectable that the pharmaceutical firms which undergo R&D investment and are exposed to these costs have a tendency to charge higher price for the medicine that they developed during the period when they are the sole provider of it. Due to this tendency, the governmental entities as the authority holders, often apply some rules in order to prevent the prices from getting so high to keep the pharmaceutical expenditures as low as they can while not totally melt away the profit of the developer company.

In the next chapter, we will be introducing these rules which will be mentioned as "regulations" from now on, and examining the cons and pros of them in detail. We will be also giving examples of some country cases.

[25] H. Bronwyn Hall, Josh Lerner, "The Financing of R&D and Innovation", **NBER Working Paper**, No. 8773, w. Place, August 2009, p. 6.

3. REMARKS ON REGULATION IN PHARMACEUTICAL MARKETS

Spending on pharmaceuticals is in a constantly increasing trend in almost all countries through the years with the exception of some stabilization during the last couple of years most probably due to the financial distress affecting many countries. (Table 1.1.) There might be numerous reasons that can be count for this increase. However, there is no doubt that the top and most important one is the supply and demand structure of the pharmaceutical market.

As opposed to the other regular markets, decision on purchasing a specific medicine or even purchasing a medicine is not at the consumers' sole discretion. At the same time, the source that the consumers take the information regarding the medicine do not come from the producer or seller of it as it is usually the case for the other products. This is mostly valid for the RX medicine but they are also true for some OTC medicines apart from the simple ones that are known prevalently by the consumers and can be found at almost everywhere in most of the countries like painkillers and common cold medicines which are not too strong. For these types of painkillers and common cold medicines, consumers usually apply to the pharmacists with a brand name on their mind and as long as the pharmacists do not suggest any other brands, they are purchasing it. As the consumers are the sole decision maker on these, it is understandable that the regular demand dynamics like price and expected utility will work for these medicines. Consumers will try to maximize their utility functions under certain budget constraints within a full information environment.

There are two possibilities for the other kinds of OTC medicines. The consumers will buy the medicine either with the advice of a physician or by applying to the consultancy of a pharmacist. In none of these cases, the consumers have 100% power of decision but they can choose between medicines suggested by the pharmacists in the case that they take the second way which gives them a restricted power of decision.

On the other hand; the consumers have to follow the lead of the physicians for RX medicines in almost all of the countries apart from the ones which allow direct to consumer (DTC) marketing of these kinds of medicines and give initiative to the pharmacists to change the prescribed brand with another one by regulation that we will explain later on. Physicians are supposed to play an intercessor role between the consumers and the pharmaceutical firms by taking the information from the producer and transmitting it to the consumer. Notwithstanding, physicians are keeping the information that they take from the producers for themselves and prescribing the medicine to the consumer without explaining him/her every option that he/she may choose. The causes of this transmitting mechanism not to work is a subject of another study but it might be because of the time restrictions of the physicians, the education level of consumers or just the traditions of the country in question.

Considering that the physicians are exposed to promotion about the medicines which have the similar efficacy and level of risk in the same therapeutic area by many different companies, subjective opinions of the physicians about the medicine itself or the company which produces it plays an important role for prescription decision. Certainly, the various marketing activities of the pharmaceutical firms have substantial influence on the personal decisions of the physicians. Just for the record, due to the misuse of these activities, there are widespread restrictions on the promotions of the medicines to the physicians in some of the countries.

Apart from the lack of decision power, as the social state principle requires, there is a general health insurance system provided by nearly each country in the world to its citizens, even if the scope of it changes from one country to the other or even from one state to another state within the same country. In addition to those general insurances, there are some private insurance companies working similarly, as well. Due to the coverage of these insurance systems, consumers do not have to pay for the medicines that they purchase or at least pay only a small proportion of the cost for some specific medicines which, makes them less price sensitive. Another important point worth to be mentioned here is the fact that the physicians are not always aware of the prices of the medicines that they prescribe, as well.

For the reasons that the consumers do not have the power to choose between the medicines and do not have to bear the costs of them as mentioned above, the demand in pharmaceutical market is highly inelastic, which makes the consumers reckless about the prices and the alternative medicines, and their demand curves vertical.

$$e^{d} = \frac{dQ^{\alpha}}{dP^{\beta}} x \frac{P^{\beta}}{Q^{\alpha}} = 0 \qquad (6)$$

Where,

P^{β}= Price of the drug β

Q^{α}= Quantity of the drug α

e^{d}= Cross price elasticity of demand

As it is understood from the general cross price elasticity of demand equation given above (6), even if there is a change in the price of drug β, the consumers will not notice the change, so that the change in price will be equal to "0" in their perception. Thus, their value for elasticity will be equal to 0, as well.

Furthermore; the patent rights acquired by the pharmaceutical firms provide them a kind of monopoly power in the market so that, the price can-not be determined by the adjustments between supply and demand until the two meet at an equilibrium point as it usually is in the competitive markets. Therefore; the pharmaceutical firms are free to charge whatever price that they want without any intervention. In the table below; prices of some medicines in Europe and US are shown. It can clearly be seen that the prices are much higher in US where there is no regulation.

Table 3.1. Prescription Medicine Prices in US and Europe *(US Dollars)*

For a 30-day Supply		
Drug	**U.S. Price**	**Europe Price**
Allegra 120	$69.99	$20.88
Atarax	$28.62	$4.20
Biaxin 250	$113.25	$61.94
Claritin	$63.06	$16.05
Coumadin	$37.74	$8.22
Glucophage	$30.12	$4.11
Lipitor	$52.86	$41.25
Premarin	$17.10	$9.90
Prozac	$71.94	$44.10
Zestril 5	$25.92	$5.52
Zithromax 500	$486.00	$176.19
Zyrtec	$50.10	$17.73

Source: Congress of USA, **Congressional Record - House**, June 2001, p. H3495.

The lack of regulation does not only make U.S. prices different from the prices of the other countries but also might cause a bigger gap between prices of medicines within the same country. Regarding this argument, when we dig into the prices in both U.S. and Europe, we see that the two data groups given above have different statistical distribution. As it can easily be acquired from the distribution charts given below, the prices in Europe are closer to each other.

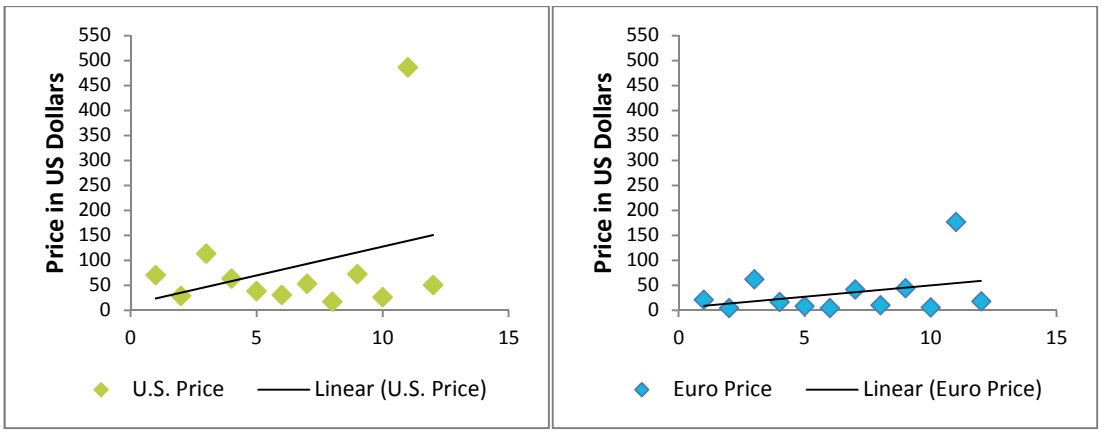

Figure 12. Distribution of Medicine Prices in U.S. & Europe

Notwithstanding that both samples have a right skewed, leptokurtic distribution as is also understood from the descriptive statistics; the standard deviation of U.S. prices

from mean is higher than that of Europe prices so that there is a higher rate of the fluctuation in U.S. price list compared to the European one.

The combination of supply side market power and the price inelasticity of the consumers repulses the governments, which are the main purchasers of the pharmaceutical products due to the extensive insurances they provide, to convey a variety of regulations primarily in order to control the overall pharmaceutical expenditures. There are several different types of regulations applied depending on the mechanisms that they work through. Some of them can be classified in three categories as follows: Price and Reimbursement Control, Restriction on Promotion, Prescription Barriers.

From the table below, we can see which country applies which type of regulations:

Table 3.2. Types of Regulations in Some European Countries, Canada and Australia

Country	Direct Price Control	Control Reimbursement Prices	Reference Pricing	Profit Controls	Volume Controls	Budget for Physicians	Promotion Restrictions
Australia			**X**		**X**		X
Belgium	**X**	**X**	**X**				**X**
Canada			**X**				**X**
France	**X**	**X**	**X**		**X**	**X**	**X**
Germany		**X**	**X**	**X**		**X**	**X**
Italy	**X**	**X**	**X**	**X**			**X**
Japan		**X**	**X**	**X**			**X**
Spain	**X**	**X**	**X**	**X**			**X**
Sweden		**X**	**X**				**X**
Switzerland		**X**					**X**
UK				**X**		**X**	**X**

Sources: ***John A. Vernon, "Price Regulation, Capital Market Imperfections, and Strategic R&D Investment Behaviour in the Pharmaceutical Industry: Consequences for Innovation", (Unpublished Ph.D. Thesis) University of Pennsylvania, Managerial Science and Applied Economics, US, 2003.
**Chris Gladin, "Pharmaceutical Pricing and Research and Development Investment: A Secondary Analysis That Investigates Product and Patent Output", (Unpublished Ph.D. Thesis) Capella University, Minneapolis, December 2005.
***International Trade Administration, **Pharmaceutical Price Controls in OECD Countries**, Washington, December 2004.

In the preceding sections of this chapter, we will be focusing on each and every of these regulations in detail and we will try to demonstrate the way that they work in the countries they are applied.

3.1. Direct and Indirect Price and Reimbursement Control

There is no general health insurance provided by the government, which covers all the citizens in the United States. "A study conducted by the Massachusetts Institute of Technology Industrial Performance Center found that, while European governments of U.K., France and Germany pay between 60 to 90% of their respective national drug pills, the U.S. government pays for only about 40%.[1] This is because there are only Medicare and Medicaid insurance plans which are funded by the government itself in US and these just cover the senior and low-income citizens respectively. Every other people have to work with the companies which offer private insurances. The scope of these insurance plans differs from one to the other.

Most probably; lack of a general insurance contributes making United States the only country which does not apply any regulations on prices in pharmaceutical industry directly or indirectly among the countries that we are aiming to work on in this study as we mentioned before. US government is totally focusing on establishing a setting that would boost the tendency of the firms to invest on R&D to generate a consistent flow of new inventive medicines. Thus, it allows the prices to be determined in the free market conditions. By doing so, the US government aspires to secure that consumers would have the advantage of not only accessing the new technologies but also the competition that the deeply innovative environment generates. No doubt that the strong generic market of US also is expected to put further pressure on the prices.

[1] Chris Gladin, "Pharmaceutical Pricing and Research and Development Investment: A Secondary Analysis That Investigates Product and Patent Output", (Unpublished Ph.D. Thesis) Capella University, Minneapolis, December 2005, p. 8.

On the other hand; other countries in question rely heavily on the government regulations to set the prices instead of spontaneous competition and decrease the pharmaceutical spending. There are a variety of regulatory systems being applied by these countries mainly to limit spending on pharmaceuticals by using different ways of controlling either from the demand side or from the supply side. One of the most direct of these regulations on the supply side is to fix the sale price of one specific medicine and declare sales at any other price as illicit. The other method imposed in a similar manner is to set a reimbursement price at a considerably lower level for a new medicine which causes the consumers to bear the remaining amount of the cost if the market price of the medicine is above the fixed price by government. Even if it is rare, there are also some countries that apply these reimbursement quotas even on the existing medicines in certain circumstances, but what we will focus on this study is mainly the ones for the medicines which are entering the market for the first time.

Apart from these methods, the authorities may try to cut prices through volume limitations and profit controls in which the firms that put a new medicine on the market can charge any price until a quota is reached. When the quota of profit or sales volume is reached, the firms are expected to decrease the prices or provide compensation by paying cash to the government.

3.1.1. Direct Fix Price Controls

Direct fix price controls, namely the price caps, which can be defined as setting the possible highest price for each type of medicine can be applied either at the manufacturer level or the seller level. It aims to secure the most reasonable price for the pharmaceuticals. To be effective, the price cap needs to be set lower than the profit maximising price which would be charged by the firms in case of monopoly.[2] Even if these controls are mostly valid for the medicines which are in the context of

[2] Kurt R. Brekke, Astrid L. Grasdal, Tor Helge Holmas, "Regulation and Pricing of Pharmaceuticals: Reference Pricing or Price Cap Regulation?", **European Economic Review**, Vol.LIII, w.Place, 2009, p. 171.

reimbursement, there are still some countries which apply them to all kinds of medicines in the market.

Several different approaches are used to set the prices such as negotiations, statutory pricing or obligatory price notifications to pharmacists associations or medicines agencies. It is important to notify that this kind of pricing is mostly used only for the medicines which are within the reimbursable medicines. For example; Belgium is one of the countries which use statutory price control in which the price is secured through a law when it is first launched if the medicine is reimbursed by the general insurance. France and Italy prefer to apply to price negotiations method first by taking into account direct and indirect costs, prices of comparable products and subjective factors such as novelty. If there is no common decision reached through the negotiations with manufacturers, they set a price via statutory pricing method. Germany, on the other hand, does not apply any direct fix price controls. Instead, it lets the price to be determined in the market freely.[3]

"Many countries have additionally applied cuts and freezes to fixed prices, usually resulting in a one-off and very short-lived decrease in pharmaceutical expenditures."[4] We have mentioned before in this paper that Germany has frozen the prices until 2013 because of the financial crisis. Canada, in which there is a highest allowable price determined for the medicines by Canada's Patented Medicines Prices Review Board and any higher prices than that are prohibited normally, is another country which applies to the price freeze technique from time to time in order to prevent the firms to charge price raises for inflation compensation.[5]

[3] Industrial Pharmacists Commission of Istanbul Chamber of Pharmacists, **Avrupa Ülkelerinde İlaç Fiyatlandırma Politikaları**, w. Place, July 2010, p. 3.
[4] Elias Mossialos, Tom Walley, Monique Mrazek, "Regulating Pharmaceuticals in Europe: An Overview", **Regulating Pharmaceuticals in Europe: Striving for Efficiency, Equity, and Quality**, Ed. By Elias Mossialos, Moniques Mrazek, Tom Walley, England, Open University Press, 2004, p. 10.
[5] U.S. Department of Commerce, **Pharmaceutical Price Controls in OECD Countries: Implications for U.S. Consumers, Pricing, Research and Development, and Innovation**, Washington, December 2004, p. 5.

3.1.2. Reference Pricing

One of these price control mechanisms is defined as “reference pricing”. It is a strategy used to determine sales prices according to the international prices or relative prices within the same therapeutic area. Compared to the direct price control, this method is considered to be less effective. While price caps aim to restrict the pharmaceutical firms’ freedom to charge higher prices to gain profit from market power, reference pricing intents to decrease the prices through its effect on reimbursement.

In the context of reference pricing method; the authorities fix a maximum reimbursement level for different medicine clusters. The price determined signifies the highest price that the reimbursing entity is willing to pay for that specific medicine. This reference price is usually based on relatively minimum or middle priced medicines. If the retail price of the medicine is higher than that price, the remaining amount of payment has to be borne by the consumers. It works in the following way:

If $P_\chi < P_r \longrightarrow P_\gamma = cP_\chi$; If $P_\chi > P_r \longrightarrow P_\gamma = P_\chi - P_r + cP_\chi$

If there is no co-payment applied in the market $\longrightarrow P_\gamma = 0$ (7)

Where,

P_χ = Retail price of the medicine

P_r = Reference price

P_γ = The amount that will be paid by the consumer

C = Co-payment rate

Through this, it is aimed to increase demand sensitivity of consumers to prices and promote competition between pharmaceutical firms.[6] If the price of the medicine is higher than the reference price decided by the authority, the consumer will have to pay for the remaining amount of the price out of his/her own pocket. If there is no co-payment applied, this amount would only be equal to the difference between the actual price and reference price. However, if there is also a co-payment rate that every consumer has to pay to get medicine, the difference in price will be added upon it, which will increase the burden on consumers. It is expected that with this double charge, the consumers' price elasticity of demand would be more elastic, which will eventually force the firms to decrease their prices.

Germany is seen as a pioneer in this type of regulatory system. It introduced reference pricing of prescription medicines in 1989. Germany is followed by Netherlands (1991), Denmark & Sweden (1993), Spain (2000), and Belgium & Italy (2001). This system is also applied in Australia and some states of Canada.[7]

This regulation is actualised through two different ways that are named as "therapeutic reference pricing" and "external (international) reference pricing". In the forthcoming subsections, we will be examining these reference pricing methods in further detail.

3.1.2.1. Therapeutic Reference Pricing

In therapeutic reference pricing system, the medicines are classified into clusters according to their therapeutic effects. These clusters can be composed by pursuing several definitions which make each of them different in a sense. These definitions can be summarized as follows: Medicines with the same active chemical ingredients, medicines with chemically related active ingredients, and medicines that may be

[6] Marisa Miraldo, "Reference Pricing and Firms' Pricing Strategies", **Journal of Health Economics**, Vol.XXVIII, 2009, p. 177.
[7] Kurt R. Brekke, Ingrid Königbauer, Odd Rune Straume, "Reference Pricing of Pharmaceuticals", **Journal of Health Economics**, Vol.XXVI, 2007, p. 614.

neither chemically identical nor pharmacologically equivalent but have comparable therapeutic effects.[8]

First of the definitions mentioned above is usually named as "generic reference pricing" by many others. Even if it is also a kind of therapeutic reference pricing, it differs from the others due to the fact that it only affects generics and the off-patent medicines rather than the others which may be used on on-patent medicines as well. This type of reference pricing is used in Germany for level I medicines which are defined as pharmaceuticals with identical active ingredients.

Brekke et al. (2007) analyses the effects of each of these different pricing systems on price and finds out that the wider the cluster comprises, the fiercer the effect of it will be on competition. Their work supports that the prices of the medicines are highest under no reference pricing system. The study also suggests that the effect of generic reference pricing on on-patent medicines are not insignificant because if the competition on the generic prices are so fierce, it may also force the patent-holding firms to lower the price of its medicine in order to refrain from market share losses.[9]

Therapeutic reference pricing is seen as controversial by many critics. According to therapeutic reference pricing; within the same therapeutic cluster, the first medicines are believed to be innovative while the others which have similar effects are considered to be "me too" medicines. However, this is not always the case because some of the subsequent medicines might come up with cumulative new ideas due to the knowledge put forward by the first one. Thus, gathering all similar medicines in the same cluster may discourage the firms to invest on improving the first medicines' knowledge.

There are some countries which manage to solve this problem in a way, though. For example; in Japan the price of a new medicine is determined by comparing the prices of the similar medicines currently in the market, as well. However; medicines are also evaluated regarding their safety and effectiveness, so that the medicines which are more effective and safe are priced higher. On the other hand; if there is no current

[8] Kurt R. Brekke, Ingrid Könibauer, Odd Rune Straume, **op. cit.**
[9] **Ibid.**, p. 615.

similar medicine in the market to be compared with the new one, the price is determined by calculating the manufacturing cost, even if it is not reflecting the true cost of the medicine, and the prices of the same medicine in different countries namely by international reference pricing which we will refer in the forthcoming section. [10]

Another important controversy about the therapeutic reference pricing is the possibility of its pushing the patients to use less suitable medicines for themselves. Just to give a specific example; let's think about the third cluster in which there are medicines that have similar therapeutic implications with different active ingredients. For instance; there are so many different osteoporosis medicines which aim to slow down the bone fraction process by strengthening bones which means that they have the same therapeutic effects. However; they differ in terms of active ingredients such as Bisphosphonates (alendronate sodium, ibandronate sodium, risedronate sodium, zolendronic acid), Raloxifene, Teriparatide Parathyroid Hormone or Estrogen treatments. In this case, it becomes important that which patient gives the best reaction to which active ingredient. Therefore, replacing the medicine with a counterpart within the same cluster may cause to use unsuitable medicines if done inappropriately.

3.1.2.2. External Reference Pricing

External reference pricing, which is also referred as international reference pricing, works in a similar way as the other reference pricing systems work however pricing is done through indexing prices to the prices in the other countries charged for the same medicine in this one. It can be applied either to all the medicines or only to the medicines within the reimbursement list, RX medicines or breakthrough medicines. However, the most common usage is for the reimbursable medicines, which can be

[10] Mark Chang, **Monte Carlo Simulation for the Pharmaceutical Industry - Concepts, Algorithms, and Case Studies**, USA, CRC Press, 2011, p. 139.

interpreted by the expenditure reducing aims of the authorities in an economic perspective.

The selection of the countries to be taken as reference mostly depends on the benchmark of owing an identical purchasing power. Notwithstanding, there are also some countries which take the country of origin of the medicine in question as the reference price country as well. The number of countries that are taken as reference changes from one country to the other. While some countries take only 1 country as reference, some may take more than 30 countries. Thus, this policy leads to a significant interdependence of prices between countries.[11]

The majority of EU countries use external reference pricing as the main systematic criterion when setting the price of a new drug. The methodology used when applying this system changes from one country to the other. Some countries use external reference prices as supporting data. For instance; Belgium, Italy, Spain, Australia and Germany use this system as a supportive criterion. On the other hand, some countries like France, Switzerland and Canada are taking the data as the key source for their decision. As a different method, Japan is using the external reference pricing system in order to adjust its prices upward or downward to catch the ones in France, Germany, UK and US. [12]

Furthermore; the calculation of the reference price may also change across the countries. Some countries such as Belgium and Switzerland take the average of the prices that belong to the reference countries. Spain, on the other hand, takes the lowest price among the chosen reference countries whereas France applies a similar price to the ones in its reference country basket. Another way of calculation is to take the average of 3 or 4 lowest prices within the reference countries.[13]

Even if this type of reference pricing is commonly used within the EU and the non-EU countries which take EU as reference as a tool to reduce the prices for in-patent

[11] Nicolas Houy, Izabela Jelovac, "Drug Launch Timing and International Reference Pricing", **GATE Working Papers**, WP1301, w. Place, January 2013, p. 2.
[12] Mondher Toumi et al., **External Reference Pricing of Medical Products: Simulation-Based Considerations for Cross-country Coordination**, w. Place, December 2013.
[13] **Ibid.**

pharmaceuticals, the literature related to its impact is very limited.[14] One of those scarce studies is conducted by Stargardt and Schreyogg which proves the interdependence of the price levels across the countries. According to their study; 1€ reduction in German drug prices would lead to a reduction of 0.15€ to 0.36€ decrease in the EU-15 countries which use external reference pricing system because of the interdependence of the prices. [15]

3.1.3. Volume Limitations and Profit Controls

Limitations on volume and profit are some other ways of indirect regulations applied on the supply side of the pharmaceutical markets. The agreements on price-volume balance are signed after negotiations between regulatory authorities and the agents in the industry. Usually, the agreed volume is based on forecasted volume of sales. If a company exceeds this pre-determined volume, they either have to reduce their price or pay some amount of the revenue gained from the sales of that medicine back to the reimbursing institute. This works in a similar way in terms of profit control. If the proportion of the profit exceeds the agreed percentage, the pharmaceutical firm in question has to compensate this for the insurance provider.

As an instance; in UK which is the primary user of profit control method, the rate of profit that a company can earn is negotiated between the Association of the British Pharmaceutical Industry and the Department of Health under the Pharmaceutical Price Regulation Scheme (PPRS).[16] According to the result of this negotiation;

[14] Mondher Toumi et al., **op. cit.**
[15] Tom Stargardt, Jonas Schreyögg, "Impact of Cross-Reference Pricing on Pharmaceutical Prices", **Applied Health Economics and Health Policy**, Vol.V, Issue 4, December 2006, pp. 235-247.
[16] Aaserud M. et al, "Pharmaceutical Policies: Effects of Reference Pricing, Other Pricing, and Purchasing Policies" (review), **The Cochrance Collaboration**, w. Place, John Wiley & Sons. Ltd., 2006, p. 4.

pharmaceutical firms are not allowed to gain more than 29% since 1998. Spain, on the other hand, restricts the profit growth rates to 7%.[17]

Until this point, we have discussed both the direct and indirect controls on the price of the marketable medicines. However; as it is touched upon before, there are also some other regulation types imposed on the pharmaceutical firms through approval and prescription processes. The remaining part of this chapter is dedicated to bring the audience a brief knowledge about these kinds of regulations.

3.2. Delays in Marketing and Price Approvals

All new medicines that are getting in the market have to get an approval from that country's authority managing the medicines which take place in the market. Within the context of this mandatory approval, the pharmaceutical companies have to provide proof of safety and efficacy of their new product. Besides, some countries also request pharmaceutical firms to obtain approvals for its price. Sometimes, obtaining these approvals may prolong the preparation period for the market.

Most of the time the approval process of the new medicines has no standardization and it is unnecessarily complex and non-transparent. As it contains various stages of approval and multiple government and regulatory bodies, bureaucratic delays tend to be common.[18] Being uttered before in the R&D processes in pharmaceutical industry section of chapter 2, the standard duration for a new medicine to become a marketable product is already time consuming which takes away about 10 years of the patent protection duration. This burdensome system might be combined with deliberate delays against the approval in some countries with regulations which may take up to 5 years more than the usual process.

[17] Neeraj Sood et al., "The Effect of Regulation on Pharmaceutical Revenues: Experience in Nineteen Countries", **Health Aff (Millwood)**, Vol.XXVIII (1), 2009, pp. 125-137.
[18] U.S. Department of Commerce, **op. cit.**, p. 6.

Among the countries that we are studying; France and Belgium, two of the countries that apply a direct fix price control have the longest average delay between medicine approval and marketing. (About 9 months)[19] Expecting that a new medicine would provide a better technology so that the demand for it would be higher at the time of its market launch in ceteris paribus, the loss of revenue of the firms in 9 months will be a considerable discommodity.

The regulations applied by the authorities do not end with the market launch of the new product. Countries carry on implementing adjustments on the medicines after the market launch as well by restricting the firms' marketing activities. In the next section, these marketing restrictions will be reviewed briefly.

3.3. Limitations on Promotion

There is also another type of regulation which is not directly aiming to decrease the level of price in the market but to restrict the freedom of the firms to promote their products in order to decrease the amount of spending by consumers on the innovative medicines. This regulatory restriction of the promotion is a burning question in the industry, as some are defending that it is good to restrict promotions which will lead to unnecessary pharmaceutical expenditures and cause misusing of medicines while the others defend that it is not good to restrict promotions because promotion increases awareness in public regarding the illnesses and keep the physicians up-to-date about the new treatments.

The restriction on promotion may be applied to all marketable medicines, both OTC and RX, however most of the time it is limited only to patented drugs. The scope of

[19] Patricial M. Danzon, Y.Richard Wang, Liang Wang, "The Impact of Price Regulation on the Launch Delay of New Drugs – Evidence from Twenty-Five Major Markets in the 1990s", **Health Economics**, Vol.XIV, John Wiley & Sons Ltd., 2005, p. 270.

the restrictions can only be on direct-to-consumer advertising (DTCA), only on direct-to-physician promotion (DTPP) or both.[20]

DTCA, promotion of medicines directly to the consumers through all sort of communication, is currently allowed only in United States and New Zealand in the world in terms of RX medicines while DTPP that contains activities such as printed advertisements in category journals, detailing to physicians, sampling, organizing promotional meetings with key opinion leaders and gifting is carried out legally in almost all countries under certain restrictions.

DTCA is thought to be increasing awareness of the consumers about the new medicines in the market which would result in an incremental level of substitution to these newer medicines that would eventually increase spending on medicines, as the prices of new medicines are considered to be more expensive compared to the previous treatments.[21] It is rational to deduce that this can be the primary reason why DTCA is banned in the countries where the governments are the main purchasers so that they want to minimize pharmaceutical spending.

Even if allowed, DTPP is conducted by the pharmaceutical firms only under strict regulations in order to prevent physicians to over prescribe a specific medicine and to prescribe only the new medicines by standing up for themselves.

Granting that every country has its own guide to clearly manifest the rules of medicine promotions, the scope of these regulations is similar across all the countries. For instance; UK has a guide named Blue Book just to explain the regulations over pharmaceutical advertising in detail. According to these regulations; promotional aids such as pens, notepads, mugs etc. that are usually used as a reminder by the pharmaceutical marketing teams should not be valued more than £6 and nothing but the name of the brand should be written on them. Also it is stated in the same guideline that the medical sales representatives must be supplied all the necessary information about the medicine that they are promoting and have to provide the

[20] Dhaval Dave, Henry Saffer, "Impact of Direct-to-Consumer Advertising on Pharmaceutical Prices and Demand", **Southern Economic Journal**, Vol.LXXIX, No.1, 2012, pp. 97-126.
[21] **Ibid.**

summary of the product characteristics as a written or electronic document to the physician. British regulations also prohibit gifts or any kind of offers that might encourage physicians to prescribe that promoted medicine unless it is again less than £6 (it can be up to £130 if and only if it is given as a prize of a competition) and relevant to the practice of medicine.[22]

As another example; Germany has also similar regulations on promoting medicines which are collected in a guideline called "Gesetz über die Werbung auf dem Gebiete des Heilwesens". As stated in this document; sales representatives can give small numbers of samples only upon written request by the physicians. These samples cannot exceed 2 packages per year. Moreover, neither the physicians are allowed to accept gifts nor the sales representatives are allowed to offer except for some promotions that will provide professional expertise to the physician. Hospitality is only allowed if it is "work related" and up to €50-60 in value.[23]

Identical policies such as restricting the time schedules that the sales representatives can make detailing to physicians or recruiting sales representatives who have a certain level of education and etc. are applied in some other countries.

In addition to these regulations imposed directly on the firms' marketing and promotion capabilities, there are some regulations applied on the demand side on which we will be focusing in the next chapter.

3.4. Prescription Barriers

Most of the time, only supply side regulations are not enough to minimize the spending on pharmaceuticals. As a consequence; countries often tend to combine the supply side measures with demand side measures in order to create an effective

[22] Medicines and Healthcare Products Regulatory Agency, **Advertising and Promotion of Medicines in the UK**, Third Edition, London, August 2012, p. 34.
[23] Peter Dieners, Marc Oeben, **Germany Chapter – Pharmaceutical Advertising 2013**, 10th Edition, London, Global Legal Group, 2013.

regulation system. The demand side regulations consist of restrictive formularies and compulsory substitution of generics, and prescribing guidelines and budgets applied for physicians which all aim to decrease the number of prescriptions for higher priced medicines.

3.4.1. Formula Restriction and Generic Substitution

There can be two types of substitution schemes applicable, one towards physicians and one towards pharmacists. From now on, we will refer the one directed to physicians as formula restriction. As the other regulations, both aim at decreasing the amount spent on pharmaceuticals via encouraging the prescription/dispensing of generics instead of branded equivalents through substitution.

In some countries pharmacists are obliged to change the prescribed branded medicine with one of the generic versions of it, which has the similar therapeutic effects keeping in mind that it is only under the condition of no notification is written by the doctor. In some countries, on the other hand, the pharmacists are not obliged to substitute generics but they can gain financial incentives if they do so.

On the physicians' side, the authorities can create a variety of formulas which suggest the medicines (generics most of the time) that can be prescribed in certain therapeutic conditions. Some countries keep it mandatory for the physicians to prescribe exactly those medicines while some others let the choice to the physicians but make restrictions on the reimbursement of those medicines which are not in the formula list.

As it is stated; generic substitution both in pharmacist and physician side can either be suggestive or mandatory. Germany is one of the countries that give the right to substitute generics to pharmacists. Nevertheless, the rate of substitution is not high due to the fact that it is not mandatory and there is no significant incentive for pharmacists. Moreover, most of the pharmacists tend to refrain from explaining the

consumers that generics are as good as their branded counterparts.[24] Moreover, German physicians are required to let the patients know if there is any payment that will be borne by the patients due to the price of a medicine which is higher than reimbursement rate.[25] It can easily be deduced that German authorities still try to have an influence on spending through consumers in the case where the physicians do not prefer prescribing generics instead of branded medicines.

UK, Sweden, France, Spain, Italy and Belgium are some other countries which apply similar kind of regulation for pharmacists. For instance; in UK pharmacists are taking a fixed amount of financial incentive for every medicine they dispense. Considering that UK has also a fixed percentage of reimbursement level, the pharmacists in UK tend to dispense cheaper medicines in order to earn higher incentives. In Belgium and Italy regressive scaled margins method is applied which means when the cost of the medicine dispensed is higher; the profit that the pharmacist makes is lower. Moreover; in France and Spain, pharmacists are allowed to substitute generics whatever written on the prescription.[26]

As specified through this section; most of the countries that we aim to study on are using generic substitution rules for pharmacists and formulas to push physicians to prescribe generics by some means or other. In the next section, we will evaluate other methods of effecting physician decisions directly in course of prescribing.

3.4.2. Guidelines for Prescriptions and Physician Budgets

Physicians, the direct actors of demand for pharmaceuticals, do not necessarily pay attention to the prices of the medicines that they prescribe as they are not the ones who bear the costs like the consumers under 100% regulation without any co-

[24] Elias Mossialos, Adam Oliver, "An Overview of Pharmaceutical Policy in Four Countries: France, Germany, the Netherlands and the United Kingdom", **International Journal of Health Planning and Management**, Vol.XX, 2005, p. 300.
[25] Valérie Paris, Elizabeth Docteur, "Pharmaceutical Pricing and Reimbursement Policies in Germany", **OECD Health Working Papers**, No.39, w. Place, 2008, p. 19.
[26] Elias Mossialos, Tom Walley, Monique Mrazek, **op. cit.**, p. 22.

payment. Nevertheless, with the physician budget regulation; physicians are provided with an annual pre-determined budget for their prescriptions. They are allowed to prescribe any medicines at any amount as long as they do not over spend. If the physicians overrun cost, they encounter financial enforcements. On the other hand, if the physicians manage to keep the cost of the prescriptions under the contemplated budget, they get incentives. In a sense; this system resembles to formula restriction method that we mentioned above. However, the burden is taken by the consumer in the formula restriction, while here it is directly on physicians. Thus, we could expect that the effect of physician budgeting on suppressing the expenditures would be stronger compared to the first one.

Even if UK was the first country that applied to this regulation, Germany is the primary user of this system. It used this technique in 1998 for once and restarted it again in 2001. It has been using this method of regulation since then. The budget is determined with a negotiation between physicians' association and the health insurance institution.[27] According to a study conducted by Danzon and Chao, this regulation reduced prescription drug spending by 18% in Germany. [28]

According to the "quality outcomes framework" implemented by UK, the physicians may earn incentives up to £42 000 if they manage to keep the costs of their prescriptions within the targets.[29] Physician budgeting system is also used in some regions of Spain with different rules applied by each. In addition to this system, Spain is trying to control expenditures on some specific pharmaceuticals through inspection services by regional evaluation committees. The responsibility of these committees is to confirm that the medicine in question is used for the right indications before it is dispensed.[30]

As a different encouraging incentive, physicians have the right to dispense medicines on their own and take the reimbursement amount for themselves in Japan. This

[27] Neeraj Sood et al., **op. cit.**
[28] P. Danzon, W. Chao, "Cross-National Price Differences for Pharmaceuticals: How Large and Why?", **Journal of Health Economics**, Vol.XIX, 2000, pp. 159-195.
[29] Elias Mossialos, Adam Oliver, **op. cit.**, p. 299.
[30] Sabine Vogler, Jaime Espin, Claudia Habl, "Pharmaceutical Pricing and Reimbursement Information (PPRI) – New PPRI Analysis Including Spain", **Pharmaceutical Policy and Law**, Vol.XI, IOS Press, 2009, p. 223.

method of dispensation system aims to push physicians to prescribe generics or low cost medicines not only in order to retain from paying for the difference out of their own pockets when the price of the prescribed medicine is higher than the reimbursable amount but also to earn bonuses by sparing the remaining amount of payment for themselves when the counter condition rules.

Some countries also issue guidelines which explain the best practices for prescriptions. It can simply be concluded that with these guidelines, physicians are directed to prescribe the most cost efficient way of treatment. France is one these countries which apply a programme of guidelines that is called references médicales opposables (RMOs) to make prescription recommendations. Even if the physicians are sceptical about using these recommendations in RMO as they are aware that these recommendations are primarily to reduce the costs rather than providing a better medical assistance, this programme is still prosecuted.[31]

Through this chapter, different types of regulation practices are illustrated with the possible implications of them in different countries where they applied. In the next chapter, we will briefly talk about the structure and status of the pharmaceutical market of Turkey including the recent changes applied by the government, R&D practices and regulations used to control the prices.

[31] Sabine Vogler, Jaime Espin, Claudia Habl, **op. cit.**

4. OBSERVATIONS ON THE PHARMACEUTICAL SECTOR IN TURKEY

As it is for the other countries in the world, pharmaceutical sector is essential for the protection of public health by keeping the economic interests of the country in Turkey as well. It can roughly be deduced by observing the overall structure of the pharmaceutical industry in Turkey that Turkish market looks a bit more like European and Japanese markets rather than the American one in terms of the regulations applied by the government.

The Turkish pharmaceutical industry ranks 16th; behind similar developing countries such as China, Brazil, Russia and India; with its almost 11.2 billion $ size in 2011. In terms of clinical research, Turkey regresses further in the list to 36th in the same period. [1] The development of the pharmaceutical market in Turkey is seen in Figure 13 below:

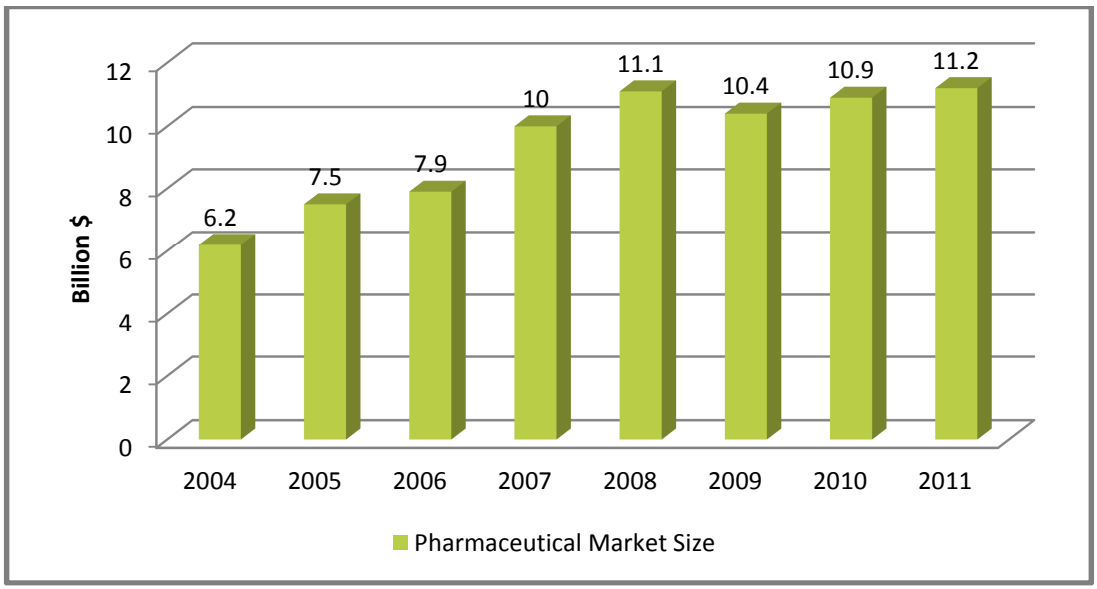

Figure 13. Pharmaceutical Market Size of Turkey, 2004-2011
Source: Business Monitor International, **BMI Database,** (Online) http://www.businessmonitor.com/industry/pharma, 21 February 2014

[1] Association of Research- Based Pharmaceutical Companies (AIFD), **Turkey's Pharmaceutical Sector Vision 2023 Report**, w. Place, August 2012, pp. 19-20.

Production of pharmaceuticals started back in 1928s in Turkey. After 1952, the plants invested by the foreigners started to be established with which the manufacturing period has also begun. “Turkish pharmaceutical industry has the capacity to produce any kind of medicine apart from the products that would require special production technologies such as biotechnology.”[2]

Currently, there are 53 pharmaceutical manufacturing facilities in Turkey, 39 of which are local firms.[3] However, medicine production mostly comprised of low value-added products rather than high value-added products which are mainly imported.[4] Such that, even if the share of local medicines is 77% in the market in terms of box scale, the value share of the imported medicines is almost 50% and sometimes even higher than the local medicines in the market. In Figure 14, the data regarding the share of local and imported RX medicines in Turkish market taken from IMS and database of Pharmaceutical Manufacturers Association of Turkey (IEIS) is shown.

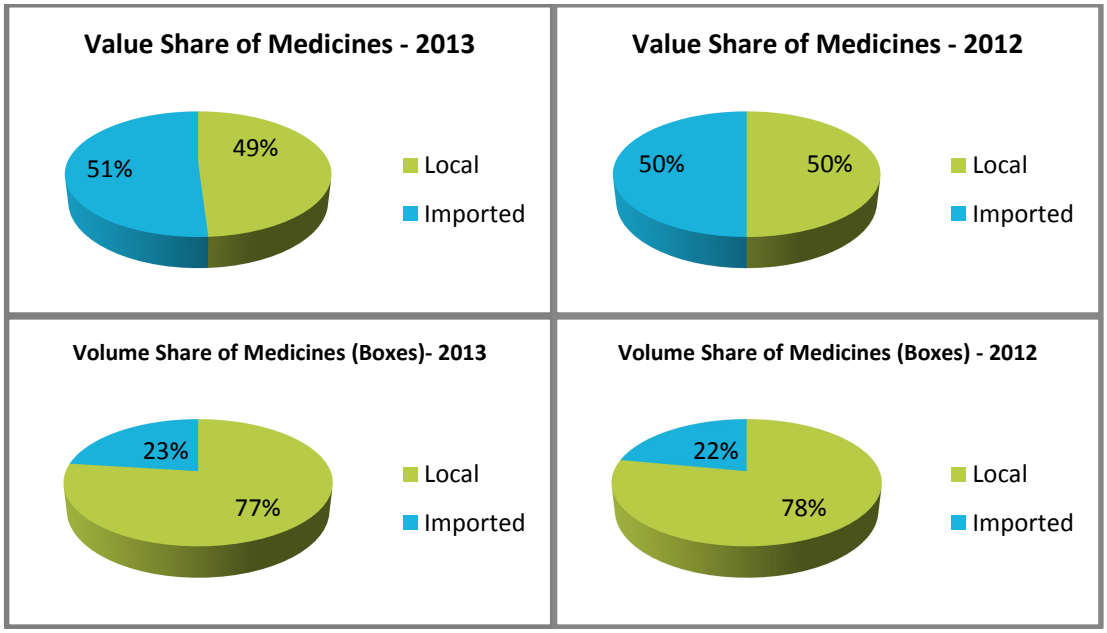

Figure 14. Local & Imported RX Medicine Shares in Turkish Pharmaceutical Market, 2012 and 2013
Source: IEIS, “Türkiye İlaç Pazarı”, **Temel Göstergeler**, (Online) http://www.ieis.org.tr/ieis/tr/indicators/33/turkiye-ilac-pazari**,** 4 March 2014.

[2] TOBB Türkiye İlaç Sanayi Meclisi, **Türkiye İlaç Sanayi Sektör Raporu**, Ankara, October 2008, p.
[3] Republic of Turkey Ministry of Economy, “Pharmaceutical Industry”, **Industry**, 2014
[4] Association of Research- Based Pharmaceutical Companies (AIFD), **op. cit.**, p. 5.

Admitting that the export amount of pharmaceuticals has increased by more than 4 times since 2000 with an average growth rate of 14% per year, the share of pharmaceutical exports in the total country exports amount has remained only 0.04% on average. In the meantime, the rate of pharmaceutical exports to pharmaceutical imports has changed from 10% to 17%, which shows the still-continuing foreign trade deficit in pharmaceutical field. Accordingly, imports of pharmaceutical products have a lower growth rate per year (8% avg.), however it still comprises 2% of the total imports which is way higher compared to the share and value of the pharmaceutical exports. Nevertheless, it is worth to remark that pharmaceutical imports has got in to a declining trend since 2011 as it is seen below in Figure 15.

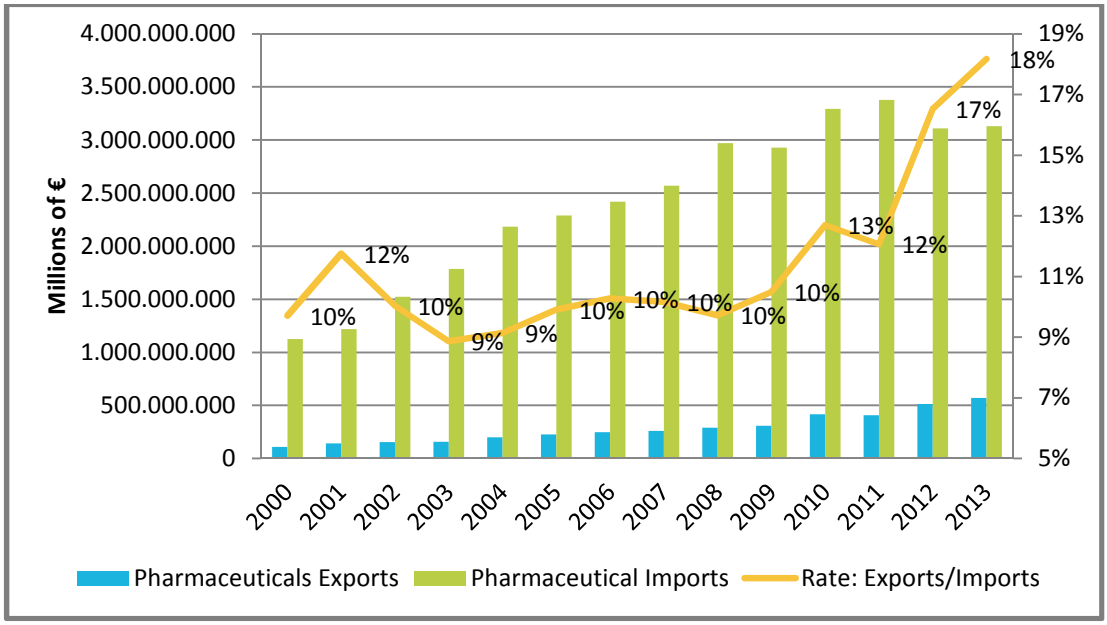

Figure 15. Pharmaceutical Export and Imports of Turkey, 2000-2013
Source: Turkish Statistical Institute, "Foreign Trade Statistics", **TSI Database**.

Turkish market has a large share of generics, even if the companies in the sector aim to increase the R&D activities in the industry to create more brand name products.[5] In 2011, share of generic medicines in the value of total market sales is accounted for 39.2% in Turkey. At the same period, this figure is much lower in the EU countries that we focus in this paper. For instance, the generic share is counting for 9.8% in Switzerland, 13.6% in France, 13% in Belgium, 15% in Sweden, and 21% in UK.

[5] Association of Research- Based Pharmaceutical Companies (AIFD), **op. cit.**, p. 4.

The closest figures belong to Italy (32.2%) and Germany (30.6%).[6] Furthermore, the statistics of IEIS shows that volume share of the generics is even higher in the market (50% on average). Moreover, the change in value and volume shares are stable through the years 2008-2013, which might be an indicator for non-existent increase in R&D.

It is understood from statistics of TSI shown below in Figure 16 that the overall R&D expenditures, the source of innovative medicines which would increase the share of branded medicines, have an increasing trend between the years 2000 and 2012. The share of R&D expenditures in GDP is also accelerated through the years. There is not much information related to the share of pharmaceutical R&D expenditures in the total R&D expenditures. However, according to EFPIA 2013 report, R&D for pharmaceutical industry solely counts for only 43 million € in Turkey in 2010 which is a very small proportion of the total R&D expenditures at that period (≈ 124 million €).[7]

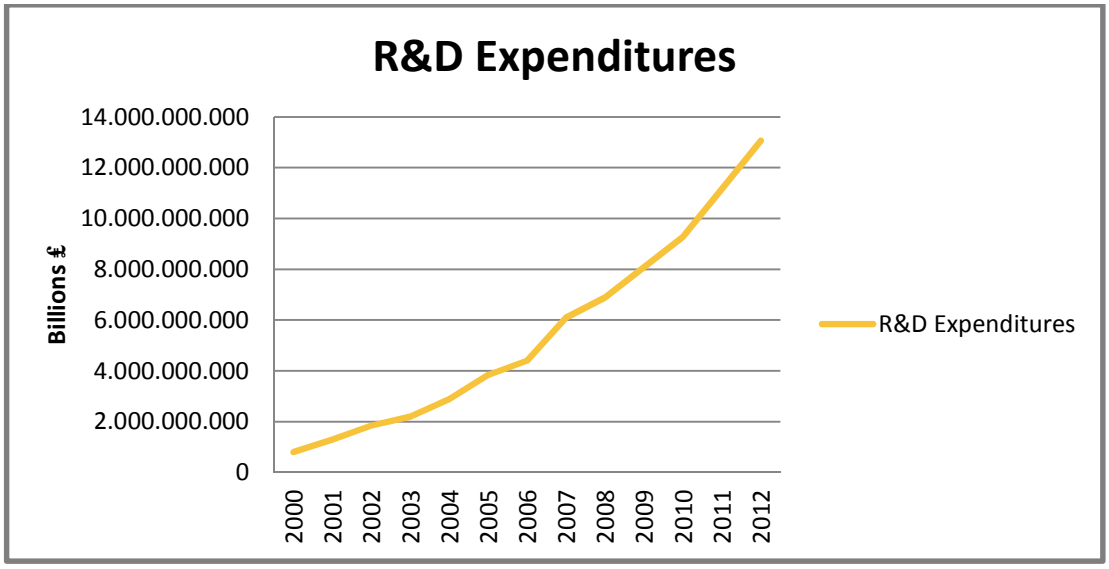

Figure 16. Total R&D Expenditures in Turkey, 2000-2012
Source: Turkish Statistical Institute, "Research and Development Activities Survey", **TSI Database**.

There are approximately 25.000 people employed in the pharmaceutical industry in Turkey. As it is mentioned before, because of the highly advanced structure of the

[6] EFPIA, **op. cit.**, pp. 2-25.
[7] **Ibid.**, p. 17.

industry in terms of technology, the people who are working in the industry have university or higher education levels in Turkey as well. Pharmaceutical industry is one of the sectors which have the highest proportion of employees with university degrees in Turkey with it is 50% of university graduates.[8]

As the European countries that we have been studying in this paper, Turkey has also an insurance system provided by Social Security Institute (SSI) which started to cover almost 100% of the population by the end of 2012 within the Healthcare Transformation Program and Social Security Reform that was started in 2003. Before the change in question, only the people who had a job and their children and spouses were under insurance coverage, apart from the families which are economically restricted. The growth in the number of people who are insured is thoroughly seen in Figure 17 below.

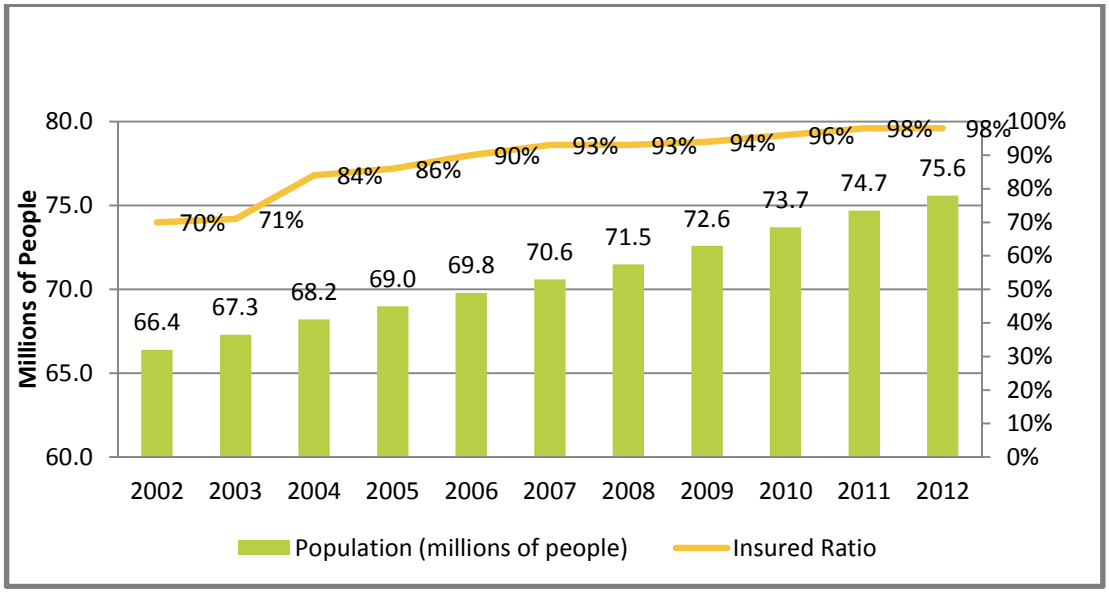

Figure 17. Ratio of Insured People to the General Population
Source: Republic of Turkey Social Security Institution, **SSI Statistical Yearbook**.

With the change of the insurance coverage rules, the demand for pharmaceuticals was expected to increase dramatically causing higher costs for the government that is

[8] Republic of Turkey Ministry of Economy, **op. cit.**

the primary buyer.[9] However, due to the strict controls and regulations that have begun to be implemented, the share of pharmaceutical expenditures is managed to be decreased even if the overall health expenditures had increased through the years. As it is conceived from the monthly statistics of SSI shown in Figure 18, both the pharmaceutical expenditure and total health expenditures have increased from 2000 to 2012. Yet, the share of pharmaceuticals in this increase is lower and lower in every year. It is crucial to keep in mind that these figures are only calculated for the medicine payments done by SSI excluding the out-of-pocket expenditures for medicine and healthcare.

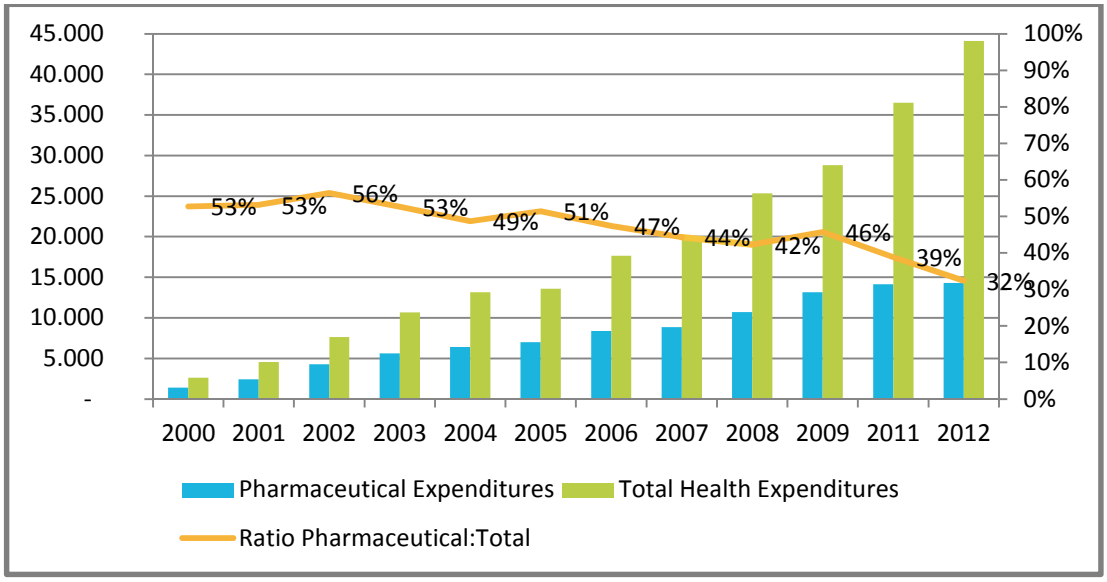

Figure 18. Total Health Expenditures vs Pharmaceutical Expenditures
Source: Republic of Turkey Social Security Institution, **SSI Monthly Basic Indicators**, May 2013

As stated by IMS and TSI databases, medicine consumption per capita in Turkey is calculated as 200.7 ₺ in 2013 with production prices. When we look at the data for the last 9 years, we come across with a downtrend beginning from 2009 even if the change from 2009 to 2013 counts only for 4.1 ₺ in total. Below in Figure 19, it is seen that pharmaceutical per capita expenditures have increased in a fast pace until it makes a peak in 2009, which can be attributed the increasing rate of access to medicine with expansion in the insurance coverage rate.

[9] IMS, "Country Report Turkey", **Pharmaceutical Market Europe,** May 2011, p. 56. (Online) http://www.imshealth.com/ims/Global/Content/Corporate/Press%20Room/IMS%20in%20the%20News/Documents/ICG_Turkey_Article.pdf, 9 April 2014.

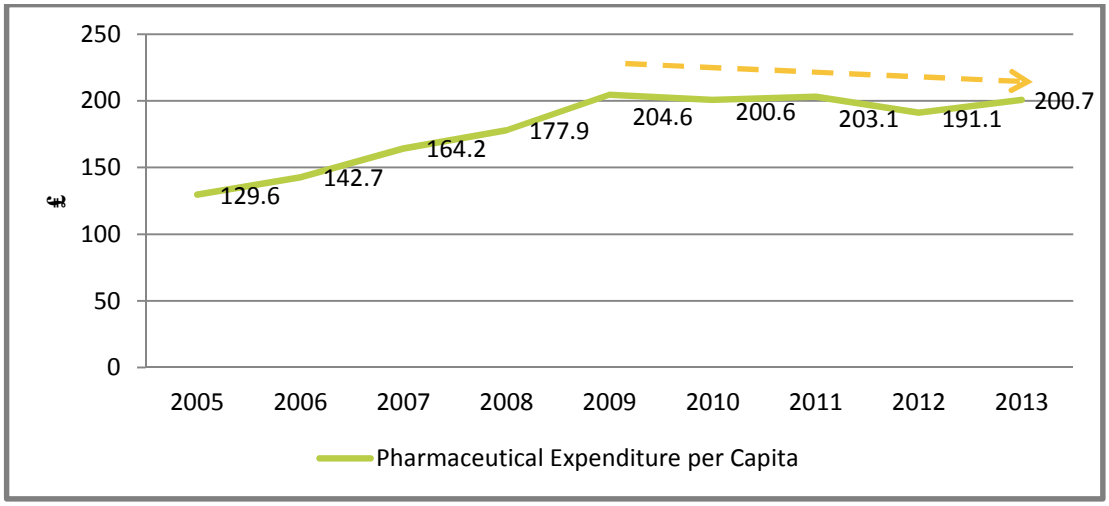

Figure 19. Pharmaceutical Expenditures per Capita
Source: IEIS, "Türkiye İlaç Pazarı", **Temel Göstergeler**, (Online) http://www.ieis.org.tr/ieis/tr/indicators/33/turkiye-ilac-pazari, 4 March 2014

It is feasible to say that the institution which has the essential role in keeping pharmaceutical expenditure from getting higher is Türkiye İlaç ve Tıbbi Cihaz Kurumu (TITCK) that is operating under Ministry of Health. TITCK is responsible for licensing the pharmaceutical products and setting the rules and standards regarding their distribution, production, export, import and etc. as well as auditing the medicines in the market. It also conducts studies in order to define the prices of the pharmaceuticals. Briefly speaking, TITCK is the constitution in Turkey corresponding to the European Medicine Agency (EMA) in Europe or FDA in US.

TITCK has implemented various regulations in recent years in order to be attuned to the EU rules and policies regarding the EU integration process. These regulations include patent protection, data exclusivity, pricing, registration, good manufacturing practices, good clinical practices, bioavailability/bioequivalence, packaging/labelling, promotion/advertising, drug research and medical product registration, stability requirements, regulation on good distribution and storage practices, and pharmacovigilance.[10]

In terms of regulation types on pricing, international reference pricing is the most common method of price control used in Turkey. In compliance with the related

[10] Republic of Turkey Ministry of Economy, **op. cit.**

cabinet decision published in 2007, Ministry of Health determines 5 to 10 EU countries as reference. In the cases, where the exporter or manufacturer country is different from the countries taken as reference, it accepts the country which provides the lowest price as the reference one. The reference, which is defined as the price that will be used to sell the medicine to the warehouse keeper is determined in Euro (€). Every three months, a commission is gathered routinely to discuss the prices of the medicines currently in the market. In this meeting, the committee members take decisions about increasing, decreasing or keeping the same prices and set the Euro exchange rate that will be used in the next period. If the new medicine is a generic rather than a brand name medicine, 80% of the reference price is taken as the basis.[11]

The profit rates of the warehouses and pharmacies are added to the price along with Value Added Tax (VAT) to create the final retail price of the medicine. At this point a regulation on profit is also applied by Ministry of Health. According to the same cabinet decision mentioned above, the profit of the warehouse and the pharmacy cannot be more than 9% and 25% respectively. The maximum profit rates that can be applied are shown below in Table 5.1 for the given reference price.[12] As the price is pre-determined by the authorities, Turkish Ministry of Health does not apply any controls on profit at the producer level.

Table 5.1. Maximum Profit Rates for Warehouses & Pharmacies

Reference Price	Profit Rate of the Warehouse Keeper (%)	Profit Rate of the Pharmacy (%)
0-10 ₤	9	25
10-50 ₤	8	24
50-100 ₤	7	23
100-200 ₤	4	16
200 + ₤	2	12

Source: Ministry of Health, Beşeri İlaçların Fiyatlandırılmasına İlişkin Bakanlar Kurulu Kararı, **T.C. Resmi Gazete**, 26568, 2007/12325, 30 June 2007

[11] Ministry of Health, Beşeri İlaçların Fiyatlandırılmasına İlişkin Bakanlar Kurulu Kararı, **T.C. Resmi Gazete**, 26568, 2007/12325, 30 June 2007.
[12] **Ibid.**

Turkey has a patent protection system that resembles to the one in EU since January 1999. Also as it was given in the section related to R&D process of the medicines in EU, it takes about 10 years for a product to come to the market. Bolar provision is applied for the generic medicines, which allows them to submit their admissions even before the patent of the brand name product expires. [13] Even if this provision decreases the duration of the branded medicines' monopoly power, it might be considered beneficial for a market structure dominated by generics like the one that Turkey has.

Furthermore, the Ministry of Health is using a listing method to define the reimbursable medicines. A Reimbursement Committee that consists of physicians, pharmacists, public health experts, economists, statisticians, specialists, pharmacologists and biostatisticians gathers around every three months in order to evaluate the applications of the pharmaceutical firms for reimbursement. [14] This committee decides the new medicine in question to be in the reimbursable medicines list or not. The rate of regulation is not determined specifically for each and every medicine. Instead, there is a same pre-determined contribution rate for the all medicines which will be undertaken by the consumers. According to SSI Health Practices Declaration, the contribution rate is 10% for the retirees who take their salaries from SSI and 20% for the others. In addition to these contribution rates, 3₤ is taken per prescription for up 3 medicines. On the other hand, some medicines are listed as "not be subject to any contribution rate".[15]

Apart from regulations on the price, retail profits and reimbursement, there are regulations on the promotion of the medicines in Turkey applied by the Ministry of Health as well. For instance, DTCA is not allowed for the RX medicines in Turkey as it is not in EU and Japan. The promotion of RX medicine can only be done to the physicians under strict rules about timing, gifting, sampling and detailed trainings for sales representatives. The guideline related to the medicine promotion principles is

[13] Yusuf Celik, Andreas Seiter, **Turkey: Pharmaceutical Sector Analysis**, Washington DC, World Bank, 2008, p. 7.
[14] Ministry of Health, **op. cit**.
[15] Sosyal Güvenlik Kurumu, **Sosyal Güvenlik Kurumu Sağlık Uygulama Tebliği**, 2013.

binding for both the sales representatives (hence the pharmaceutical firms) and the physicians in some terms.

According to the guideline, the sales representatives can-not offer any kind of gifts apart from the recalling items which cost no more than 2.5% of the monthly gross minimum wage, in order to encourage the physicians to prescribe the medicine promoted. Also, the physicians can-not accept any kind of items in exchange for prescribing a medicine. Similarly, the samples that can be given to the physicians can-not be more than 5% of the sales in the first year of that medicine in the market. The proportion of possible sampling is decreasing in following years until 1% of the total sales after its sixth year in the market.[16]

Moreover, the time that can be spared for the sales representatives can-not be during the working hours while there are still patients to be seen by the physicians. As reported by the guideline, every institution has to define a time where the sales representatives are allowed to visit the physicians. The pharmaceutical firms or the sales representatives who are working for them can-not offer any incentives to the physicians in order to get an appointment for promotion activities.[17]

On the other hand, regulation on the promotion of OTC medicines is confusing. The pharmaceuticals and medical preparations law enacted in 1962 prohibits promoting the OTC medicines on any kind of visual media and allows it to be promoted only in newspapers as long as it is done in a specific way. However, the Turkish government attempted to make some changes in the guidelines a couple of times recently by allowing the promotion for OTC medicines in every source of media. With the objection of Turkish Pharmacists' Association, the change in the guideline is retrieved.

In this chapter, we have mentioned basic indicators of the pharmaceutical industry in Turkey by briefly touching upon the size of the market, production, employment, R&D activities, exports and imports, share of generics and branded medicines in the

[16] Ministry of Health, Beşeri Tıbbi Ürünlerin Tanıtım Faaliyetleri Hakkında Yönetmelik, **T.C. Resmi Gazete**, 28037, 26 August 2011.
[17] **Ibid.**

market, and regulations on price, reimbursement and promotion of pharmaceuticals. As we implied before, there is no doubt that in terms of regulative activities the pharmaceutical market structure of Turkey resembles to EU. In this regard, even if Turkey is not involved in the countries that will be studied, the result that will be acquired from model which will be formed in the next chapter might also be associated with Turkey's condition by means of the relation between R&D and regulations on pharmaceuticals.

5. THE LINK BETWEEN REGULATIONS ON PHARMACEUTICALS AND R&D DECISION

Thus far through this paper, we spoke of the R&D decisions of the firms along with the restrictions that may be being influential in deterring firms from beginning or continuing to an investment on R&D, and the regulations directly on the price of medicines and indirect regulations which might be forming pressure on the prices respectively.

In this chapter; our focus will be on the link of these two concepts: financial restrictions on R&D and regulations on pharmaceuticals. After evaluation of overall profit margins of the pharmaceutical firms in the light of regulations via referring some preceding works, we will specify the hypotheses through which we claim that the regulations on pharmaceuticals might be affecting R&D decisions.

In chapter 2, we mentioned that R&D decisions of the firms depend on two parameters MRR and MCC. Rationally speaking, it is expected that the regulation on price and demand might have an impact on these variables through certain channels. It is discussed before that when the authorities try to keep the prices lower by restricting the monopoly power of the pharmaceutical firms using different kinds of regulations on price, they mostly consider the marginal cost of producing the medicine which is only a small proportion of the real cost of the company covers the short run cost rather than the high fix cost of R&D process.

There is no doubt that this comparably lower prices applied might limit the current profit margins and affect the expected profit margins for the future through MRR scale. Also by decreasing the cash flows inside the business, it may affect future R&D decisions through MCC scale.

Vernon in his work “Examining the Link between Price Regulation and Pharmaceutical R&D Investment” (2005) which is one of the studies that this current research is based on, analyses these elements through a theoretical mathematical

model for US by simulating the effect of regulations in case they are applied by US on contrary to reality. Vernon, who uses micro level data obtained from major pharmaceutical firms for the years 1994 to 1997, proves that cash flows (MCC) and expected returns (MRR) are the dominant factors affecting the R&D decisions. He also estimated that in case of regulations applied in US, R&D investment intensity would decrease by between 23.4 and 32.7%.[1]

$$\frac{R_{it}}{S_{it}} = \underbrace{\beta_1[\lambda_i t M_i t^R + (1-\lambda_i t) M_i t^f]}_{\text{Expected-profitability effect}} + \underbrace{\beta_2 \frac{\{1-\pi\}\{S_i t^P{}_{-1}[\lambda_i t{}_{-1} M_i t^R{}_{-1} + (1-\lambda_i t{}_{-1}) M_i t^f{}_{-1}] + \tilde{\pi}_i t{}_{-1} + R_i t{}_{-1} + D_i t{}_{-1}\}}{S_i t{}_{-1}}}_{\text{Cash-flow effect}} \quad (8)$$

The scenario in which the regulations are used in the US market:

$$\lim_{\lambda \to 1} \frac{R_{it}}{S_{it}} = \beta_1 M_i t^R + \beta_2 \frac{[1-\tau][S_i t^P{}_{-1} M_i t^R{}_{-1} + \tilde{\pi}_i t{}_{-1} + R_i t{}_{-1}] + D_i t{}_{-1}}{S_i t{}_{-1}} \quad (9)$$

$$\underbrace{\Delta\left[\frac{R_{it}}{S_{it}}\right] = \beta_1[(1-\lambda_i t)(M_i t^f - M_i t^R)]}_{\Delta \text{ Pharmaceutical profit margin}} + \underbrace{\beta_2 \frac{\{1-\tau\}\{S_i t^P{}_{-1}[(M_i t^f{}_{-1} - M_i t^R)(1-\lambda_i t{}_{-1})]\}}{S_i t{}_{-1}}}_{\Delta \text{ Cash flows}} \quad (10)$$

R_{it} = firm *i*'s R&D expenditures in year *t*

π_{it} = firm *i*'s pre-tax pharmaceutical profits in year *t*

$\tilde{\pi}_{it-1}$= firm *i*'s pre-tax non-pharmaceutical profits in year *t*

S_{it}^P = firm *i*'s total pharmaceutical sales in year *t*

λ_{it} = percentage of firm *i*'s pharmaceutical sales in year *t* from non-US markets

[1] John A. Vernon, "Examining the Link between Price Regulation and Pharmaceutical R&D Investment", **Health Economics**, Vol.XIV, John Wiley & Sons, Ltd., 2005, pp. 1-16.

M_{it}^{f} = firm *i*'s average pre-tax profit margin on pharmaceuticals products sold in the US market in year *t*

M_{it}^{R} = firm *i*'s average pre-tax profit margin on pharmaceuticals products sold in non-US markets in year *t*

D_{it-1} = firm *i*'s depreciation expense in year *t*-1

τ = Corporate tax rate

Similarly, in another study by Vernon (2003) the effects of price regulations on the profit margins of the pharmaceutical firms are examined. By running a regression analysis for the data of 20 top pharmaceutical companies between the years 1994 to 1999, he concludes that there is a possibility of regulations are affecting the R&D decisions of the firms.[2]

However, due to the unavailability of the micro level data regarding the expected profits, current profits, cash flows and etc., we will be establishing our hypothesis within a macroeconomic perspective. By working with the macroeconomic variables, we will try to guess the possible reflections of these variables on pharmaceutical R&D decisions.

5.1. Data Sample and Empirical Implementation

The main considerations in selecting the variables and the sample are the availability of the data for the complete 1999-2011 period and the major contribution to the global pharmaceutical market among developed countries as we discussed in the first chapter of this study. In this regard, the empirical analysis consists of 12 countries

[2] John A. Vernon, "The Relationship between Price Regulation and Pharmaceutical Profit Margins", **Applied Economic Letters**, Vol.X/VII, London, Routledge, 2003, pp. 467-470.

namely; Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Sweden, Switzerland, UK, and US; in total for the period of 1999-2011 and the dependent and independent variables which are explained later in this chapter. Data on the country variables are obtained from OECD and Eurostat databases and annual EFPIA reports.

The data regarding US and the other countries we mention in this study are studied separately to compare the results of the same model from a non-regulated market with the regulated ones. The countries other than US are behaved as if they were one single country by taking the arithmetic mean value of every variable for each year. SPSS 15.0 for Windows Evaluation Version is used to run a classical multiple linear regression analysis for the both models following the major assumptions for the relationship between explanatory and explained variables.[3]

First of all, assuming the fact that MRR might be being influenced by the macroeconomic condition of the country, we focus on the variables that would give us impressions about the general economic status of the country. In this sense, GDP is the one of the variables that we use in our empirical analysis. GDP, calculated with expenditure approach is used and it is divided by population in order to be standardized. By adding this variable into our analysis, we aim to see how much, if any, the welfare of the countries have impact on the R&D.

Here, there is a point that might be necessary to mention. Even if for some, older population is the driver of the demand for medicine; in this specific paper we assume that the whole population is the source of demand for medicine which would be more accurate as the empirical study is not targeting one specific therapeutic area.

[3] Assumption 1: The model is linear in parameters.
Assumption 2: X values are fixed in repeated sampling.
Assumption 3: Mean value of the disturbance term equals to zero.
Assumption 4: Equal variance.
Assumption 5: No autocorrelation between the disturbances.
Assumption 6: Zero covariance between disturbance term and observations.
Assumption 7: Number of observations is greater than the number of parameters.
Assumption 8: Variability in observations.
Assumption 9: The regression model is correctly specified.
For more information see: Damodar N. Gujarati, **Basic Econometrics**, 4th Edition, New York, McGraw-Hill, 2003, p. 66.

In order to measure the effect of demand further, we introduce expenditures on pharmaceuticals into our model as another variable. The data regarding the expenditures on pharmaceuticals includes not only public but also private spending on all kinds of medicines, both RX and OTC. This variable is also taken as “per head expenditure” in order to be standardized.

Until here in this chapter we mentioned the variables that might have an impact on R&D activities through MRR schedule. In order to capture the influence of the MCC schedule, we mainly centralize our analysis on the taxes specified earlier in chapter 2 while we were discussing the cost of internal and external funds. In this context, one of the variables added to the model is the integrated capital income tax rate which is a combination of the tax applied on retained earnings of the firms and the corporate tax rate. The second variable used is tax rates implied on dividends. Both of these variables indicate the average tax rates within a whole year period for each country.

To remind the audience the idea we mentioned in chapter 2, we should remark that the tax rates for dividend income are expected to be higher so that we assume that the companies will tend to keep income as retained earnings which will provide an inside cash flow to their businesses with a considerably low tax rate to bear. Therefore, using these retained earnings to finance R&D investment would be more beneficial for them rather than issuing new equities. Theoretically, variables such as ‘retained earnings of the firms’, ‘percentage of retained earnings used in R&D’ or the ‘ratio of retained earnings to distributed dividends’ would be presenting a clearer outcome for this kind of study. However, as it is not possible to have an explicit data regarding these possible variables, its effect are tried to be observed through the possible impact of the integrated capital income tax and dividend tax rates of the countries on the pharmaceutical R&D decisions.

By introducing all the variables mentioned above, the study model is shaped as follows:

$$PRDE = \beta_0 + \beta_1 GDP\_PC + \beta_2 EP\_PC - \beta_3 ICT - \beta_4 DT$$

PRDE = Pharmaceutical R&D Expenditure

GDP_PC = GDP Per Capita

EP_PC = Expenditure on Pharmaceuticals Per Capita

ICT = Integrated Capital Tax

DT = Dividend Tax

It is expected that the coefficients of GDP per Capita and Expenditures on Pharmaceuticals have positive signs while the two tax variables have negative signs.

5.2. Results

Even if our regression model is significant for both US and the other countries in question and the variables that we are using are strong in explaining the change in the dependent variable, Pharmaceutical R&D expenditures, due to high auto-correlation and multicollinearity the independent variables are not significant individually. The power of the independent variables' explaining the response variable and the statistical relationships between them can easily be seen from the scatter diagrams as well given in Appendix II.

The correlation analysis shows that almost all the variables are significantly correlated with each other (App. Table 2.3.) which causes multicollinearity for the model built for the countries other than US. Even the smallest correlation between the independent variables is 0.81. As a result, the t coefficients are not significant except for GDP per Capita variable and the values are exceeding the "no multicollinearity" band for VIF being more than 5 and Tolerance value being less than 0.20 (App. Table 2.1) Some techniques are used to get rid of the multicollinearity problem such as omitting some variables or adding some others and combining or separating two variables.[4] However none of these techniques were successful in solving this problem.

On the other hand, it is seen that the correlation coefficients between the dependent and independent variables are 0.83, 0,98, -0,94 and -0.93 for GDP per Capita, Expenditure on Pharmaceuticals per Capita, Integrated Capital Tax Rate and Dividend Tax Rate respectively. As expected, the integrated capital tax and dividend tax rate variables have negative signs. These results support our proposition about the direction of the statistical relationship between our dependent and independent variables.

Similar case works also for the US regression model due to the existence of autocorrelation with a Durbin Watson coefficient different than the allowed value for no autocorrelation (App. Table 2.4). Here, we also see that GDP per Capita and Expenditure on Pharmaceuticals per Capita have positive correlation with the dependent variable. Dividend Tax has a high negative correlation while the correlation could not be calculated for the Integrated Tax Rate variable as there is no change in it through the years. (App. Table 2.2) This is another violation of the pre-assumptions of classical multiple linear regression.

As the coefficients of the tax rates are not significant either, it is not possible to come to a conclusion about which of the taxes has more influence on the R&D expenditures of the pharmaceutical firms but it is obvious that both of the taxes has inverse correlations as expected.

[4] Damodar N. Gujarati, **op. cit.**, pp. 364-369.

CONCLUSION

The primary objective of this study was to explore the relationship between pharmaceutical R&D expenditures and government regulations on medicine price and pharmaceutical markets. In this context, the overall pharmaceutical market structures and the determinants affecting the R&D investment decision are mentioned along with the most common regulation methods used by the governments as a background.

In the light of these, an empirical model was established in order to detect the differences in behaviour of the determinants of R&D investment decision in the countries with regulations and without regulations. The idea behind this was the possibility of a negative effect of regulations through the general determinants of R&D investment decision like several costs, demand and expectations. Considering our previous suggestion about the fact that a micro level data would give a more realistic observation, the empirical analysis that we conducted in this paper aimed only at providing estimation for the firms' R&D decisions by using the macro indicators.

As there is only one country which does not apply any regulations on pharmaceuticals in the world, it was not possible to add a dummy for the "regulations" itself into the model as an explanatory variable. Thus, two different models are built in order to see the effect of the regulations on the countries with regulations and US which is the only country without regulations.

Mainly because of multicollinearity and autocorrelation problems that we could not solve, coefficients of our explanatory variables are not statistically significant. However, as we mentioned earlier their correlation with the independent variable is high which suggests that firms' inclination of investing in R&D is higher as the GDP per capita and the demand for medicine, welfare of the country in other terms, get higher and higher. While their intention for R&D investment gets lower and lower while tax rates which are some of the elements affecting the MCC schedule is higher.

The crucial point about the results of this study is admitting that the impact of the variables that we used for explaining the change in R&D decisions do not vary across US and the other countries in question against our expectations. However, given the data constraints of this study, this result shouldn't be perceived as the regulations have no effect on the R&D decisions at all. Depending on the availability, adding other parameters or more variables to the models, especially more specific ones such as pharmaceutical market values, firms' profit expectations, average medicine prices, firms' sales within US and the other countries in question, cash flows inside and outside the business and etc. may yield a more reliable result.

Finally, it is not possible to decide whether the governments should or should not regulate the pharmaceutical markets by just considering the analysis in this paper, as we can not estimate the effects of regulations clearly from the analysis that we conducted. US is an exception with its abundant amount of international technology intensive pharmaceutical companies which's pharmaceutical industry is getting bigger and bigger with the help of free market conditions encouraging more investments. However, just as it is evaluated in previous chapters this condition will cause higher medicine prices as it is the case in US which will not be that favourable for the social welfare of the countries with smaller economical scale.

In case of absence of regulations, the public cost would be higher which would possibly decrease the ratio of insured people or the insurance coverage. Thus access to medicine would regress. Also this could cause public debt problems as the cost the government will bear would be higher.

For the future papers, this research might be extended to cover Turkey in a wider way by including Turkish pharmaceutical market also into the analysis. The impact of regulations might be more visible by using Turkey as comparison to US market because of the differences in economical scales as we suggested before.

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APPENDIX I: DATA SAMPLE FOR CLASSICAL MULTIPLE LINEAR REGRESSION ANALYSIS

App. Table 1.1. Data Sample for the Countries Other than US *(Arithmetic Mean for Australia, Belgium, Canada, France, Germany, Italy, Japan, Spain, Sweden, Switzerland and UK)*

	GDP per capita (Constant prices, constant PPPs, OECD Base Year)*	Expenditure on Pharmaceuticals per capita (2005 constant US $ and PPPs)**	Integrated Capital Income Tax (%)***	Dividend Tax Rate (%)***	Pharmaceutical R&D Expenditure (2005 constant US $ and PPPs)****
1999	28992,79	330,89	0,36	0,40	2140001107
2000	29918,29	352,34	0,37	0,40	2302961763
2001	30275,34	380,48	0,35	0,40	2351518530
2002	30534,30	400,91	0,34	0,39	2635600998
2003	30831,28	435,97	0,33	0,39	2454508449
2004	31475,43	454,59	0,33	0,34	2439274979
2005	31979,10	474,75	0,33	0,32	2697765137
2006	32741,38	498,88	0,33	0,32	3015008490
2007	33435,82	521,19	0,32	0,30	3082934702
2008	33275,11	545,31	0,30	0,27	3272533970
2009	31888,78	569,39	0,30	0,26	3274226342
2010	32621,29	576,18	0,30	0,27	3360554521
2011	32997,74	583,55	0,30	0,28	3512890849

* OECD, Gross Domestic Product (GDP), **OECD Database**, (Online), http://stats.oecd.org/Index.aspx?DataSetCode=PDB_LV, 18 May 2014.
** OECD, "Pharmaceutical Expenditure per Capita", **Health: Key Tables from OECD**, No. 8, (Online), 10.1787/pharmexpcap-table-2013-2-en, 15 March 2014.
*** OECD, **OECD Tax Database** (Online) http://www.oecd.org/tax/tax-policy/tax-database.htm, 7 March 2014.
**** OECD, **Main Science and Technology Indicators,** Vol.MMXIII, Issue 1, w. Place, OECD Publishing, June 2013, p.16, (Online) http://dx.doi.org/10.1787/msti-v2013-1-en ,10 February 2014.
**** Eurostat, "R&D Expenditure" – **Statistics Explained** (Online) http://epp.eurostat.ec.europa.eu/statistics_explained/index.php/R_%26_D_expenditure#Further_Eurostat_information, 24 January 2014.

App. Table 1.2. Data Sample for US

	GDP per capita (Constant prices, constant PPPs, OECD Base Year)*	Expenditure on Pharmaceuticals per capita (2005 constant US $ and PPPs)**	Integrated Capital Income Tax (%)***	Dividend Tax Rate (%)***	Pharmaceutical R&D Expenditure (2005 constant US $ and PPPs)****
1999	39754,49	485,09	0,39	0,46	14598960142
2000	40930,85	540,33	0,39	0,46	14370837702
2001	40909,61	599,84	0,39	0,46	11132204263
2002	41241,51	665,63	0,39	0,45	15359051388
2003	42002,92	727,65	0,39	0,21	16929518000
2004	43206,32	778,63	0,39	0,21	32486591610
2005	44242,26	818,72	0,39	0,21	34839000000
2006	44992,59	880,94	0,39	0,21	37740799615
2007	45361,04	919,17	0,39	0,21	45111199995
2008	44806,49	937,43	0,39	0,21	44616734361
2009	43168,53	971,60	0,39	0,21	41336852286
2010	43888,63	972,69	0,39	0,21	44913443756
2011	44375,58	994,97	0,39	0,21	51090810756

* OECD, Gross Domestic Product (GDP), **OECD Database**, (Online), http://stats.oecd.org/Index.aspx?DataSetCode=PDB_LV, 18 May 2014.
** OECD, "Pharmaceutical Expenditure per Capita", **Health: Key Tables from OECD**, No. 8, (Online), 10.1787/pharmexpcap-table-2013-2-en, 15 March 2014.
*** OECD, **OECD Tax Database** (Online) http://www.oecd.org/tax/tax-policy/tax-database.htm, 7 March 2014.
**** OECD, **Main Science and Technology Indicators,** Vol.MMXIII, Issue 1, w. Place, OECD Publishing, June 2013, p.16, (Online) http://dx.doi.org/10.1787/msti-v2013-1-en ,10 February 2014.
**** Eurostat, "R&D Expenditure" – **Statistics Explained** (Online) http://epp.eurostat.ec.europa.eu/statistics_explained/index.php/R_%26_D_expenditure#Further_Eurostat_information, 24 January 2014.

APPENDIX II: CLASSICAL MULTIPLE LINEAR REGRESSION ANALYSIS RESULTS

App. Table 2.1. Coefficients of Estimates for the Data of Countries Other than US

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	Collinearity Statistics	
		B	Std. Error	Beta			Tolerance	VIF
1	(Constant)	-8E+008	4E+009		-,196	,849		
	GDPperCapita	2290,975	82564,881	,007	,028	,979	,154	6,487
	Exp.PharmaPerCapita	5650370	3547250	1,061	1,593	,150	,022	45,514
	IntegratedCapitalTax	3E+009	8E+009	,157	,380	,714	,057	17,561
	DividendTax	-4E+008	3E+009	-,045	-,125	,904	,075	13,414

a. Dependent Variable: PharmaceuticalRDExpenditure

App. Table 2.2. Coefficients of Estimates for US Data

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	Collinearity Statistics	
		B	Std. Error	Beta			Tolerance	VIF
1	(Constant)	-1E+011	8E+010		-1,769	,111		
	GDPperCapita	2668967	1892142	,337	1,411	,192	,169	5,915
	Exp.PharmaPerCapita	6E+007	2E+007	,750	3,055	,014	,160	6,252
	DividendTax	1E+010	3E+010	,122	,559	,590	,203	4,925

a. Dependent Variable: PharmaceuticalRDExpenditure

App. Table 2.3. Correlations of Variables for the Countries Other than US

			GDPper Capita	Exp. PharmaPer Capita	Integrated CapitalTax	DividendTax	Pharmaceutical RDExpenditure
Spearman's rho	GDPperCapita	Correlation Coefficient	1,000	,852**	-,825**	-,810**	,830**
		Sig. (2-tailed)	.	,000	,001	,001	,000
		N	13	13	13	13	13
	Exp.PharmaPerCapita	Correlation Coefficient	,852**	1,000	-,966**	-,949**	,978**
		Sig. (2-tailed)	,000	.	,000	,000	,000
		N	13	13	13	13	13
	IntegratedCapitalTax	Correlation Coefficient	-,825**	-,966**	1,000	,963**	-,938**
		Sig. (2-tailed)	,001	,000	.	,000	,000
		N	13	13	13	13	13
	DividendTax	Correlation Coefficient	-,810**	-,949**	,963**	1,000	-,932**
		Sig. (2-tailed)	,001	,000	,000	.	,000
		N	13	13	13	13	13
	Pharmaceutical RDExpenditure	Correlation Coefficient	,830**	,978**	-,938**	-,932**	1,000
		Sig. (2-tailed)	,000	,000	,000	,000	.
		N	13	13	13	13	13

**. Correlation is significant at the 0.01 level (2-tailed).

App. Table 2.4. Model Summary for Classical Multiple Linear Regression Analysis for US Data

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics					Durbin-Watson
					R Square Change	F Change	df1	df2	Sig. F Change	
1	,956[a]	,913	,884	4943420120	,913	31,560	3	9	,000	1,037

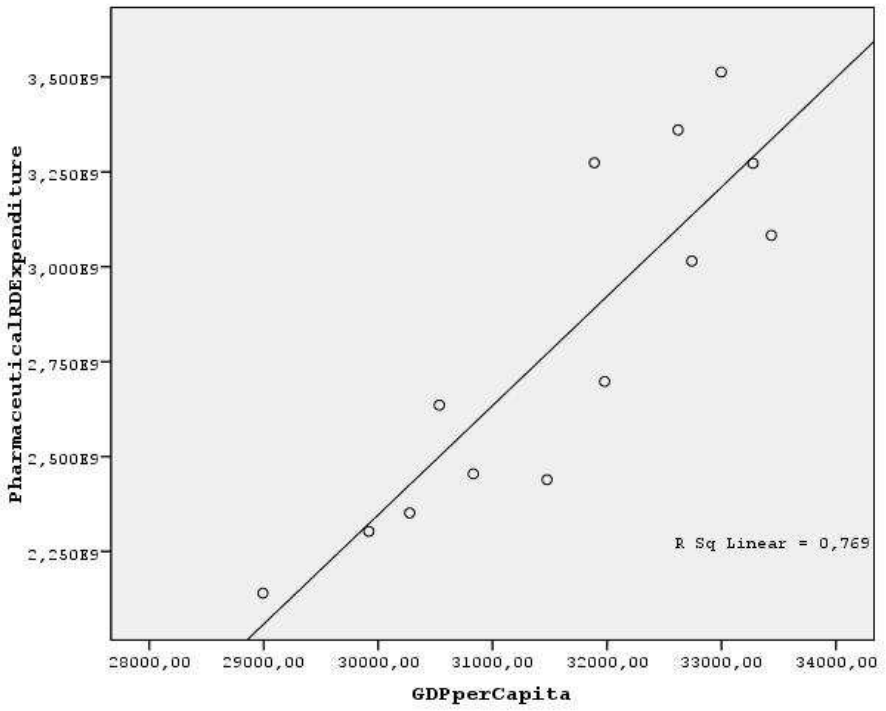
a. Predictors: (Constant), DividendTax, GDPperCapita, Exp.PharmaPerCapita

b. Dependent Variable: PharmaceuticalRDExpenditure

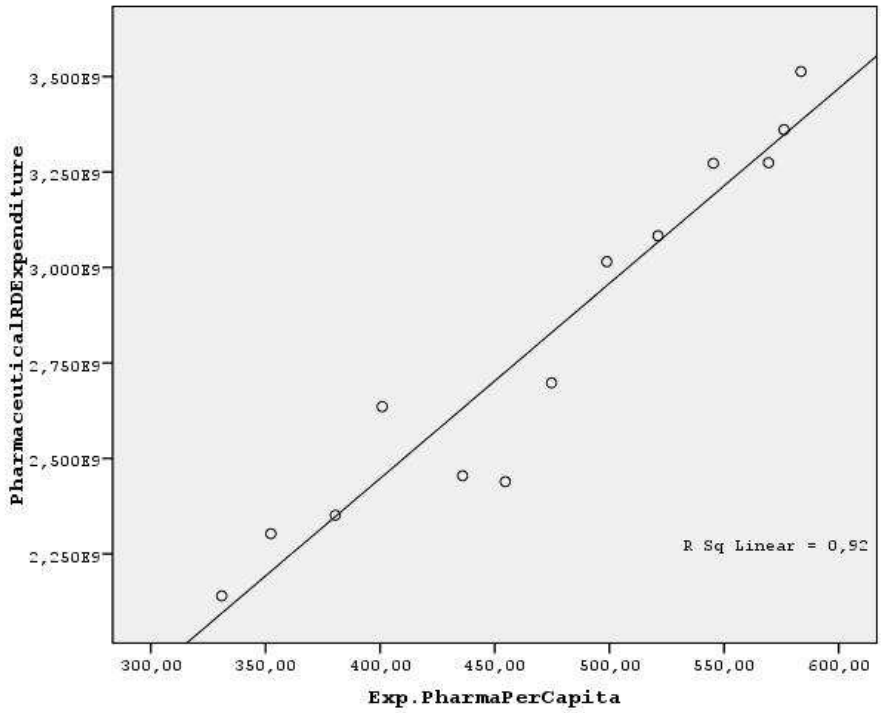
App. Table 2.5. Correlations of Variables for US

			GDPper Capita	Exp. PharmaPer Capita	Integrated CapitalTax	DividendTax	Pharmaceutical RDExpenditure
Spearman's rho	GDPperCapita	Correlation Coefficient	1,000	,753**	.	-,812**	,846**
		Sig. (2-tailed)	.	,003	.	,001	,000
		N	13	13	13	13	13
	Exp.PharmaPerCapita	Correlation Coefficient	,753**	1,000	.	-,812**	,940**
		Sig. (2-tailed)	,003	.	.	,001	,000
		N	13	13	13	13	13
	IntegratedCapitalTax	Correlation Coefficient	.	.	.	.	.
		Sig. (2-tailed)	.	.	.	.	.
		N	13	13	13	13	13
	DividendTax	Correlation Coefficient	-,812**	-,812**	.	1,000	-,812**
		Sig. (2-tailed)	,001	,001	.	.	,001
		N	13	13	13	13	13
	Pharmaceutical RDExpenditure	Correlation Coefficient	,846**	,940**	.	-,812**	1,000
		Sig. (2-tailed)	,000	,000	.	,001	.
		N	13	13	13	13	13

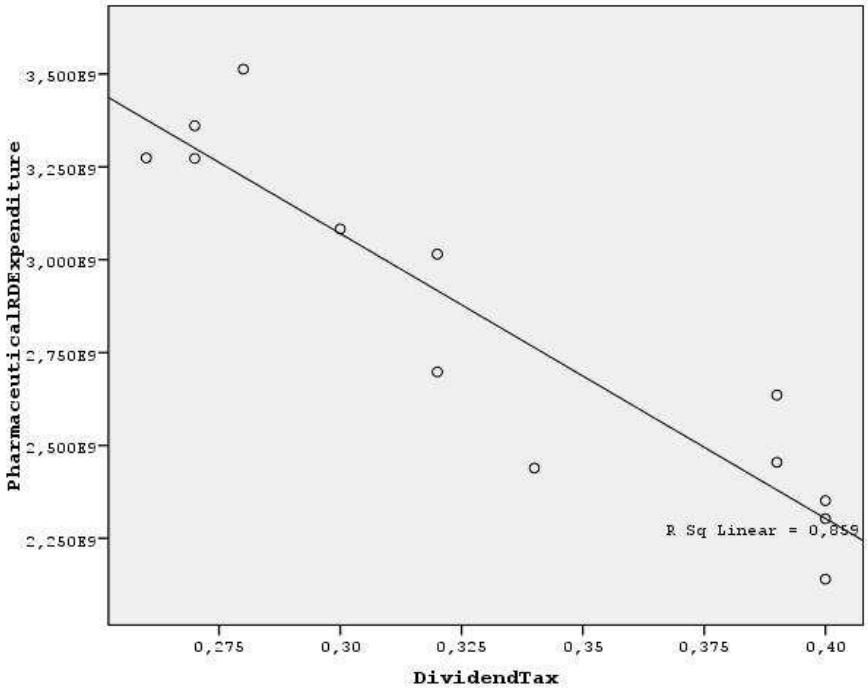
**. Correlation is significant at the 0.01 level (2-tailed).



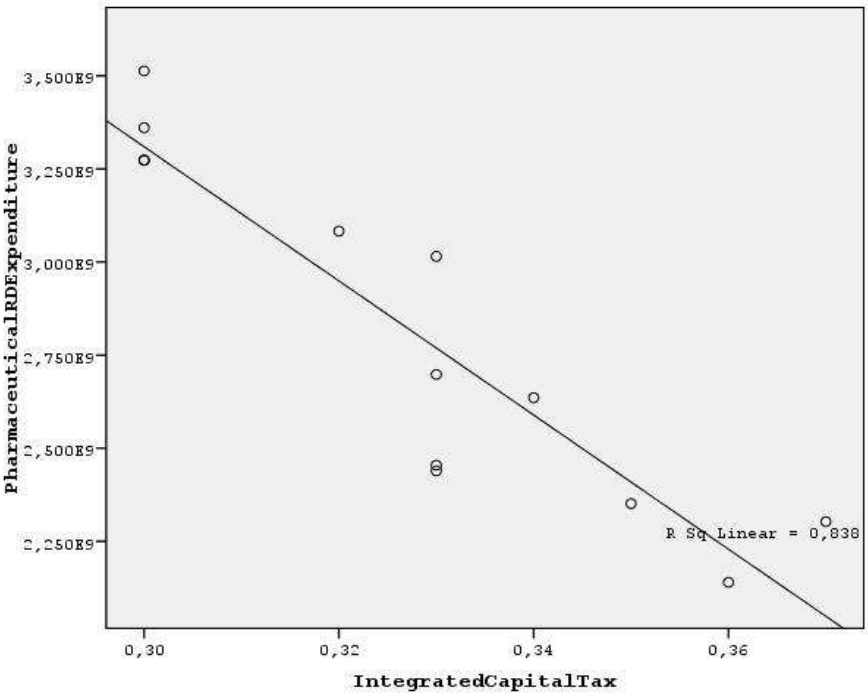
App. Figure 1. The Power of GDP per Capita in Explaining Pharmaceutical R&D Expenditures



App. Figure 2. The Power of Pharmaceutical Expenditures per Capita in Explaining Pharmaceutical R&D Expenditures



App. Figure 3. The Power of Dividend Tax in Explaining Pharmaceutical R&D Expenditures



App. Figure 4. The Power of Integrated Capital Tax in Explaining Pharmaceutical R&D Expenditures