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"Evergreening in Pharmaceuticals: "*Gaming*" the Patent System?
The ongoing backlash between the Indian and US Patent Law."

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Firma dello studente

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It is incredible how important the impact of the pharmaceutical industry is to us. Or at least some of us recognized its need only lately.

While leaving behind a very difficult year which was extremely challenging worldwide and especially here in Italy, it made a lot of people change their way of thinking and prioritizing what is really important to us as human beings. Health. Our wishes relied on being healthy together with our loved ones. And in the middle of this pandemic, all our eyes, worldwide, were pointed to them, the pharmaceuticals. We were waiting for the vaccines. We wanted this to end as soon as possible while seeing our lives changing forever.

And those vaccines took quite a few to get ready. Just like this thesis.

Long processes for new drugs. A lot of research and evaluation. A lot of effort was required then and is still required day by day in any industry for bringing innovation and new inventions. This effort was also required by me in order to be able to finish this paper.

This is how the very challenging pharmaceutical industry caught my eye as an interesting sector to focus this work.

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Abstract

When this global pandemic hit our lives, most of our attention was towards pharmaceuticals. The pharmaceutical industry have been contributing on the improvement of our health and quality of life for a long time now.
This thesis aims to analyse some of the most interesting and conflictual behaviours that pharma companies take in order to extend the patent protection of their products.
Chapter 1 introduces the patenting system, its importance on supporting incremental innovation and its trade-offs in this industry. Patents are the most important instruments by which inventors can protect their products and guarantee returns on investments from these products. Pharma undertakings go through long processes of research with heavy investments in order to develop new medicines accessible to the population.
One of the basic rationales underlying the grant of patent rights is that such rights provide incentives to the pharmaceutical companies to innovate. They are granted by the authorities of a specific country under some of the most complicated legislations under IP rights. In this chapter, we go through the patent protection laws and regulations for some of the biggest markets, the EU, USA, and India.
With regards to the pharmaceutical products, they are cheap to manufacture. That's the reason why, each time a branded patent expires, generic drugs manufacturers can offer to the market the same drug with the same therapeutic effects at noticeable reductions on prices. But when does a patent expire? In the pharmaceuticals, the TRIPS Agreement established 20 years as a standard for patent protection. On the other hand, Big pharma has been claiming for a while that the patent clock starts way much earlier. In front of the tremendous pressure to succeed and the high uncertainties in the process for developing new drugs, the limited patent protection might not be enough. So, pharmaceutical companies are trying to "play" with the loopholes in the patent system regulations for filing secondary patents through evergreening strategies. This can be done mainly done by filing disguised/artful patents on an already patent-protected invention shortly before expiry of the parent patent. The first chapter gives a full picture of these strategies providing also examples related from the pharma history.

In the second chapter, we can look at the dimensions of the global pharmaceutical industry. Going through the numbers and learning about the latest trends unfortunately could not give us quantitative results regarding the impact of evergreening. But luckily,

a lot of literature is provided by academia in order to describe and help preventing these behaviours in this industry. After that, we go through the provisions and regulations that two of the biggest markets, USA and EU have included with the aim of blocking the evergreening strategies. As we will see, these regulations are very lenient, uncomplete and not fully attentive towards evergreening.

A different approach is taken by India instead. The country, fully aware of its population needs in terms of healthcare has adopted one of the strongest (and most conflictual) provisions against evergreening in pharmaceuticals. Section 3(d) will be introduced in Chapter 3 together with a full description of the Indian pharmaceutical markets and its impact in the global pharma. Known as the 'pharmacy of the world', Indian authorities are very attentive when granting patent protection over pharmaceuticals. Many have been the cases of denial of such protection towards big pharma which under Section 3(d) of the Indian Patent Act didn't provide enough incremental therapeutic innovations for getting patent approval. We analyse specifically three of them which raised a heated debate with the other countries. By following step by step, we analyse the effect that patent denial under Section 3(d) for these three cases had in India but also in the US market.

Some important facts caught our attention and raised some questions regarding the effective impact of this Indian provision in patenting pharmaceuticals in the US market. Some of these questions got an answer in Chapter 4, others are yet to be defined.

Abbreviations

ANDA	Abbreviated New Drug Application
CAGR	Compound Annual Growth Rate
CGT	Competitive Generic Therapies
EC	European Commission
EMA	European Medicines Agency
EPO	European Patent Office
EU	European Union
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
GATT	General Agreement on Tariffs and Trade
IPO	Indian Patent Office
IPR	Intellectual Property Rights
NCE	New Chemical Entity
NDA	New Drug Application
NME	New Molecular Entity
R & D	Research and development
SPC	Supplementary Protection Certificate
TFEU	Treaty on the Functioning of the European Union
TRIPS	Trade Related Aspects of Intellectual Property Rights
US	The United States
USC	The Uniform System of Classification
USPTO	United States Patent and Trademark Office
WTO	World Trade Organization

"With any advent in technology, any technological innovation, there is the good and the bad."
- **Henry Rollins**

I.

The pharmaceutical industry. Going beyond the traditional view of patents.

1.1. Introduction

The pharmaceutical industry has been contributing to significant improvements in patients' well-being for a long time now. Today, citizens can expect to live longer than they did a century ago. The process of introducing all new medicines into the market is very long, costly and risky with high Research and Development (R&D) expenses. In order to recoup the considerable investments in drug development and approval, pharmaceutical companies rely on exclusivity provisions granted by the regulatory bodies. These exclusivity rights are given in the form of patents by the Intellectual Property (IP) authority of a state to the inventor for a limited period of time in place of disclosing the invention for the benefit of the human race.

One of the basic rationales underlying the grant of patent rights is that such rights provide incentives to the pharmaceutical companies to innovate. But in front of the tremendous pressure to succeed and the high uncertainties in the process for developing new drugs, the limited period of monopoly might not be enough. Sometimes, big pharma chooses to "play with the patent system" in order to maintain this privileged position through strategic patenting strategies. This chapter aims to highlight these strategies, especially the evergreening ones. The concept of "evergreening" refers to the various strategies that a patent holder adopts with the aim to extend the privileged position due to this exclusive right. Evergreening is common in various industries but in the pharmaceutical sector, it is intensively present because of the high financial profits that the successful patented drugs can generate.

Keywords: *innovation, patent, pharmaceutical, evergreening, generics, regulation*

1.2. Patents, the lifeblood of innovation.

In channelling the economic growth of a country, innovation definitely plays a crucial role. It is key for staying ahead on the game and an industry that turns on the principle of staying ahead is without any doubt the pharmaceutical industry.

In this industry, innovation represents one of the most defining characteristics which is driven by and drives medical progress. The pharmaceutical undertakings aim to turn fundamental research into innovative treatments that can be widely accessible to patients worldwide. This sector is characterized by extremely high investments into Research and Development (R&D) which increase the probability of introducing innovative products or processes. On the other hand, innovation itself provides high returns on investment. This is measured by Intellectual property (IP) rights, including patents, widely considered to be the lifeblood of innovation. Patents[1] grant the patent holder the right to exclude others from *making, using, selling, or importing* a patented invention. They are exclusive property rights for disclosing the innovative creations of the human mind and are provided in the laws of sovereign states. A patent can be enforced only to the extent that the application has been made.

Obtaining patent protection is crucial to safeguard the innovative, non-obvious and useful approaches used by pharma companies. Such rights provide an incentive for inventors to innovate and can contribute to roughly 80% of the overall revenues of drug manufacturers. The period of exclusivity allows the patent holder, who becomes a monopolist for a limited period of time, to charge *higher-than-competitive prices*[2] in order to recoup part of the R&D costs but also to provide incentives for inventors to create new technological inventions.

However, the relationship between patents and innovation is much more complex than already acknowledged in the current innovation policy rhetoric.

First of all, the pharmaceutical industry is one of the three technology-based industries in which the patent virtually equals the product, which is relatively cheap to manufacture. So, patent protection becomes the only way to receive exclusivity on the market in order to reap the returns

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[1] According to Article 28 (a) of TRIPS: "1. A patent shall confer to its owner the following exclusive rights:

a. where the subject matter of a patent is a product, to prevent third parties not having the owners' consent from the acts of: making, offering for sale, selling or importing for these purposes that product;

b. where the subject matter of a patent is a process, to prevent third parties not having the owners' consent from the act of using the process, and the acts of using, offering for sale, selling or importing for these purposes at least the product obtained directly by that process."

[2] The influence of some States in the regulation of prices and reimbursements for pharmaceuticals has been growing in the last decade.

from R&D. Even though developing and launching a new drug involves huge costs, with patent protection the rate of return on successful drugs can be much higher than the costs associated with introducing the drug to the market.

On the other hand, it's important to acknowledge that the patenting system has long been considered to represent a trade-off between the incentives to innovate, the competition in the market, and the diffusion of technology. An IP right always creates a monopoly and with that, there is associated a deadweight loss. As a monopolist, the patent holder is interested in influencing the market price above the marginal cost. This limits access for users, who are willing to pay a price above the marginal cost of using the intellectual good which is below the profit maximizing price set by the holder. So, there is a loss and it results in a static inefficiency. This inefficiency constitutes a dilemma that always requires a compromise between competition policy and IP law.

Last but not least, the pharmaceutical industry is also characterized by enormous uncertainties on whether or not the drugs make it into the market.

Figure 1: The new drug development process

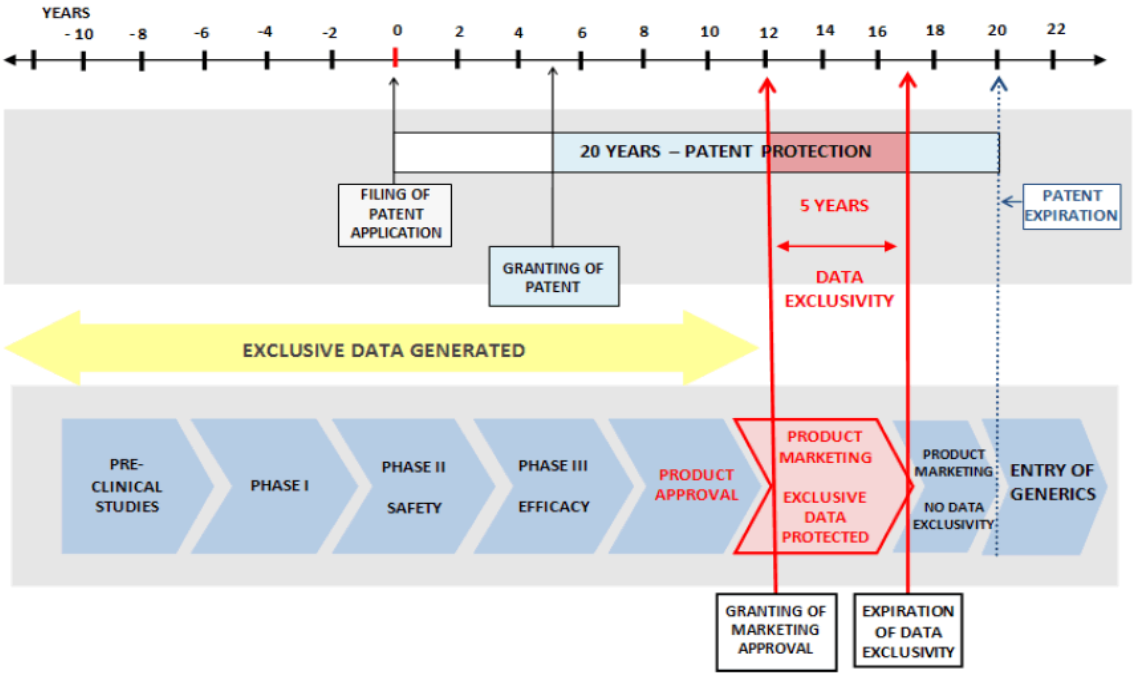


Fig. 1 explains the "infinite" steps a pharmaceutical company goes through on developing a new molecule. The process itself is estimated to take up to 10 – 13 years. And once the new drug is confirmed by the market, it can also be easily reverse engineered at a low cost by rivals - generic competition. On an average of 20 years from the date of application, patent holders enjoy around 10 or 11 years of exclusivity. That means that as soon as a drug goes off-patent, generic manufacturers are free to launch generic version of the drug and with their entry the

price of the branded drug inevitably falls. Since the generic company has to spend less on R&D, they are able to provide drugs at lower prices.

For the originators, developing a new drug can be risky in at least three levels. It is risky in the sense that attaches in general to technical success: the path from idea to application is a long path with twists and turns, dead ends and the real possibility of failure. Drug development is risky from a commercial point of view because of uncertainty about the profitability of a drug, if it goes to market - a drug, once marketed to the general public, may be revealed to be ineffective - it may turn out to have harmful side effects. And then, drug development is risky because the outcome of the long regulatory process through which a drug must pass before it is permitted to go to market is very uncertain.

Big pharma has been claiming for a while of not being able to reap all the necessary returns during this *limited* period of exclusivity. This raises the question on whether it directly affects the innovation level in the industry. (Nelson, 1959) and (Arrow, 1962) presented the problem of underinvestment specifically in basic research and pointed out that inventors' incentives to be inventive will suffer if they cannot appropriate the returns to their inventions.

In absence of institutional provisions for inventions, like patents, society would face a state of under-provision in inventive activities, due to the problem of free-riding. In front of these conflicting aspects, economists have to decide which is more important to society: more available knowledge in the future or less accessible knowledge in the present?

Unfortunately, no conclusive answer is currently available.

1.3. Introducing the Global Regulatory Background.

Pharmaceutical products are some of the most regulated products in the market. Pharmaceutical regulations are defined as the combination of legal, administrative, and technical measures that authorities take to ensure the safety, efficacy, and quality of medicines, as well as the relevance and accuracy of product information. (Lezotre, 2014)

From what *Figure 1* brings us, the life cycle of a pharmaceutical can be divided into *three phases*: the prelaunch period, the marketing and sales period and the last period when the patent protection expires and generic entry is possible. All steps of the product's commercialization are regulated: there are a myriad of rules for pharmaceutical companies to navigate in. The patent itself covers the territory of a specific individual state.

For ensuring efficacy of the drugs and the safety of customers, governmental regulations make expensive clinical trials necessary in this industry as the drugs cannot be marketed without approval.

In determining whether or not all the requirements have been met for a drug approval, the authorities compare the claims of the patent applicant against the body of existing literature in the field, including also the previously issued patents.

1.3.1.The comprehensive WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS)

Before introducing the specific regulations for each country, it is important to start with the common base of patent protection. The WTO Agreement on Trade-Related Aspects of Intellectual Property Rights of 1994 is the most comprehensive multilateral agreement on intellectual property. Its aim is to facilitate the trade in knowledge and creativity, to help on resolving trade disputes over IP, and assures to all WTO members the *space* to achieve their domestic policy objectives. The Agreement frames the IP system in terms of innovation, technology transfer and public welfare.

Specifically, for the pharmaceutical sector, the TRIPS Agreement establishes *the minimum rights that must be conferred by a patent which are similar to those to be found in most patents laws.* The most fundamental right given to the patent owner is the privilege to prevent unauthorized subjects from using the patented process and making, using, offering for sale, or importing the patented product or a product obtained directly by the process. TRIPS also established the 20 years period of patent protection from the date of application.

In order to adapt their legislation and practices to their TRIPS obligations, WTO Members had some periods of time available. Developing countries for example, had until January 2000 to apply the provisions of the TRIPS and an extra period was provided, until January 2005, for those developing countries which did not grant such protection for pharmaceutical products until the first deadline. While on the other hand, the least-developed countries originally had time until 1 January 2006 to meet their TRIPS obligations but with the pursue of the instructions in the Doha Declaration on the TRIPS Agreement and Public Health, the deadline was extended up to January 2016. The Doha Declaration (2001) recognized the gravity of the public health problems resulting from HIV/AIDS, tuberculosis, malaria and other epidemics, afflicting many developing and especially the least-developed countries, and in light of its Paragraph 4 introduced some flexibilities for these countries in order to protect their public health.

The flexibilities in the TRIPS Agreement have subsequently been clarified and reinforced not only by the Doha Declaration on the TRIPS Agreement and Public Health, but also by the Waiver Decision of August 2003 and the Amendment Decision of December 2005 to facilitate compulsory licenses for export to those countries in need. All WTO Members strongly believe that a powerful and vibrant multilateral trading system is essential to create the conditions for

economic growth and providing the possibility of generating all the resources required to tackle health problems. The next paragraphs present the specific regulations that some of the biggest markets such as the EU, USA and India, have introduced for protecting the pharmaceuticals.

1.3.2.The European Patent Law

Traditionally, the EU has played a pioneering role in pharmaceutical's research and development, including generic medicines and biosimilars. The European patent was originally created in 1973 as part of the Munich Convention, which also established the European Patent Office, an intergovernmental organization that is not an institution of the European Union. Its pharmaceutical sector is a highly regulated one. In line with initiatives of national member states, the sector inquiry rearticulates the EU Commission's general policy objective of : "*providing European patients with safe, effective and affordable medicines while creating the necessary conditions for a business environment for stimulating research, boosting valuable innovation and supporting the competitiveness of the industry.*"

The heart of EU legislation on medicinal products are Directive 2001/83/EC on the Community code relating to medicinal products for human use and Regulation (EC) 726/2004 on the authorisation and supervision of medicinal products and establishing a European Medicines Agency (EMA). They define the key concepts such as what constitutes a medicinal product, and regulate, among others, the marketing authorisation procedure, and the supervision of medicines upon authorisation. The Agency scientifically evaluates the medicines developed by pharmaceutical companies for use in the EU and also the applications for European marketing authorizations for both human and veterinary medicines. (Philipp, 2011) The most noticeable characteristic of the present state of the patent law in the EU is its *dualism*. It refers to the *coexistence of two different ways for obtaining patents* with the same effects, namely limited to the territory of the Member State for which they are granted or a European-wide protection. If you need protection in only one European country, you can register a patent at the national level. For European-wide protection instead, you can register a European patent with the EPO. The European patent then needs to be validated by the national patent office in each country where protection is required. Until today, no Community patent which would cover the entire territory of the EU and have the same effects throughout the EU countries is available because the majority of EU Member States did not ratify the 1989 Agreement Relating to Community Patents. (Straus, 1997)

From the undertakings' point of view, they have to adhere to a healthcare policy framework mainly influenced by patient safety and fiscal concerns in order to benefit from opportunities to legally protect their products from product imitation. On the other hand, the pharmaceutical

sector – like any other industry – is subject to competition law, which is regulated and enforced at both EU and national member state level.

As outlined in the Treaty on the Functioning of the European Union (TFEU) - Section 1, competition law *prohibits behaviour and practices that restrict the functioning of the free internal market environment.* More precisely, Art. 101 of the Treaty bans certain restrictive multilateral business practices, while Art. 102 makes the abuse of a dominant market position illegal which brings us to the trade-off between the incentives to innovate in the pharmaceutical industry (and not only) and the competition in the market. It is extremely crucial for the functioning of this market to find the right balance between the two of them.

1.3.3.Pharmaceutical patent's regulation in the USA

In the United States, the exclusivity rights for new pharmaceutical products are governed by both U.S. Patent Law and Food and Drug Administration (FDA) law.

The primary regulation of pharmaceuticals in the US is at the federal level by the Federal Food, Drug, and Cosmetic Act (the FD&C Act), codified at Title 21 of the US Code (USC).

The U.S. Food and Drug Administration reviews and approves human drugs and biologics and regulates their manufacturing and marketing. To obtain approval, the manufacturer must submit a new drug application (NDA) that demonstrates among other things that the drug is safe and effective for its intended use. There approvals are specifically related to the product which is defined by the chemistry, manufacturing and control information provided and also to the facilities and processes included in the application to the FDA. (Agneshwar, et al., 2021) The patent information provided by the NDA owner is then listed for the approved drug along with regulatory exclusivity information in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the Orange Book). The listing of patents in the Orange Book facilitates the resolution of eventual patent disputes raised by generic filers.

In order to encourage innovation and to incentivise the development of new drug products with lower costs, in USA, the Congress has also passed significant legislation such as the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments), which amended the FD&C Act to establish *the generic drug approval pathway*. (Kracov, et al., 2020) According to the definition provided by the US FDA, an abbreviated new drug application (ANDA) consists in data submitted to this authority with the scope of getting potential approval for a generic drug product. Once FDA approves the application, the applicant may manufacture and market the generic drug product to provide *a safe, effective, lower cost alternative to the brand-name drug* it references. The term "abbreviated" for the generic drug

applications is used because generally they are not required to include preclinical and clinical data to establish safety and effectiveness. However, the generic applicants must provide scientific proofs that their product has the same performance as the innovator drug. In fact, one of the main requirements for getting approved by FDA, is that the generic version must deliver the same amount of active ingredients into a patient's bloodstream for the same amount of time as the originators' drug. According to the Hatch-Waxman Amendments, *bioequivalence* was defined as the basis for the approval of generic versions of drug products.

At the same time, to the generic drug companies was given the ability of challenging existing patents in court (known as patent challenges) prior to marketing with a *180-day generic drug exclusivity.* So, other than incentives in the form of statutory exclusivities, the US patent system grants also exclusive rights to generic pharma companies to make, use, sell or import into the US inventions for even if a patent has already been granted. US Patent and Trademark Office (USPTO) is also governed by Section 35 of the US Code. This section was amended into law in 2011 by The Leahy-Smith America Invents Act in order to implement, among other changes, *a first-to-file system*.

In the US market, just like the European one, participants in the pharmaceutical sector are subject to antitrust laws which influence how participants may contract with each other, acquire and enforce patents, settle litigations as well as how they may market their products.

The key antitrust laws impacting the pharmaceutical sector are: Section 1 of the Sherman Antitrust Act, which bans unreasonable contracts or conspiracies in restraint of trade; Section 2 of the Sherman Antitrust Act, which outlaws "monopolization or attempts at monopolizing any aspect of interstate trade or commerce"; Section 7 of the Clayton Antitrust Act, which bans mergers or acquisitions that may *"substantially lessen competition or tend to create a monopoly*"; and Section 5 of the Federal Trade Commission Act, which outlaws *"unfair methods of competition"* and *"unfair or deceptive acts or practices."*

As previously emphasized for the EU pharmaceutical market, the USA is also one of the most highly regulated ones.

1.3.4. The evolution of patent law in the developing countries: focusing on India.

Over the past decades, the Indian pharmaceutical industry has been one of the most successful, high-technology-based industries with a very consistent growth. The liberalisation of the Indian economy has had a huge impact in the revolutionization of Indian industries making them emerge from domestic markets and aiming for *international competition.* Today, on the global scale, the Indian pharmaceutical industry is positioned third largest in volume terms and tenth largest in value terms. Known as *the pharmacy of the world*, the healthcare imperatives and the resultant laws and regulations around health in India and also the strong competition with the biggest markets like US and EU, are unique and object of interest for this work.

For India, the Doha Declaration on the TRIPS Agreement and Public Health is considered as victory because it re-established the primacy of the *duty to respond to public healthcare needs over the duty to protect the private intellectual property* (IP) claims of pharmaceutical companies. In 1970, the Patent Act was passed, repealing all previous legislations. However, the newly introduced Patents Act excluded pharmaceuticals and agrochemical products from eligibility for patents. This exclusion was in order to break away India's dependence on importing drugs and formulations and provide for development of a self-reliant pharmaceutical industry. This lack of protection had a significant impact on the Indian pharmaceutical industry and resulted in the development of considerable expertise in reverse engineering of drugs that were *patentable as products throughout the industrialised world but unprotectable in India.* (Zacharias & Farias, 2019)

As a result of this, the Indian pharmaceutical business speedily began to develop cheaper versions of a bigger range of medication proprietary for the domestic market moving then into the international market once the international patents expired. The TRIPS agreement was negotiated during the Uruguay round trade negotiations of the General Agreement on Tariffs and Trade (GATT) and one of the main reasons for incorporating intellectual property issues into the GATT framework was the pharmaceutical industry. India signed the GATT on 15 April 1994, thereby making it mandatory to comply with the requirements of GATT, including the agreement on TRIPS. (Zacharias & Farias, 2019)

The country was thereby required to meet the minimum standards under TRIPS in relation to patents and the pharmaceutical industry. India's patent legislation needed thus to include provisions for availability of patents for both pharmaceutical products and processes inventions. In 1982 India introduced a new legislation amending the Drugs and Cosmetics Act of 1940 which also provided for the Central Government to make rules, *inter alia,* for the cancellation or suspension of a licence for a contravention of the provisions of the Act dealing with *import,*

manufacture, sale, and distribution of drugs, or if there has been non-compliance with the conditions subject to which the licence has been issued.

Regulation-making power has been extended to cover prescription of the use of packing material that comes into direct contact with the drug. The focus of successive Indian governments has been introducing *reductions in out-of- pocket expenditure on healthcare and drugs* due to the absence of a significant reimbursement system in the country.

As known, the market is dominated by generics thus laws and regulations of the country (IP, drug regulatory, drug pricing, prescriptions, etc.) are mainly focused towards *governing and strengthening a generic market.*

1.4. Is generic entry a real threat for innovation?

The pharma industry is unique on its own. While the demand is mostly driven by the prescriptions of the doctor or pharmacist (not the patients themselves), two firms - the originators and the generics - dominate the supply chain. The interplay between and within these parties heavily influences the progress in the industry regarding innovation and price effects. (Ndubuisi, 2015) On one hand, generic manufacturers which produce generic solutions can enter the market upon the end of the exclusivity period of the pre-existing original drugs. Their situation is considerably more advantageous: little or no research costs, no risks assumed, not even marketing costs since the road has already been cleared by their predecessors - the originators. (Tuominen, 2011) As previously emphasized, the originator companies are actively involved in R&D and preclinical trials for market authorizations for the new drugs. In return they are given market exclusivity for a period of 20 year, with a possibility of extension depending on national legislation. Specifically, of an average of 20 years from the date of application, patent holders enjoy around 10 or 11 years of exclusivity.

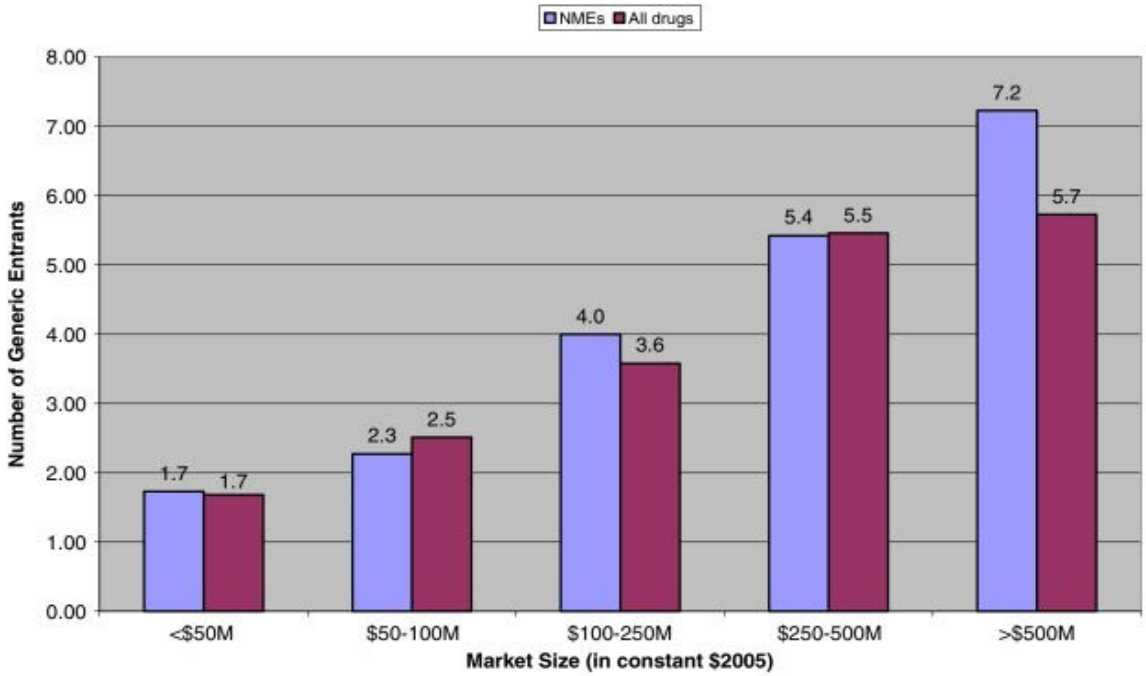
By making the knowledge public in exchange for market exclusivity, the innovator helps in increasing in some way both knowledge transfer and technology diffusion. (Hall, et al., 2005) This also helps in preventing duplicative research. (Kremer, 1998)

Traditionally, generic companies have always emphasised that due to their presence on the market, customers can have access to medicines at more affordable prices. In fact, their entry is associated with the falling prices of the drugs due to price competition. It is estimated that drugs which go off patent lose up to 80% of the revenue generated by the originators. But how do the generic manufacturers decide which entry strategy to choose?

Grabowski & Kyle (2007) analysed the dimensions of the generic competition and market exclusivity periods for pharmaceuticals that had experienced their initial generic entry between 1995 and 2005. The results showed that generic competition has increased over several

dimensions. First, during these years, an increasing number of drugs were subject to generic entry, including drugs with relatively modest annual average sales. Then, blockbuster drugs attract more generic entrants hence have shorter market exclusivity periods than smaller selling drugs. (Grabowski & Kyle, 2007) In fact, as we can see in *Fig. 2*, markets with less than $50 million in market sales have less than 2 generic competitors after Year 1, whereas markets with sales greater than $500 million have more than 7 generic competitors. Third, the higher selling drugs with annual sales in excess of $1 billion experienced significant decreases in their market exclusivity periods in recent years due to generic entry which captures most of the market share within weeks of their launch.

Figure 2: Average number of generic entrants within 1 year, by market size.



Source: Grabowski & Kyle (2007)

These results are consistent with several studies which highlight the fact that product sales are a key determinant of generic entry and competition. What concerns the economists is that generic manufacturers are *disproportionately targeting high-sales drugs* (blockbusters), reducing in this way their market life and showing that just like their originator competitors, generics manufacturers are businesses in pursuit of profit.

Another aspect observers worry about are generic *patent challenges* which are on the rise and that may reduce effective market life of drugs. These patent challenges take the form of generic drug applications with so called "Paragraph IV" certifications and provide a means for a generic firm to pursue entry when the relevant patents are invalid or do not cover the proposed generic product. (Hemphill & Sampat, 2012)

Part of the increase is due to the regulatory pathway in the US, permitting generic drug makers to challenge branded drug makers' patents, with a view to securing early FDA approval and market entry. Hemphill and Sampat (2012) analysed the causes and effects of these patent challenges using a unique dataset of all instances of first-time generic approval between 2001 and 2010 connected with information concerning every drug's patents, patent challenges and different characteristics. They showed that challenges are more common for higher sales medicines and by examining which patents are challenged on each drug, the results showed that lower quality and later expiring patents disproportionately draw challenges.

All this targeting on the high-sales drugs by the generics that are trying to cut down their market life may indirectly have an effect innovation within the trade. Along this line, we know that originator companies are highly dependent on the revenues from mostly best-selling drugs and they inevitably wish to maintain these for as long as possible. So, this data leaves them with two choices: *defend the prevailing patents* or *acquire new patents by inventing new drugs*.

As emphasized before, developing a replacement drug needs years and years of investments in R&D without none guaranteed success. So, the originators may opt for the "*quickest*" strategy: they involve in *strategic patenting* (evergreening strategies) geared toward delaying or deterring generic entry to prevent price competition or block market entry for other originators, try to increase their bargaining power within the trade and self-insure themselves against future risk of infringement once they enter into a new line of R&D. All these strategic patenting methods *affect the amount of innovation in the industry* as a result of the increased breadth and duration of monopolistic restrictions on the foundational technology and put future originator competitors at a disadvantage. The result is a dynamic inefficiency because undertakings focus more on the patent competition instead of innovation competition. This limits other future originators' ability to innovate in related areas which may completely abstain from further research in the field.

To stress the evergreening phenomenon effect further it is important to fully understand in what it specifically consists of and how it affects innovation and price competition in the pharma industry, as well as its social welfare effect.

1.5. Pharmaceutical patenting practices: there's life in the old drug yet.

Evergreening refers to different ways through which patent owners take *undue advantage of the law* and extend their IP monopoly particularly over highly lucrative blockbuster drugs. This can be done mainly done by filing disguised/artful patents on an already patent-protected invention shortly before expiry of the parent patent. (Bansal, et al., 2009)

1.5.1 Defining 'evergreening'

Although there are provisions in patent laws that are specifically enacted to provide innovators sufficient exclusivity period to enjoy monopoly[3], with time and with the rise in the number of generic drugs industries, *strategic attempts to exploit the loopholes in patent laws* and related regulation to extend patent protection especially on what they consider *bestseller drugs*, over the market have become more common. With rising R&D expenditures, it is important for pharmaceutical companies to make positive returns from the innovation. These returns can be achieved by improving both *effectiveness and efficiency* of the processes. Hence, various instruments and strategies can be combined by the originators in order to succeed.

Table 1: Examples of Strategic Evergreening

Strategic options	Description	Exclusivity period	Source
Strategic patenting ("later issued patents")	Obtaining patent protection on different aspects around the base compound patent	20 years from the date of filing	Hutchins (2003), Burdon and Sloper (2003)
Patent term restoration	Granting of additional market exclusivity for the time lost due to FDA approval process (Title II of Hatch–Waxman Act)	Maximum of 5 years	Agrawal and Thakkar (1997)
SPC	Protective mechanism serving as an extension to patent right	Maximum of 5 years	Hitchcock and Tugal (2003)
30-month stay provision	Filing a patent infringement suit to fight ANDA	30 months from the date of notice or till court decision	Bhat (2005)
Orphan drug	Applying for orphan drug status for an already authorized drug	7 years of market exclusivity in US, 10 years in EU	Haffner et al. (2008), Minghetti et al. (2000)
Pediatric exclusivity	Submission of pediatric clinical trials on the FDA's request	6 months of market exclusivity	Kvesic (2008)
Patent settlement agreements	Involving in settlements with generic manufacturers to delay the market entry	Duration of the agreement	Bulow (2004)

A way can be by filing disguised or artful patents *on previously patented inventions* just before the end of the term of the parent patent. These strategic moves are known as evergreening practices or strategic patenting. Evergreening is a strategy acquired by the innovator companies to recover high costs incurred by them in Research and Development and as a means to legally protect any minor modifications that are *intentionally made* to patent just to obtain multiple patents on the same drug and hence extend the overall term of the patent to enjoy monopoly for extended period. (Kumar & Nanda, 2017)

The scheme is very easy: first the company launches a drug product and obtains patent protection for it. Then, just before the end of the term of that patent, the company files a new patent for a *minor modification* in the original molecule that extends the overall term of protection. To put it in an example, consider an innovator firm named AstraPharma which formulates a new molecule for curing a particular disease. The company applied for patent

[3] Data exclusivity, Orphan drug exclusivity, Paediatric exclusivity, the 180-day exclusivity, Supplementary protection certificate

protection for this new molecule on 3 March 2001. Once the application is approved by the patent office, it will result in a patent that provides protection for the next 20 years, up to 3 March 2021, starting from the date of application. By July 2018, AstraPharma files another application for a minor improvement of the previous molecule. The patent office approves the application and it results in an extensive patent protection that will end in July 2025. With this new patent, a generic manufacturer can launch the generic version of the original molecule after the 3 march of 2021. The generic version cannot include the modifications that AstraPharma made to the molecule in July 2018. While for the future originator companies, after March 2021 they can build on innovation only using the previous technology without incorporating the new developments of July 2018. The different attributes of drug development that can be patented include *delivery profiles, methods of manufacture, chemical intermediates, formulations, packaging, biological targets, mechanism of action and method of medical treatment* etc. (Gupta, et al., 2010)

Although evergreening can occur in any industry, it is said to be more frequent in the pharmaceutical sector where patents cover such aspects of drugs. Firms utilise one of these attributes to obtain additional patents shortly before the end of the term of primary patent.

The debate on the economic, public health and policy aspects of "evergreening" has tended to be polarised. In summary, critics of the innovator pharmaceutical industry have argued that the "incremental modifications" behind these evergreening tactics are simply a low-risk way of cashing in more money on the success of established products. According to critics, this brings little or no health benefit at the expense of fragmenting the market and/or delaying generic entry, diminishing the rewards rightly due in respect of the originators' product and imposing strain on R&D resources that would be better applied elsewhere.

In reply those defending the industry have argued that what is complained of is in reality a consequence of parallel development programmes and improvement that results in greater therapeutic choice for patients, safer and more effective medicines and a valuable source of competition both during and after the patent life of the "breakthrough" product that exerts a beneficial influence on drug pricing. (Parker & Mooney, 2007)

It is not the purpose of this work to advance this debate but rather to step back and consider the right issues on which the debate is (or should be) founded. The next paragraphs introduce some of the most common practices of evergreening in the pharma industry.

1.5.2. Extensions and creation of 'next generation drugs'

A first typical strategy of evergreening that pharmaceutical companies apply is the use of a technically minor improvement in form of a *reformulation and repackaging of the formula.* Basically, the innovator company releases a successor drug with a different brand name and with minor changes in design, colour, dosage or else, in order to extend the overall term of highly lucrative blockbuster drugs and maintain monopoly for longer durations. Then, they pursue heavy marketing strategies on the promotion of such new drugs. This type of practice is persistent in this sector and there are plenty of famous cases in pharma history.

The most famous example of this strategy is AstraZeneca's Prilosec. It was the most profitable blockbuster of its time with US $6.2 billion/year and was used to treat heartburn. The CEO of AstraZeneca, Tom McKillop, faced one of the biggest dilemmas of large pharmaceutical firms. (Conley, et al., 2006) Within the year, the firm's patent for Prilosec (active ingredient omeprazole) was in expiration and it was more than a fact that the competition from other drug manufactures would be inevitable. So the solution to this faced problem was one of their other drug in the pipeline named Nexium, an improvement on the original Prilosec molecule. With this new idea, AstraZeneca had also the opportunity to choose between the introduction of its own version of generic omeprazole and/or introduce an OCT version of omeprazole that might tap into other markets. The main idea was to introduce and move the brand-loyal customers of Prilosec to the new version Nexium. AstraZeneca launched Nexium as the successor of Prilosec and claimed that it was more effective than Prilosec and other drugs in the same category. Even though later clinical trials showed that both were the same drug just with some minor changes in dosage, colour, and design, the success and profits achieved from the direct-to-customer advertising was remarkable. Later clinical trials[4] showed that both were the same drug just with some minor changes in dosage, colour, and design. Rather than investing huge amounts in incremental innovation, AstraZeneca spent a lot of money in the promotion of Nexium. This case confirmed one of the most negative effects of evergreening in pharma industry: a decreasing level of innovation. Several major U.S. retailers sued AstraZeneca, accusing it for using illegal tactics to maintain its monopoly over the heartburn medication Prilosec even after the drug's patent expired. In 2008, The District Court of Columbia (US) claimed the pharmaceutical major liable for used fraud and "exclusionary conduct" to hold on to its dominant position.

[4] (Plaintiffs v. AstraZeneca Pharmaceuticals LP, 2008) – See Table of Cases for Ref. number

1.5.3. The Rx to OTC switch

The OTC (over-the-counter) drugs are pharmaceutical products that do not require professional supervision and that can be safely administered by the patient status. In these cases, the innovator just needs to show the safety ratio to benefit to the FDA and whether it will be easy for the patient to self-administer the drug product. The OTC status has many benefits and between them we can list the opportunity for *direct advertising to consumers* through different channels such as advertising in television, magazines, retail displays, brochures and packaging without any restrictions which apply on prescription drugs.

The process of reclassifying a prescription drug to Over the Counter is termed as *Rx to OTC* switch. This is another strategy used by the innovator companies in order to maximize their monopoly over the blockbuster drug molecules. Normally, the consumer himself knows that the new OTC is from the innovator company which he knew before, so it would be preferred and choose that one. The effect is that there will be an immediate *undercut demand for the generic version* in the market. To picture this strategy with a real example we can nominate the Sanofi had originally developed Nasacort 24 h drug as an intranasal steroid and in 2014, after patent expiration switched it for OTC for the treatment of allergies. Nasacort received approval from the US Food and Drug Administration (FDA) to switch from prescription to OTC on October 2013, and today is still available on retail shelves all over US[5].The approval of the application by the FDA was considered by experts as a smart move that helped to expand Sanofi's OTC portfolio, which has been a key strategic sector for the company since 2008. This permitted the pharmaceutical major to acquire Chattem, the US consumer healthcare company, in March 2010, giving it a presence in the US consumer healthcare market.

1.5.4. The Pay for delay (reverse payments) settlements

Known as one of the *most anti-competitive strategies*, the pay for delay strategy has been unfortunately well established in the industry. The originators in order to prevent or delay the entry of cheaper generic versions until their cheaper generic version is firmly present in the market, sign agreement with the generic manufacturers to delay or give up on the market entry. It is a kind of settlement between the two parties in which the latter agrees to refrain from marketing its own generic version for a specific period of time in return of huge payments from the innovators themselves. These strategies definitely block the entry of generics and are

[5] The announcement of Sanofi's Healthcare Division: https://www.news.sanofi.us/2014-2-4-sanofis-consumer-healthcare-division-chattem-announces-nasacort-allergy-24hr-nasal-spray-now-available-without-a-prescription-in-the-us

considered unlawful and Federal Trade Commission and Antitrust agencies constantly look out for such deals. In 2008, the European Commission launched an inquiry[6] in the pharmaceutical sector trying to identify the reasons behind the alleged delays in the entry of the generics in the market and the declining number of new drugs marketed in the EU. The Commission examined 698 cases of patent litigation between originator companies and generic manufacturers and in 223 cases the parties agreed to a settlement between them. To solve disputes, parties start negotiating entry dates for the generic product, either at or before the branded drug's loss of exclusivity based on anticipated litigation costs.

Sometimes, patent disputes between innovators and generic companies settle. Most of these settlements start from patent challenges. Generics try to enter early in the market trying to prove that the originators patent is invalid. For postponing the generic entry, the originator drug company pays the generic manufacturer as part of the settlement.

As already introduced, in US generics can play the Paragraph IV card by assuring the FDA that it would not infringe upon the patent of a branded drug by proving whether that the patent was invalid or that the sale of the generic drug itself would not infringe the already granted patent.

This rule wasn't applied by Solvay Pharmaceuticals which filed a New Drug Application and received a patent in 2003 for its brand-name drug, Androgel. Actavis and Paddock, two generic drug makers filed ANDA applications for their generic versions of Androgel within the same year. Solvay chose to sue Actavis for patent infringement, but the FDA chose to approve its generic drug even though the dispute between two companies continued for three years. But after the approval, Actavis took another direction. Rather than bringing its generic drug to the market, the generic drug company entered into *a reverse payment settlement* with the originator Solvay. Under the terms of the agreement, Actavis would keep its generic drug off the market for a specified number of years and also agree to promote Androgel to doctors. The Federal Trade Commission filed suit[7], alleging that Actavis had unlawfully abandoned its patent challenge by agreeing to share in the "monopoly profits" of Solvay, and withdrawing its generic drug from the market. In *FTC v. Actavis* (2019) the Court claimed that the reverse payment settlement between the parties was subject to antitrust law because they were delaying the entry of the generic competitor. It's incredible how many are the infringement cases in the pharma's history regarding these pay-for-delay settlements.

Chapter 3 focuses especially on three of them, trying to bring these strategies to the table and understand how they get performed and what is their impact to the industry.

[6] See Commission Decision of 15 January 2008 initiating an inquiry into the pharmaceutical sector pursuant to Article 17 of Council Regulation (EC) No 1/2003, OJ 12008] C 59/0

[7] (FTC v. Actavis, 2019) – See Table of Case for Ref. number

1.5.5. Establishment of generic units by innovator companies

Over the past decade, Big Pharma has acquired small generic units to *expand their business model.* (Kumar & Nanda, 2017) In order to compete with the generic players, originator companies show an increasing interest in *setting subsidiaries and entering partnerships with major generic companies* and building in this way a position in generics before the end of the term of the parent patent and before the competition from rival generic players rise.

For example, Novartis, the well-known Swiss pharmaceutical company, established Sandoz as a subsidiary unit for manufacturing generic drugs and thanks to this strategy saw its profits in generics rise up to US 7.5 billion dollars in 2009. The division was established in 2003, when Novartis united all of its generic's businesses under the name Sandoz. This new Business Unit would have the aim to produce high-quality generics for both the pharmaceutical and biotechnology industry at competitive prices. By having their generic version associated with their expertise in production and formulation, originators can choose to imply defensive pricing strategies. Once the drug goes off patent, innovator companies may respond to the generic competition by decreasing the price of their generic version or by introducing improved generic versions at a lower price that may leave generic competitors a generation behind. As long as this type of strategy delays or block generic entry, it is considered part of evergreening tactics.

1.5.6. Combining two or more drug products

The United States and the European Union have specific laws that provide supplementary patent protection in case of combination of drugs. Knowing that, innovators are launching a mixture of soon to go off-patent drugs with another drug to supply treatment for 2 closely associated medical conditions. This sort of combination may attain the identical position which the branded drugs attained during the exclusivity period and such follow-on products provide a troublesome competition to the generics. (Kumar & Nanda, 2017) Also huge amounts of cash is being pumped to the brand company to make sure that their product is prescribed over the older versions, regardless if the combined product lacks experimental evidence of enhanced efficacy and safety. Venlafaxine, an antidepressant medication was earlier marketed as Effexor and sold by Pfizer. The drug showed some important side-effects to patients. Pfizer reduced these side effects by suggesting that the drug was administered in extended release form. In spite of this fact, the combination of Venlafaxine and the extended release version of venlafaxine to overcome the side effects two separate patents were granted by the patent owner for the two versions of venlafaxine which in turn delayed entry of generics by two and a half

years. Clinical trials later showed that the combination was an obvious knowledge and no new innovation was brought in. The evergreening patents were later declared invalid.

1.5.7. De-listing reference listed drug from the Orange Book (USA)

As previously mentioned in the paragraph related to the US patent law, every innovator drug that is patented gets entry into the Orange Book and before a generic gets approved it is necessary for the ANDA filler to prove that the generic version is comparable to the innovator drug. So basically the innovator drug serves as a reference for the launch of the new generic version. Delisting it from the Orange Book and "cancelling" in this way the possibility for the generic manufacturer to use the innovation as a reference is another evergreening tactic to significantly delay the entry of generics. A company that practiced this tactic in the pharmaceutical industry was Ferring which owned a patent for DDAVP tablets, containing active ingredient as desmopressin acetate, a medicinal for diabetes. Glenmark, a major Indian generic company was waiting for Ferring's patent expiry in order to launch its generic version in the US market.

In an effort to discourage Glenmark's marketing of launching its generic version, Ferring applied to FDA for de-listing the patent from Orange book. In front of this fact, Glenmark petitioned against the de-listing (Glenmark Generics Ltd. v. Ferring B.V., 2014) claiming it was an unlawful practice with the aim of blocking generic versions of desmopressin acetate. The Court[8] accepted Glenmark claim and its generic was approved.

[8] (Glenmark Generics Ltd. v. Ferring B.V., 2014) – See Table of Cases for Ref. number

II.

The Economic and Geographic dimensions of the Market

2.1. Background

For more than a year now, pharma companies are in the midst of an unprecedented change. While this was true even before COVID-19, the pandemic and the ensuing economic downturn have brought major challenges in the way organizations look at the road ahead. This pandemic has spurred the adoption of technologies and other innovations to support new solutions. While creating opportunities for the biopharma industry to demonstrate the industry's value, it also has led to potential short- and long-term challenges. Global market growth, strengthening R&D, and transformation of digital and IT are currently the top strategic priorities for biopharma companies, and will continue to be so in the future. This chapter keeps however its focus on the evergreening strategies and the secondary patenting, in order to identify their economic and social impact.

This impact is definitely influenced by the market size and also the operating model of the pharmaceutical companies. Big pharma companies' business model in the last decades has transitioned from the *one-size-fit-all medicine* to a *specialty one*. This evolution has been dictated by various trends and operational challenges that big pharma had to face. To get a clearer full picture of the dimensions of this market, as one of the most significant ones in terms of investments and innovation, we look through data, latest trends, and the future perspective of the pharmaceutical industry. Between these numbers, unfortunately, it is difficult to measure the impact of evergreening practices due to the complicated nature of these strategies. Literature itself tries to highlight and measure somehow the economic and social impact that these practices have.

Regulators, especially those in the main markets such as USA and EU, acknowledge these effects and have introduced provisions on trying to limit the expansion of the evergreening tactics on the pharmaceutical market. But these provisions seem uncomplete and not well specified. Are these the actual regulatory loopholes that consent pharma undertakings to exploit evergreening?

Keywords: *business model, literature review, social welfare, provisions, evergreening*

2.2. Big Pharma's business model

The pharmaceutical industry has always been a prisoner of its past successes. While the business environment has been changing drastically in the past years, the pharma companies' business model took a long time to upgrade.

Traditionally, most big pharma's undertakings have done everything by themselves, from Research and Development (R&D) to marketing and commercialization of their products following a *"profit alone"* path. The historic model was that of a *large diversified company* with large R&D footprints in multiple global hubs around developed countries and primary care businesses driving a huge portion of revenues. Only a minimal contribution was coming from the emerging economies. Referring to the mid-90s and the early 2000s period, there was a push for the *"bigger is better"* model. In fact, the biggest merger and acquisitions operations were registered at that time, starting with Astra and Zeneca merger, Pfizer and Warner-Lambert, Glaxo and SmithKline, Sanofi and Aventis, culminating in 2003 with the Pfizer-Pharmacia merger. (Gautam & Pan, 2016) This wave of mega acquisitions was largely triggered by the declining R&D productivity and pharmaceutical firms were using the economies of scale as one justification for integrating the dispersed research units around the merged companies. Scale would help companies to diversify the risk of uncertain investments in R&D. Big Pharma believed that it would boost their power to launch new products, expand their in-licensing capacity and would help them exploit next generation technologies.

The 1995-2005 period is known also as the blockbusters' drugs era for big pharma. In fact, the largest mergers in the industry were primarily driven by single blockbusters[9] which were at the basis of how pharma companies measured their productivity and profitability. This because of the huge returns that these blockbusters would bring in. An average drug is expected to deliver only 5% return on investment (ROI), while a successful blockbuster can bring up to 10 - 20 times as large returns. The majority of a company's investment was on creating these blockbuster products. At the time, the biggest selling drugs in the industry were primary care therapy drugs and accounted for roughly 80% of revenues for most big pharma portfolios. The leading major markets were North America and Europe and none of the big pharma companies had more than 20% of revenues deriving from the emerging markets.

Soon things started to change as the pharmaceutical industry was facing new challenges in an always intensive and competitive environment.

[9] Blockbuster drugs - drugs that could achieve global sales for more than US $1 billion.

Table 2 - The Transition from Massive-to-Lean strategy

Massive-to-lean strategy.

Expanding organizations		Company	Leaner, focused organizations	
Astra and Zeneca merger **Acquired MedImmune**	1999 2007	AstraZeneca	2014	Narrow therapy areas from five to three
Merged with Schering	2006	Bayer	2014	Divested material science and specialty chemicals businesses
Acquired biologics expertise through Medarex	2009	Bristol-Myers Squibb	2008 2009 2014	Divestiture of medical imaging and wound care businesses Spin-off of nutrition business Mead-Johnson Divested diabetes business to AstraZeneca; focus on three therapy areas
Merger of GlaxoWellcome and SmithKline Beecham	2000	GlaxoSmithKline	2014	Swapped oncology for consumer health and vaccines with Novartis
Acquired Schering-Plough	2009	Merck	2014	Divested consumer health to Bayer
Merger of Ceiba-Geigy and Sandoz	1996	Novartis	2014	Divest animal health to Eli Lilly; swapped vaccines and consumer health for oncology with GSK
Acquired Warner Lambert **Acquired Pharmacia** **Acquired Wyeth**	2000 2003 2009	Pfizer	2006 2012 2012 2015	Divested consumer health to JNJ Spin-out animal health unit (Zoetis) Divested nutrition business to Nestle Acquired Hospira for biosimilars On track to split into three businesses: innovative pharma; established products; oncology/vaccines
Acquired biologics expertise through Genentech	2009	Roche		
Merger of Synthélabo and Sanofi **Merger of Aventis and Sanofi**	1999 2004	Sanofi	2011	Acquired biologics expertise through Genzyme
		Abbott	2013	Split into two companies: Abbott for diversified healthcare products and AbbVie for innovative pharma business
		AbbVie	2015	Acquired Pharmacyclics for oncology business
		Baxter	2015	Divested innovative pharma business as Baxalta

Source: Gautam & Pan (2016)

The blockbuster model, considered the most successful one, started to show major failures. Further declining R&D productivity, rising costs of commercialization and shorter exclusivity periods had driven up the average cost per successful launch up to $1.7 billion and reduced average expected returns on new investments to the unsustainable level of only 5%. Several studies have reviewed the industry's declining productivity challenges, the transitioning of commercial models and the growth of emerging markets as key revenue contributors created a natural environment to lead to the creation of a fundamentally *new business model*. And in fact, and as seen in *Table 2*, recent years have seen a significant change in the operating model of the pharmaceutical companies. The current big pharma model is transitioning to that of a *lean, focused company* with a research footprint within innovation bioclusters and a growing revenue

stream from specialty products, biologics, and emerging markets. (Gautam & Pan, 2016) In an interview for "The Guardian" in 2008, J.P. Garnier, former chief executive of GlaxoSmithKline pointed out the specificity of pharma business claiming it as a "business model where you are guaranteed to lose your entire book of business every 10 to 12 years."

Gautam & Pan (2016) in their article "The changing model of big pharma: impact on key trends" analysed data in order to understand the changes and any trends over the past two decades. Their data review revealed *4 main trends* that big pharma's operating model was going through: *from massive to lean; from hubs to hotspots; from West to East and from primary to specialty.*

Starting from the late 2000s, pharmaceutical companies began to embrace a leaner and focused model by divesting non-core assets and focusing on their areas of strength. For example, GSK and Novartis divided their businesses to create focused organizations with GSK increasing the focus on consumer health and vaccines and Novartis on oncology. This period witnessed still big acquisitions but this time they were largely driven by strategic rationale and to build complementary capabilities rather than a desire to be 'massive'. The earlier wave of mega-acquisitions built mega hubs all around the globe that were used as research units for high-throughput technologies that later on started to create *self-contained silos*. So, there was the need for a shift from these big hubs to bioscience hotspots - the innovation clusters such as Boston, San Francisco, San Diego, Cambridge, London, Shanghai - which are the key centres for producing breakthrough science.

With the coming of closer patent expiry of products in the USA, Canada and the EU pharmaceutical firms as AstraZeneca, Pfizer, GSK etc., got convinced to grow their portfolios to comprise at least 25% of the total revenues from the emerging countries. There was an immense *shift towards the Eastern countries* during the last decade with growth of their largely primary care business in these countries. Not just commercially, the emerging countries, especially India and China, have also seen an increase in innovation capabilities. With the support of significant government and private capital, a growing talent pool of experienced Western-trained returnees and an evolving life science ecosystem, these countries are progressing as hotspots for global innovation. In China for example, most big pharma companies have already established their research units in Shanghai.

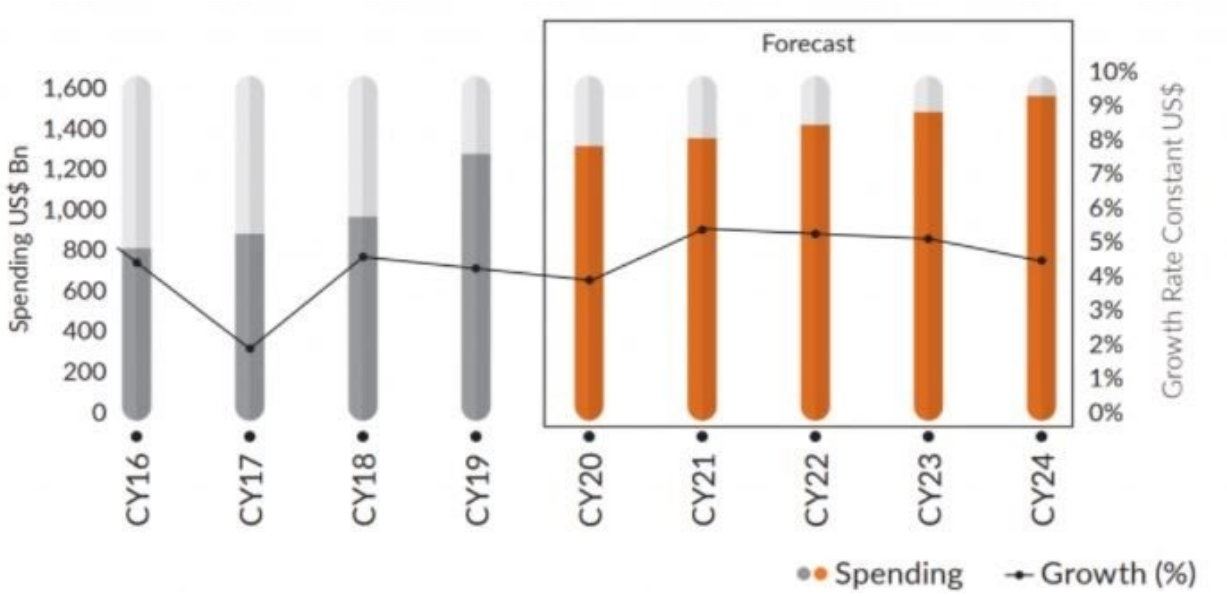
On the other side, the growing understanding of the disease's biology, the technology innovation for biologics and the favourable regulatory frameworks for such medicines shifted big pharma away from developing primary care and small-molecule medicines towards specialty medicines and biologics for high unmet medical needs, over the past decade. In 2014 for example, primary care medicines only accounted for approximately one-quarter of new FDA-ap-

proved new molecular entities (NMEs) according to the consulting firm PWC's Health Research Institute study. All these changes have definitely contributed to a more efficient business model for the pharmaceutical firms. But still, this upgraded business model cannot save the industry from facing significant challenges such as the continued patent expiration, the R&D productivity, pricing and reimbursement, regulatory barriers etc. Some of these challenges are linked to the emerging countries where therapies continue to be expensive and new pricing and reimbursement strategies are needed to make them more affordable for patients. On the other hand, positive steps have been made on the convergence of IT and healthcare. With new players such as Apple and Google, big data and mobile health are starting to transform healthcare and diagnostics in a significant way. Big pharma is adapting to the *'beyond-the pill'* model with medicines accompanied with apps and wearable devices to help patients monitor key parameters. The increasing investments, the growth of technology start-ups, and the expiry of several key patents, as well as increasing inter-organizational collaborations and a favourable regulatory environment, are definitely spurring innovation across the pharma industry trends.

2.2. Going through the numbers

All the trends that affected the development of the pharmaceutical companies' business model have been canalized not only into bringing new medicines that can improve health and quality of life for patients but also in the growing profits. In fact, the research-based pharmaceutical industry is one of the most important key assets of the global economy.

Figure 3 - The pharmaceuticals' growth (2016 – 2024)



Source: Data provided from *Pharmaceuticals Global Market Report 2021*

If we look at the forecasts[10] of the *Pharmaceuticals Global Market Report 2021* of the Business Research Company the market has been growing from $1228.45 billion in 2020 to $1250.24 billion in 2021 at a compound annual growth rate (CAGR) of 1.8% and is expected to expand at a CAGR of 3-6% to $1.5-1.6 Trillion by 2024. The market is expected to reach $1.7 Trillion in 2025 at a CAGR of 8%.

The growth is mainly based on the returns on investment from R&D. Pharma companies have been rearranging their operations in two different directions: chasing the volume growth in emerging markets - known as *pharmerging* markets - on one hand, and launching high-end specialty innovative products in the developed markets on the other hand. Their key Research & Development focus is immunology, oncology, biologics and cell and gene therapies. Global R&D spend is estimated to grow at a CAGR of 3% by 2024, lower than that of 4.2% between 2010 and 2018, partially driven by companies' focus on smaller indications, with lower clinical development costs. These smaller indications, known as *specialty medicines,* help on treating chronic, rare and complex diseases and have already made significant difference in patient outcomes. Their growing demand has been a steady growth driver in global pharmaceutical spending during the last decade, mostly in the developed markets[11].

They are likely to account for 40% of global pharmaceutical spending by 2024, with the fastest growth expected to be in the developed markets, where contribution of specialty products is likely to cross 50% by 2024. According to *Pharmaceuticals Global Market Report 2021*, the pharma spending in these markets grew at ~4% CAGR between 2014-19 and is estimated to grow at about 2-5% CAGR to reach US$985-1015 Billion by 2024. The developed markets accounted for ~66% of global pharmaceutical spending in 2019, with North America itself accounting for around 45% of it.

The uptake of specialty products is slower in pharmerging markets due to absence of or inadequate prescription insurance coverage for the masses. Some latest generation innovative medicines are likely to be launched in these markets, but given the high price of such products, the uptake may be limited. Instead, growth in pharmerging markets is still powered by higher volumes for branded and pure generic medicines with increasing access among the population. Pharmerging markets are likely to continue registering faster growth than developed markets, with a 5-8% CAGR through 2024, lower than the 7% CAGR recorded during 2014-19.

[10] The data and analysis throughout the report is sourced using end notes. The report covers market characteristics, size and growth, segmentation, regional and country breakdowns, competitive landscape, market shares, trends and strategies for this market.

[11] The prices of specialty medicines are very high so the majority of these products' uptake is likely to be in markets with robust reimbursement systems.

The second largest region accounting for 26% of the global pharmaceuticals market is Asia Pacific followed by Africa as the smallest region. *Tab.3* reflects a summary of all the main regional trends starting from Y2019 with forecasts for Y2024.

Table 3: Regional Data Summary

Region/Country	2019 *(in US$ bn)*	2014-2019 CAGR	2024 *(in US$ bn)*	2019-2024 CAGR
USA	510	4,30%	605-635	3-6%
WE5	174	4,00%	210-240	3-6%
Germany	52	4,90%	65-75	4-7%
France	35	1,60%	38-42	0-3%
Italy	34	5,10%	41-45	3-6%
UK	29	4,50%	37-41	4-7%
Spain	25	4,00%	30-34	3-6%
Japan	87	-0,20%	88-98	(-3)-0%
Canada	23	4,60%	26-30	4-7%
South Korea	16	7,30%	21-25	5-8%
Australia	12	3,50%	13-17	3-6%
Developed markets	**823**	**3,80%**	**985-1015**	**2-5%**
Pharmerging	**358**	**7,00%**	**475-505**	**5-8%**
Other	**71**	**4,80%**	**85-95**	**2-5%**
Global	**1250**	**4,70%**	**1570-1600**	**3-6%**

Source: Data provided from *Pharmaceuticals Global Market Report 2021*

With oncology as the main R&D focus area in the biopharma industry, the prescription drug sales are expected to grow at the forecast annual CAGR of 6.9% by 2024. While for the Consumer health products that do not require prescription from healthcare professionals and can be purchased Over-the-Counter (OTC) from a pharmacy store, the market is projected to grow at 4.3% CAGR by 2024. Today's informed patients believe in taking better healthcare decisions and are engaging in effective health management through digital tools.

In terms of players, the pharmaceutical industry is still dominated by the traditional players ones. The Worldwide Prescription Drug Sales number one spot in 2024 is reserved to Pfizer which has once again pushed ahead of Novartis and Roche. Novartis jumps to the number two spot after exhibiting 2.3% CAGR between 2018-24 as opposed to Roche's 0.8% CAGR. AstraZeneca has also shown impressive 7.7% CAGR, due to breakthroughs in the Chinese market and high sales of its oncology products.

When focusing instead on the most innovative pharma companies and value creation, the tenth annual *Pharmaceutical Innovation Index*[12] by IDEA Pharma, sees Eli Lilly at the top the of industry for the first time. The pharmaceutical company's raise can be attributed to multiple clinical data wins, and notable novel FDA approvals, as well as strong performance of recently launched drugs.

Table 4: Pharmaceutical Innovation Index 2021

2021	COMPANIES	CHANGE	2020
1	Eli Lilly	+4	5
2	Roche	-1	1
3	Regeneron	+7	10
4	Seagen	-	NR
5	Incyte	-	NR
6	GlaxoSmithKline	+5	11
7	Sanofi	+10	17
8	AstraZeneca	+1	9
8	Pfizer	+7	15
10	Gilead Sciences	+5	15
10	Novartis	-7	3

Source: IDEA Pharma

The Index defines innovation as *"return on invention"*, and measures the pharmaceutical company's ability to deliver innovation to patients, by objectively evaluating performance based on a rolling five-year period (2015-2020), and operates on the simple premise*: if you gave the same molecule to two different companies in early phase, which would make the best of it?*

As can be seen by *Tab.3*, the top 10 Innovation includes new players – Seagen and Incyte - as well as a significant rise for Regeneron, suggesting that smaller companies are, more than ever, able to bring their products to patients without a traditional large pharma partner. (IDEA Pharma, 2021) According to the index, the success is achieved by developing meaningfully great medicines and supply them to patients. More than ever, in this industry, excellence is unevenly distributed because not every company is equally able to realise the same value in their pipeline.

[12] The Pharmaceutical Invention Index by IDEA Pharma introduces a ranking of the industry's best pipelines, evaluating novelty and meaningful development, across first in class development, breakthrough medicines and more.

2.2.1. The future of Pharma & IT

As in all the other industries, pharma companies are also recovering from the COVID-19 impact, which had earlier led to restrictive containment measures involving social distancing and remote working that resulted in operational challenges. On the other, further challenges are raised due to the fact that the population profile of most countries is becoming older. According to the *United Nations*, the share of population over the age of 65 in the global population increased from 8% in 2015 to 9% in 2019 to around 703 million of people worldwide. The rise in the aging population has increased the patient pool of many chronic diseases such as rheumatoid arthritis, hypertension, diabetes, and cancer. This increased the demand for pharmaceuticals used in the treatment of these diseases, significantly impacting market growth.

On the other hand, leveraging uninterrupted access to information, the consumer is wielding growing power, leading to creation of new market segments and new models of healthcare. Today's informed patients believe in taking better healthcare decisions and are engaging in effective health management through digital tools.

The continuous progress in artificial intelligence and machine learning will carry important implications within data science for optimisation of decision-making, ethical handling of patient privacy, and proper use and management of extensive data sets. The main source in generating important patient insights will be genomic data, as it helps the genetic basis of diseases and their treatment with targeted gene-based therapies. The use of artificial intelligence in collecting accurate patient experiences, managing their historical records, and *augmented, virtual, and mixed reality (AR, VR & MR)* solutions is not a distant future anymore. On this day, quite a third of pharma start-ups are working on finding new software solutions and flexible pharmaceutical manufacturing to provide access to basic medicines in many areas of the world.

Finally, digital technologies have played a big role in supporting the communication between patients and doctor during the COVID-19 period since a face-to-face consultation seems difficult. Experts cannot agree whether this trend will continue even after the pandemic.

2.3. Back to evergreening: Implications on innovation and price competition.

The previous paragraphs aimed to display the dimensions of the pharma industry, as one of the biggest key assets in the global economy. Between those numbers, unfortunately, we could not identify the impact of evergreening practices due to the difficult nature of these strategies.

A recent conducted study regarding the top twelve drugs by gross U.S. revenue found that pharmaceutical innovators granted on average up to seventy-one patents for every single one of them. This is a significant number considering that they revolve around the same active ingredient. The debate around the evergreening phenomena is a heated one because the reasons from both sides can be considered valid. Both parties, critics, and defenders of evergreening put pressure on their own arguments. On one side, critics believe that by obtaining secondary patents through evergreening, pharmaceutical undertakings unfairly shield a pharmaceutical product from generic or biosimilar competition, thereby resulting in higher prices. And in view of evergreening critics, more of these secondary patents are of questionable validity. Also, the cost of litigation which is around $1.8 million doesn't help in challenging these patents. Thus, when a product is protected by comparably weak patents, critics argue that the cost of invalidating those patents strengthen the branded products' position in the market and can lengthen its effective period of exclusivity. Defenders on the other hand respond that the term ‘evergreening’ is a term ‘inherently pejorative’ because it creates the impression that pharmaceutical companies are exploiting the patent system. They say that there is nothing suspect for the secondary patents which just any other patent must meet the same requirements for patentability and pass through the same examination procedures of any other patent. According to them, the value of a follow-on patent is comparable to or even might exceed that of a primary patent. Defenders also argue that the ability to receive a patent on a later-development formulation provides a significant incentive to address problems with the original formulation. The original formulation of Lumigan for example, which is used to treat glaucoma, resulted with strong side effects that lead patients to stop the use. Researchers subsequently developed an improved formulation with significant decreased risk of side effects. Without the possibility of patent protection, defenders say that it would have been impossible to perform this sort of research due to the significant costs involved.

Moreover, pharma manufacturers themselves argue that the secondary patents will obviously be narrower than the primary patents because they are actually improvements to these primary patents. Doctors and patients can then decide whether the benefit conferred by a product covered by a secondary patent is worth the increased cost over the generic versions of the product formerly covered by the primary patent.

Secondary patents are also defended on the grounds of being necessary to recoup development costs. As mentioned before, even though the patent term is generally 20 years, the effective market exclusivity is shorter than that, 12-13 years on average.

For the cost of litigation that critics bring up front, defenders on the other side say that the recent congressional action has decreased the cost of challenging patents, decreasing the impact of these later-filed 'evergreening' patents. The median cost for litigation and IPR to the final decision is $324.000. Thus, IPR provides a relatively fast and relatively inexpensive method to challenge issued patents, particularly when compared to litigation in the courts. The direct financial impact of the evergreening practices unfortunately cannot be identified in the numbers presented in the previous paragraph for the pharmaceutical market. Studies have tried to measure instead the effects on the innovation level of the industry of these practices, the effects on the price competition and on the social welfare.

In chapter 1, we introduced the debate on the effects of patents on innovation, independently of the theoretical deadweight loss associated with the monopoly position. As a consequence, it is indisputable that strategic patenting has its effects on the innovation level. While a patent grants a monopoly right to recoup R&D costs, a secondary patent derived from an evergreening practice not only guarantees that but also is used to prevent other future originator competitors from inventing. The extension ends up limiting sequential or complementary innovation and does not grant much incentive to venture into new R&D while it ends up blocking rivals. Thus, consumers are stuck with old high-priced drugs with no alternative to measure efficiency.

The second aspect of evergreening that is of interest in competition policy is its price effect. From the theory of the imperfect market structure, the originator company is naturally interested in influencing the market price above the marginal cost. And with the evergreening practices, by getting secondary patents this influence can get prolonged. In this way it delays the generic entry, which entrance has important effects on the falling of prices. To stress the price effect, it is important to consider how it affects public health, particularly the price of medical care. Although empirical results seem to be unclear about that, theoretically, the monopoly price reflects in the form of a high medical cost. And the effect of the increased medical costs is important in both developed and the emerging countries. In the developed economies, it reflects in the form of increased cost of social security. For developing countries instead with problematic medical insurance, these expensive drugs are considered as a form of social exclusion and may negatively correlate with life expectancy. Strategic patenting ends up imposing a huge burden on taxpayers in the form of high health expenditure/budgets.

2.4. A literature review on pharma evergreening

Even though providing data that measures the financial effects of evergreening in pharmaceuticals in terms of social welfare or increased profit margins for the big pharma is very difficult, many have been the authors that study these tactics in the industry. For this thesis, we made a literature review that identified 20 publications, which included 18 papers and 2 reports from FTC and EC. The oldest one is from 2005. The literature research was based in Google Scholar and Scopus Library. The used keywords were specifically '*evergreening' 'evergreening in pharmaceuticals' evergreening in the pharma industry' 'secondary patenting'*. These synonyms emerged subsequently after reading papers.

By far the most cited paper is by Hemphill & Sampat (2012) with a total of 227 citations and an average of 25 annual citations. The article appeared in health-related economic journal, Journal Health of Economics.

Bansal, et al. (2009), Dwivedi et al.(2010), Thomas (2009) and Wyllie (2005) were mostly concerned in the definition of the evergreening practices in pharmaceuticals from the point of view of originators. These papers were published in cross-disciplinary journals related to legal, and medical contents. Very few of them appeared in mere business-related journals. We can cite Jain and Conley (2012) as one of the few ones with managerial focus on IP.

In contrast, there were less papers and studies available regarding evergreening strategies by generics. For the purpose of this thesis we identified specifically the analysis of Gaudry (2011) and Higgins and Graham (2009) which are against too much possibilities given to generic drug makers to enter the market. The authors report the Paragraph IV of US patent law that allows firms to bring generics to the market, even before the originator has its parent patent expired. Another publication by the Federal Trade Commission (2002) is included in this literature review as it examines whether the 180-day exclusivity incentivised by the Hatch-Waxman Act is susceptible to delay access to generic alternatives to branded drug products.

As for critics and defenders of these practices in the industry, we identified two crucial papers from Vines & Faunce (2011) and Leitzan (2020) who claimed the need of breaking the evergreening myth as a strategy with negative impact. While studies criticising these tactic were more frequent. Most articles are concerned on how the national policy level allows space for these strategies which have a negative impact on costs for health insurance system of a specific country. Specifically for the US, Hemphill and Sampat (2012), Darrow (2010), Newsome (2017), Beall et al. (2017) were some of the most cited papers on such matter. Addressing the EU, we identified one report by the European Commission addressing the situation in EU as a whole (EC, 2008). While, moving on in India, as a country which attracted interest of this work, we found Kumar et al. (2009), Bansal (2009), Nair (2008) addressing the general situation while

the paper by Rathod (2010) offers a comparative analysis of the evergreening practices across two or more countries: in this case among Canada, India, Australia, Philippines and Thailand. Chalmers (2006) examines evergreening behaviour in the US - Australia Free Trade Agreement. Even though evergreening behaviours are fully studied by academic literature, very little quantitative data is available with patent statistics. The analysis remain mostly descriptive.

2.5. Provisions in USA and Europe to prevent Evergreening

Evergreening is influenced by three fields of regulation: the pharmaceutical regulatory law, patent law and competition law. Finding an equilibrium between them is difficult since they pursuit different policy objectives. A heated debate in aligning the intellectual property law and competition law in the context of pharmaceutical patent is still open. This complicated relationship can lead to difficulties in identifying and applying the competition rules in case of evergreening.

2.5.1. EU provisions against evergreening

In the European Union the patent laws are still too lenient and there are not much laws concerning ever-greening.

When a dominant position has been established, the analysis turns to the assessment of whether that position has been abused. How can we distinguish legitimate from illegitimate behaviour? A risk associated with applying Article 102 too aggressively, and especially in relation to exclusionary conduct, is that competition is chilled rather than encouraged. Such a result would obviously be counterproductive: a law designed to promote competition should not have the effect of diminishing it. Article 102 (b) states that conduct consisting of "limiting production, markets or technical development to the prejudice of consumers" is an abuse. This is the more traditional sort of exclusionary abuse. But more subtle, non-price strategies aimed at excluding competitors may also be abusive, e.g. patent litigation, use and abuse of regulatory procedures and launch of second-generation products. Lately, new forms of abuse have been identified under Article 102. One of them is evergreening. Even though a notable amount of doctrine has been published on the concept of abuse of dominant position, the meaning and scope of Article 102 in relation to evergreening is uncertain.

The consideration of evergreening under Article 102 is still uncertain as it lacks clarity between the lawful and unlawful abuse of the abuse of the dominant position in relation to evergreening as patent laws being specific to a country therefore a community law such as the Article 102 cannot challenge a country's patent law, this is major allegation made by those convicted of the abuse of the dominant position. Moreover, a patent is an exclusive right granted to the patentee

and the patentee has the right to exploit the patent for monopoly, so this does not necessarily count as the abuse of dominant position. Evergreening seems to be forced fit into the scope of Article 102, so this article needs a narrow and clear definition to fit evergreening since the present definition is too broad and the exploitation of the provision seems inevitable.

Another aspect of the application of Article 102 to evergreening is that pharmaceutical product markets have been narrowly defined, for example in AstraZeneca, making it easier to become dominant. Classical abuses take place on the market. On the contrary, evergreening does not. Instead, evergreening usually takes place in a regulatory context which has an effect on the market. As been described, the effect of evergreening may be to exclude or delay generic competition (an exclusionary abuse) but instead of creating economic barriers to market entry, as most of the classical abuses do, evergreening creates legal barriers. Thus, the exclusion of competitors is not a result of a pricing policy or any other exclusive practice, but merely the use of regulatory framework. Still, the effect of the conduct will take place on the market, just as the classical abuses. This should not cause any problem when applying Article 102 to evergreening. Article 102 prohibits any conduct that has an effect on the market. It is settled case law that the abusive conduct can take place in market different from the one where the effects are caused. It follows that the conduct can take place outside the market but still be abusive, as long as the conduct has effects on the market.

2.5.2. USA regulations against evergreening

In USA, the Hatch-Waxman Act (Patent Term Restoration Act) of 1984 was enacted to create a balance between the generic and the brand drug industry through certain provisions useful for both the generic manufacturer and the innovator companies. The underlying fact behind the scheme is that if the innovator drug is already approved then, to obtain market authorization and to launch its generic version, a generic company is required to demonstrate an identical biological effect rather than repeating clinical trials all over again. To balance the interests of the innovator companies the act requires generic applicant to choose one of the four certifications in relation to the patent status of the competing generic drug:

- Paragraph I: Drug is not patented
- Paragraph II: Drug patent has expired
- Paragraph III: Patent will expire by the time the generics drug hits the market
- Paragraph IV: Patent won’t be infringed, or the patent is invalid

The Hatch - Waxman Act in this work will be at the basis of our analysis regarding evergreening. Through this Act, a new procedure was introduced under which an ANDA application can be filed by the generic drug manufacturer to the US Food and Drug Administration (FDA) looking for marketing authorisations for the generic's versions. ANDAs are eligible for two types of exclusivity periods: 180-day 'patent challenge' exclusivity and 180-day competitive generic therapy exclusivity. On the one hand, 180-day patent challenge exclusivity provides ANDA applicants with an *incentive to challenge a listed drug's patents by providing 180 days of exclusivity to the first applicant that submits a substantially complete application containing a 'Paragraph IV' certification to the listed drug's patent or patents.* (Kracov, et al., 2020) During the exclusivity period, which starts on the date of the first commercial marketing of the ANDA, the FDA may not approve an ANDA containing a Paragraph IV certification that references the same listed drug.

The filing of an ANDA with a Paragraph IV certification with regard to a patent is sometimes referred to as an 'artificial' act of infringement because the generic company has not yet sold a product covered by any of the Orange Book-listed patents. (Kracov, et al., 2020) Within 20 days of the FDA's acceptance of an ANDA containing a Paragraph IV certification, the ANDA applicant is required to provide written notice to the NDA owner and each owner of the challenged patents that the ANDA has been filed along with the ANDA filer's detailed basis for its opinion that any of the listed patents are invalid or will not be infringed. (Kracov, et al., 2020)

If the NDA owner files an infringement action within 45 days of the receipt of a Paragraph IV notice, FDA approval of the generic application is stayed for a *period of 30 months while the patent dispute is litigated*. For new drugs that have NCE exclusivity (explained in Section III), the stay of FDA approval extends until seven and a half years after NDA approval. A court may order that this period be shorter or longer 'because either party to the action failed to reasonably cooperate in expediting the action'. (Kracov, et al., 2020)

The 30-month stay of generic approval provides time for the NDA owner and ANDA filer to litigate patent issues prior to final FDA approval of the ANDA and therefore prior to sales of the generic drug. If an Orange Book-listed patent is held valid and infringed, the district court will order that the effective date of generic approval will be not be earlier than the expiration date of the patent. The district court can also grant injunctive relief to prevent the commercial manufacture, use, offer to sell or sale within the United States, or importation into the United States of the infringing product and can also award monetary damages if there has been a commercial sale of the generic product. No statute currently specifically forbids evergreening. Instead, substantive patent law, particularly the law of obviousness, provides limits on whether

the PTO may grant later-filed patents. Specifically, a patent may not be granted if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the patent application was filed. The Supreme Court has not articulated a specific test for whether an invention would have been obvious, instead preferring a flexible approach that takes the facts and circumstances of the state of the art into account. The Court has identified, however, some situations in which an invention likely would have been obvious. For example, if the invention involves "the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement," the invention likely would have been obvious. At bottom, if the invention is "a predictable variation" of what came before, then the law of obviousness "likely bars its patentability." Other doctrines also affect the viability of later-filed patents. Because the patent statute limits a person to "a patent" for a new invention, a single patentee may not obtain a later patent that covers the exact same invention as an earlier patent. This doctrine is referred to as "statutory double patenting" because it derives from the patent statute and prevents patenting of the same invention twice by the same inventor. The courts have extended double patenting to bar an inventor from patenting obvious variations of his earlier patents as well. This second form of double patenting, referred to as "obviousness-type double patenting," prohibits a later patent that is not "patentability distinct" from an earlier commonly owned patent. In other words, the doctrine bars a patent owner from receiving a patent on an obvious variation of one of its earlier filed patents.

III.

India's tryst with evergreening: a battle or opportunity?

3.1. Background

India has been for long a pioneer in the developing world for attempting to adapt its pharmaceutical patent law to take account of domestic health needs and to be in line with its level of development. This country provided an example in patent law also for other developing economies such as Argentina and Brazil. With its established export-oriented pharmaceutical industry complemented by civil society awareness, India has been at the centre of global access to medicines and at the centre of this chapter and this thesis.

The country known for its high reverse engineering on drugs and the advantages of lower capital expenditures has been able to be powerfully present into the global generic markets. The TRIPS Agreement established certain minimum standards that must be adhered to by each member nation in order to protect and enforce Intellectual Property Rights. The Agreement per *se* doesn't specify the patentability criteria for the countries, just some basic standards, leaving space to the country member to define "*inventions*" for the purposes of the patent law. TRIPS has granted certain flexibilities to the member nations in framing their Patent Laws considering their social and economic needs. (Shalini & Rekha, 2016) By signing the TRIPS, India introduced product patents for pharmaceuticals in 1995. For protecting its public health, in 2005 India also introduced a special provision, Section 3(d). Under this new provision, new forms of already known substances were not granted a patent unless they are proved to have enhanced the known efficacy of that already known substance. The country declared "war" to evergreening practices and through the years many patent applications were denied by the Indian Patent Office claiming that no enhanced efficacy had been presented. This chapter analyses 3 of them, which have been at the centre of global attention, especially in the US, where the impact of Indian pharma is huge.

The decisions of the Indian authorities regarding these cases had broader implications and still today the Section 3(d) presents significant hurdles to Western pharmaceutical companies trying to market their products in this country. Many have been claiming that the ruling of the Indian Patent law is not compliant with TRIPS or even that it shows signs of discrimination towards the western drug manufacturers. While on the other hand, it's interesting to monitor the strategic moves of the Indian drug manufacturers of generics in the US market.

Keywords: *TRIPS, Section 3(d), Indian Patent Law, Gleevec, patentability criteria.*

3.2. India against evergreening on pharmaceuticals

India was the first country that raised the voice that many of the multinational drug companies were abusing their market monopoly in the face of a catastrophic human disaster. The anti-retroviral revolution that was able to help millions of AIDS patients across the world was possible only thanks to India. Cheap production from India enabled HIV medicines to reach millions of people in the developing countries, reducing the price from $10,000 a year, to only $350 a year. The country currently has significant expertise in process chemistry, reverse engineering, designing, enjoys the advantages of lower capital expenditures, plant operating expenses, costs of innovation which enabled it to foray into the global generic markets.

Prior to the TRIPS Agreement, patent laws varied across countries, and in many, including India, patent protection for pharmaceutical drugs was not permitted. Largely in response to the India-initiated public health-oriented patent law reform, the multinational pharmaceutical industry set in train efforts to form a global patent law. Subsequently, the TRIPS Agreement established certain minimum standards that must be adhered to by each member nation. Upon joining the WTO, each country must ratify a number of Agreements, including the TRIPS Agreement which establishes minimum standards for protecting and enforcing intellectual property rights for all WTO member countries. Among these basic standards are that patents must be available for inventions that are “new”, involve “an inventive step” and are “capable of industrial application.” Additionally, patents must exist for twenty years and must confer the exclusive right to prevent others from *making, using, or selling the claimed invention*.

India introduced product patents for pharmaceuticals in 1995 by signing the TRIPS agreement and as a part of its TRIPS and WTO and commitments amended its Patent Act in three phases with the final deadline in 2005. A main characteristic of the TRIPS Agreement is the flexibility that the WTO members enjoy which allows them to define what is to be considered "invention" for the purpose of the patent law. Like most patent laws in the world, TRIPS don’t define what an invention is. The policy space left open to national laws to distinguish between inventions that are patentable or not.

In 2005, India introduced new patentability standards which were further restricted by the inclusion of a unique provision, Section 3(d). Under this new provision, new forms of already known substances were not granted a patent unless they are proved to have enhanced the known efficacy of that already known substance. Along with bringing in product patents for pharmaceuticals, it also made legislative changes for the introduction of stricter patentability standards, introducing post-grant opposition while considerably remodelling the then existing pre-grant opposition, clarifying the system for using patented products within the patent term for generic approval and bringing in a structured compulsory license mechanism.

The statutory intent behind the introduction of Section 3(d) was to discourage the unethical practices of evergreening. It restricts the patentability of certain new forms of older substances unless they satisfy the requirement of enhanced efficacy criteria.

Section 3(d) of the Indian Patent Act says:

"The following inventions are *NOT* inventions within the meaning of this Act, - […]

(d) the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use of a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.

Explanation: For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same."

Hence, Section 3(d) laid down higher patentability standards for new forms of already known substances and has proved as an effective provision in checking the unethical practices followed by innovators to extend the patent term. (Rathod, 2010)

Denied on the grounds of not having met the standard of efficacy required by Section 3(d) of the 2005 Patent Act, on April 2013, the Supreme Court in India decided to dismiss Swiss drug maker Novartis AG's attempt to win patent protection for its anti-cancer drug Gleevec. In doing so, the Supreme Court held that "incremental improvements or modifications to an existing drug are not patentable under India's patent laws". (Brougher, 2013) This case attracted global attention on the broader implications including the question of patenting with net benefits to society and consideration of the specific conditions of a country. While the ruling may be a victory for Indian companies manufacturing cheap generics, it presented significant hurdles to Western pharmaceutical companies trying to market their products in this country.

3.2. The major role in the American healthcare by Indian Pharma

While trying to redefine and redesign its patent laws, India has been attracting strict opposition from the United States. In fact, the United States Trade Representative (USTR) has regularly cited Section 3(d) as the reason of listing India as one of the countries whose intellectual property rights regimes are of 'concern' to the US. For that, the US FDA opened in 2008 its two overseas offices in New Delhi and Mumbai in order to monitor the product approvals to generic companies in India. The United States is the largest pharma market in the world with current generic sales accounting for 127.8 billion $, and India is its largest supplier. In terms of regional trends, Indian companies continued to dominate the market of final generics approvals, followed by US, EU and then China.

To better explain the high concern of USA in front of the Indian patent Law is important to understand the *strategic penetration of Indian pharmaceutical industry in the US generic market.*[13]

For the purpose of this work, a descriptive and comprehensive study of product registration pattern of Indian pharmaceutical companies in the US was made. We analysed the ANDA approvals of Indian companies by US FDA based on the Orange Book and also Drug@FDA database, updated on December 2020. The collected information included human drug products along with their dosage forms, strengths, marketing status etc. approved in US pharmaceutical market during the 2010-2020 decade. The study considered all the Abbreviated New Drug Applications (ANDA) for all human products approved by the Centre for Drug Evaluation and Research (CDER) and from them identified those which came from Indian companies.

Table 5: ANDA approvals and Indian companies' shares (2010-2020)[14]

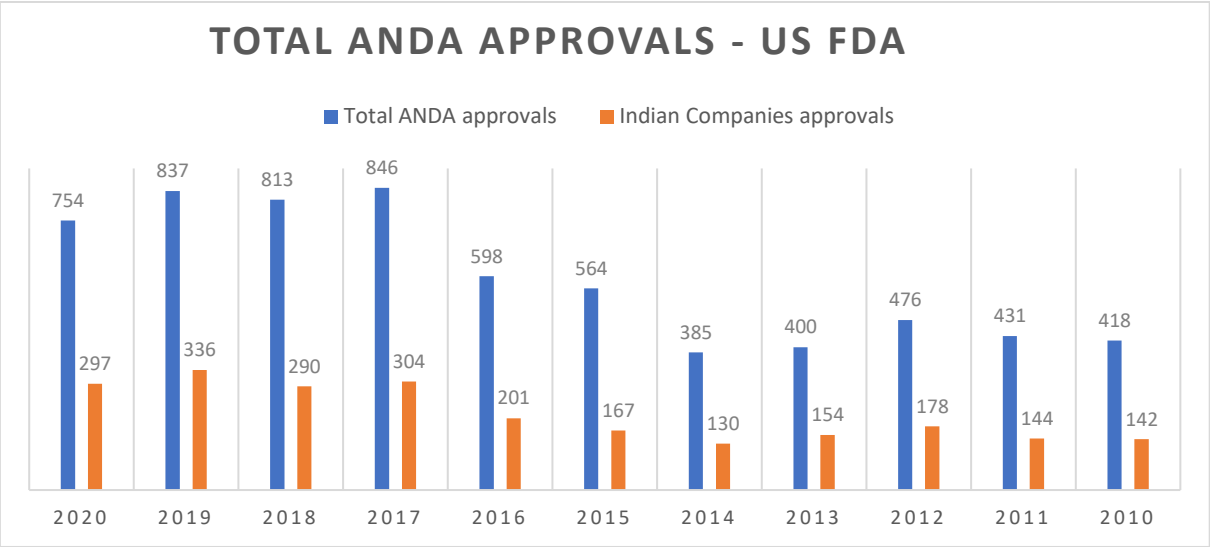
Year	Total ANDA approvals	Indian Companies approvals	Indian Companies share
2020	754	297	**28%**
2019	837	336	**40%**
2018	813	290	**36%**
2017	846	304	**36%**
2016	598	201	**34%**
2015	564	167	**30%**
2014	385	130	**34%**
2013	400	154	**39%**
2012	476	178	**37%**
2011	431	144	**33%**
2010	418	142	**34%**
Total	**6522**	**2370**	**36%**

Source: Research based on US FDA Orange Book and Drug@FDA

The US FDA approved a total of *6522 ANDAs during the last decade*, 2010-2020 and specifically Indian companies received *2970 ANDA approvals*, grabbing in this way over 36% of the approvals. The research methodology does also consider the foreign subsidiaries of Indian multinational companies.

[13] According to US FDA: a generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use.
[14] The yearly applications are considered from January to December.

Figure 4: Number of approved applications from India (2010-2020)



Source: Research based on US FDA Orange Book and Drug@FDA

Focusing on the last two years, it is easy to notice that the Indian presence is still strong in the US generic market, even though the effects of COVID-19 in the whole global economy. We've seen that India has been aggressively filing ANDAs over the past 10 years.

In 2019, Indian pharma companies secured 336 ANDA approvals comparing to 290 in the previous year. The US FDA approved 837 ANDAs in 2019, and from them around 40% were from Indian companies. Similarly, total tentative approvals[15] were at 165 in 2019 as against 194 in 2018, guaranteeing this way 49% of total tentative approvals.

Considering the huge size of US pharma market and the high expected earnings, several players try to strengthen their product pipeline by increasing their spending on R&D. Every player constantly works for launching new products after loss of marketing exclusivity. (Pingle, 2020) India's major pharma players like Sun Pharma, Cadila Healthcare & Zydus Pharma, Aurobindo Pharma, Lupin, Alembic Pharma and Alkem Laboratories received over 20 ANDAs approvals during 2019. (Pingle, 2020) The Indian companies were well set to continue the ANDA filing trend in 2020 also with the help of R&D investment. But with the pandemic hit, the effects were visible. In 2020 the FDA approved less new generic drugs with respect to the previous years. Of 754 ANDAs, 28% of them were from Indian companies' generics. The Authority also tentatively approved an additional 195 ANDAs. The dip in approvals comes after FDA increased its focus on generic drug approvals as part of the drug competition action plan championed by

[15] Tentative approvals occur when a drug has been found to be generic but is prohibited from being marketed due to existing patent exclusivities (or other exclusivities) for the original "reference" drug.

former FDA Commissioner Scott Gottlieb. The influence of the COVID-19 pandemic in FDA's performance to approve generic drugs is unclear due to restrictions in conducting facility inspections and shifting resources to respond to the pandemic. (Mezher, 2020) Finally, from the study of FDA databases, it resulted that Indian companies have received the highest number of ANDA and tentative approvals during the last decade, granting an average share of 35% and leaving behind US pharma manufacturers and the European ones.

3.4. To patent or not to patent in India?

As already introduced, in the Indian Patent Law there are certain inventions which are deemed specifically under Section 3(d) which is known as the provision against evergreening.

Under Section 3(d) of the Act an invention that claims an already known substance and an already known medicinal activity, shouldn't be eligible for granting patentability unless it proves significant improvements of *therapeutic efficacy* considering the previously known compound. This provision has created various disputes with some of the big pharma. *Table X* presents some of them regarding pharmaceutical undertakings. These disputes have ended with the refusal of the patent grant under the Section 3(d) of Indian Patent Law. According to the Supreme Court of India, no significant difference with regard to therapeutic efficacy has been proven by the Applicants so they weren't eligible for granting patentability.

The Indian patent law allows pre-grant as well as post grant opposition. In most of the case we can see on the *Table 6*, various patents have been challenged by the Indian manufacturers through the years. Three of them caught our particular interest as study cases regarding evergreening in pharmaceuticals. All three of them have had an opponent on the other side: an Indian pharma company claiming that the specific drug presented by the Applicants didn't prove further improved therapeutic effects.

Table 6: Representative landmark cases of Section 3(d) rejections/oppositions

Applicant	Application no./ Patent no.	Name of the drug/ trade name/Date of revocation/ rejections	Opponents	Utility	Grounds of objection under Section 3(d)
Novartis AG	1602/MAS/1998 (Pre-grant opposition)	Imatinibmesylate (*Glivec*) (Revoked April 2013)	Cancer Patients Aid–Association Natco Pharma Ltd. Cipla Ltd. Ranbaxy Laboratories Ltd.	Anti-leukemia drug	No significant difference with regard to therapeutic efficacy in spite of increased bioavailability of the salt form over Imatinib.
Hoffmann-La Roche	IN'507	(Rejected)	–	Lung cancer drug	The application IN'774 was rejected as there was no significant enhancement in the therapeutic efficacy.
Abraxis Bioscience	4572/CHENP/ 2006 (Pre-grant opposition)	*Abraxane* (Revoked June 2015)	Natco Pharma Ltd.	Anti-cancer drug	Combination of known substances, namely paclitaxel and anti-SPARC antibody, no demonstration of enhanced efficacy.
Boehringer Ingeleim	558/DELNP/2003/ IN254813 /(Post-grant opposition)	Crystalinetio-tropium bromide monohydrate salt) (*Spiriva*) (Revoked March 2015)	Cipla Ltd.	Asthma drug	No considerable enhancement related to therapeutic efficacy over existing tiotropium bromide.
Hoffmann-La Roche	959/MAS/1995 /IN207232 (Post-grant opposition)	*Valganciclovir* (Revoked Jan 2014)	Ranbaxy laboratories Ltd. Cipla Ltd., Bakul Pharma Pvt. Ltd., Matrix Laboratories Ltd. INDIA network for people living with HIV/AIDS and TAMILNADU networking people living with HIV/AIDS	HIV drug	Mere use of a known process and known compound with no improvement in efficacy.
Novartis AG	1440/MAS/1998 (Pre-grant Opposition)	Crystalline Ascomycin derivatives (Revoked July 2007)	Ranbaxy Laboratories Ltd.	Anti-inflammatory (used in the treatment of auto-immune diseases)	Therapeutic efficacy of the crystalline form was not disclosed by the applicant
Novartis AG	237/MAS/1998 (Pre-grant Opposition)	*Oxcarbazepine* (Revoked January 2007)	Ranbaxy laboratories Ltd., Torrent Pharma Ltd	Treatment of psychosomatic disturbances, of epilepsy and of trigeminal neuralgia	Applicant failed to prove efficacy

Source: Shalini & Rekha (2016)

3.4.1. *Novartis AG v. Union of India* - A Case Perspective[16].

Novartis International AG [*hereafter Novartis*], the giant pharmaceutical company, filed during the '90 different patent applications in the US, for a drug containing "imatinib". After granting this patent, Novartis then filed another patent application for the "beta crystalline" form of the imatinib mesylate salt. The US Food and Drug Administration approved the active ingredient imatinib mesylate for use against *cancer and treating chronic myeloid leukaemia*, in the form of Novartis marketed drug "Gleevec". Gleevec was Novartis' top-selling oncology drug in 2015 with sales of $4.66 billion. Through the years, several patents were obtained for the beta crystalline form of imatinib mesylate by Novartis in other countries. Novartis claimed that the company had filed patent applications for its beta crystalline form in more than 50 countries and had successfully obtained patents in 35 of them.

But this was not the case in India.

After TRIPS and India's patent laws changes, Novartis sought patent protection for the beta crystalline form of imatinib mesylate in 1998. The application was processed through a long period until 2006, when it got rejected on the grounds that it failed to satisfy novelty and non-obviousness requirements. Novartis application was opposed by several generic drug companies such as Natco Pharma Ltd. [*hereafter Natco*] and an NGO cancer patient Aid Association on several grounds. They claimed that there was lack of novelty, non-obviousness in the application and also no significant enhanced efficacy was presented. All criteria required under Section 3(d) of the Indian Patent Law. Novartis was in this way accused for trying to *evergreen* its original formula. The Swiss company claimed in its defence that the Indian Patent Act didn't meet the rules set down by the WTO and lodged appeals before the Madras High Court, which was then transferred to the newly formed Intellectual Property Appellate Board - IPAB[17]. The orders subject to appeal before the IPAB are those passed by the Registrar of Trademarks during rectification or opposition proceedings.

The Appellate Board modified the previous decision, stating that novelty and non-obviousness were present in the application because actually the invention of the beta crystalline form of imatinib mesylate is new and inventive. However, the patent application had to be rejected on the grounds that the invention was not *a new substance* but an amended form of a known

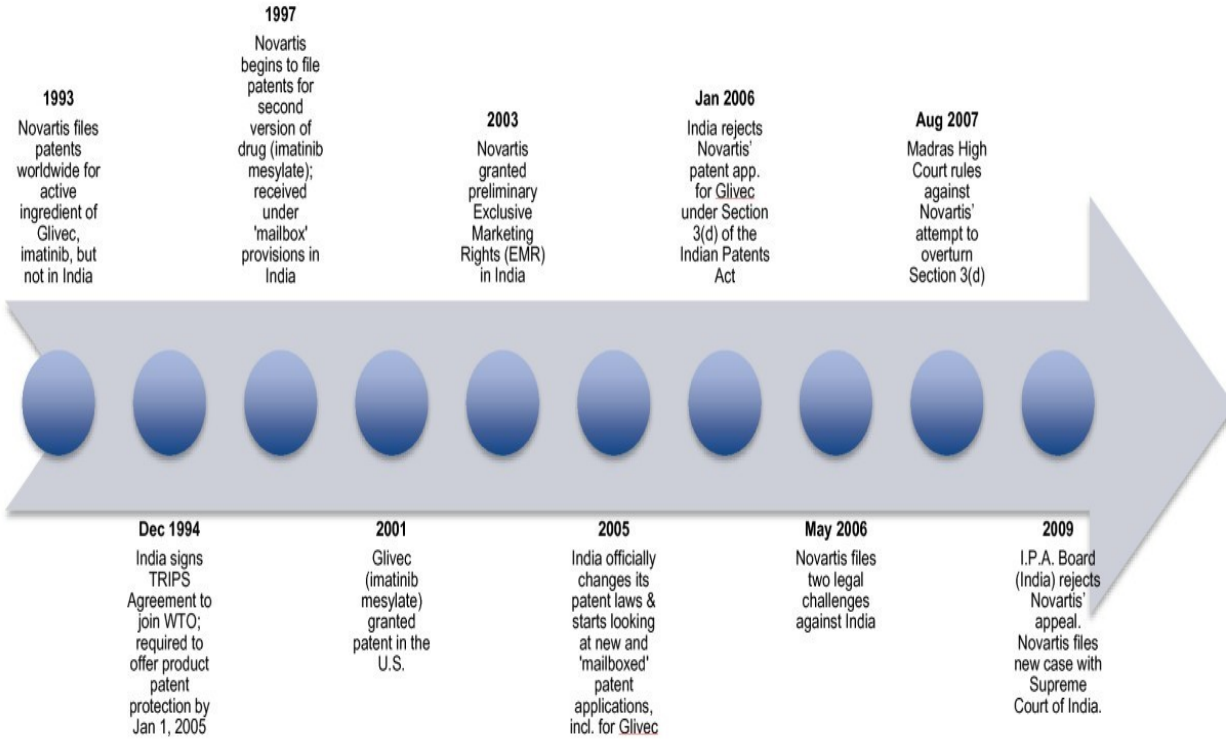
[16] (Novartis v. Union of India & Others Civil Appeal No. 2706 – 2716 , 2013)

[17] The primary purpose for the establishment of the IPAB is to provide an appellate forum to expeditiously adjudicate upon appeals from the orders or decisions passed by the Registrar of Trademarks and Geographical Indications as well as the Controller of Patents.

compound. Novartis was unable to show increase in efficacy as laid down in section 3(d) of the Indian Patents Act.

After this decision, Novartis then appealed the case to the Supreme Court through a Special Leave Petition. Novartis's argument was based on the fact that the beta crystalline form presented more beneficial flow properties along with better thermodynamic stability, lower hygroscopicity and also an increased bioavailability.

Figure 5 - Timeline of the Novartis case.



Source: Gabble & Kohler (2014)

After evaluating all the documents presented, the Court concluded that on the basis of the previous issued patents and literature all the improvements on flow properties, thermodynamic stability etc, presented by Novartis had nothing to do with therapeutic efficacy.

Therefore, the beta crystalline form of imatinib mesylate did not meet the requirements of an "invention" as specified in the Indian Patents Act.

The Court held that with regards to the genesis of Section 3(d), and more importantly to the circumstances in which this provision was amended, there were no doubts that the therapeutic efficacy of a medicine needs to be judged strictly and narrowly. Unfortunately, no therapeutic improvements were guaranteed by the beta crystalline form of imatinib mesylate.

In April 2013, The Supreme Court of India rejected the Novartis patent application.

The SC judgement came as a huge relief for those people who couldn't afford the lifesaving drugs manufactured by this big pharma giant. In a way, these companies who have already made billions of dollars prevent people from purchasing the drugs at low price thus endangering the very life of the poor people by acquiring patents over their drugs. The Supreme Court mentioned that a patent cannot be denied *preventing a new invention* under India's Patent Act. However, the Supreme Court in its judgement made clear that India is a developing country and the availability of medicines at a cheap price is necessary for the lives of over 1 billion people. (Jeswani, 2016) Experts said that The Supreme Court was justified in its decision thereby prohibiting the evergreening approach in granting patents and granting patents only to genuine inventions as against frivolous inventions. (Collier, 2013)

3.4.2. Abraxis Bioscience LLC v. Union of India – A case perspective[18]

In 2008, Biocon Ltd, one of India's pioneering biotechnology companies, and Abraxis BioScience LLC [*hereafter Abraxis Bioscience*], a fully integrated biotechnology company announced the launch of ABRAXANE (paclitaxel formula) in India. The drug was approved in 2007 by the Drug Controller authorities of India and is used to treat a number of *types of cancer*, including ovarian, breast, lung and pancreatic, among others. The approval was based on the clinical trial data that was the basis of approval in the United States. In 2010, Abraxis Bioscience Inc was acquired by New Jersey-based Celgene Corporation during 2010 and the upfront payment value of Abraxis BioSciences was at around $2.9 billion.

The same year of the launch, the company faced a pre-grant *opposition* was filed by Natco Pharma, same opponent of Novartis in the previous case, which had launched Albupax, a biosimilar drug. The Indian drug company claimed that the composition was merely a new form of a known substance and, hence, under Section 3 (d) of the Indian Patent Act was not patentable unless it exhibits *enhanced efficacy.*

The Applicant clarified in the submission while replying to the other grounds of opposition of Natco Pharma that: *"the excipients on acting on its own will yield no effect, whereas the surprising effect conferred in the present [new] invention is only by the virtue of the therapeutic agent paclitaxel conjugated to the anti- SPARC antibody and not the excipients per se".*

Considering both the claim of Natco Pharma and the provision of the Section 3(d) of Indian Patent Law, the Office refused the patent on Abraxis Bioscience. Basically, on the same grounds under which The Indian Patent Office refused the patent on Novartis – Section 3(d) –

[18] (Abraxis BioScience LLC v. Union of India & Others. Case number M.P.NO.57/2010 IN OA/3/2010/PT/DEL and OA/3/2010/PT/DEL, 2015)

it also denied the privilege to the US firm's anti-cancer drug by citing the lack of novelty and inventive step as the reasoning behind the denial.

According to the Indian Patent Office, Abraxis Bioscience did not quote anywhere about the inventive features of the composition *per se.* The Applicant mentioned in the Court the Section 59 of the Patents Act, as a basis for claiming the compound *per se* invention as composition of that compound. The Section 59 (1) claims that "*No amendment of an application for a patent or a complete specification or any document related thereto shall be made except by way of disclaimer, correction or explanation, and no amendment thereof shall be allowed, except for the purpose of incorporation of actual fact, …"*

The Controller responded by citing the prior art and the previously issued patents hence agreeing with the Opponent - Natco Pharma - that the invention paclitaxel coupled to an anti-SPARC antibody or fragment thereof binds specifically to *osteonectin* (an already existing formula). This showed an absence of enhanced efficacy and in the case the application is not patentable under Section 3(d) of the Patents Act 1970. After that, Abraxis BioSciences appealed against the order in the Intellectual Property Appellate Board (IPAB). The IPAB concluded that there existed sufficient evidence to prove that the appellant had been denied of an opportunity to be heard despite having made specific requests to that effect. The Controller was therefore factually wrong in holding that no such request had been made within the prescribed time limit. Given the mandate of such an opportunity having to be provided to the parties, it was therefore clear that the appellant had been wrongly denied of his statutory right in this case.

The IPAB considered the cases cited by the appellant and held in the appellant's favour, stating that the Patent Office had wrongly considered an additional ground of opposition that had not been raised by Natco Pharma in its opposition petition.

In January 2015, the IPAB directed the matter to be reheard by the Patent Office for fresh consideration, and to be decided within a specific time frame of 3 months. The matter was heard in April and a final decision was passed on June 2015, rejecting the application, again.

In one of its articles that analysed this decision, India Writes Network wrote: 'The rejection of the patent to the US-based company will encourage the Indian pharmaceutical companies in making generic versions of the drug available to India and other developing countries at a fraction of the original cost. The Indian pharmaceutical industry is already mired in a controversy over the production and export of cheaper varieties of drugs that have been reportedly pioneered by the western countries. Abraxis' loss meant another blow to the western pharmaceutical companies looking to improve sales in India and elsewhere, while marking a victory for local generic drug-makers.

3.4.3. F. Hoffmann – La Roche AG v. Union of India – A case perspective[19]

Another legal battle that generated much heat and dust in the pharma industry was the revoke of Valganciclovir patent to F. Hoffman - La Roche AG [*hereafter Roche*] in 2015. Valganciclovir is an oral prodrug of Ganciclovir that is used in the treatment of cytomegalovirus infections, primarily in immunocompromised patients such as HIV/AIDS patients or patients who have undergone organ transplants. The drug is sold worldwide under brand name Valcyte by the Swiss pharma major. In India, the patent application for Valganciclovir was filed in 1995 and the patent was granted by the Indian Patent Office in 2007.

The life-span of the granted patent of the drug was 20 years from the date of filing of the application, hence until 2015. Roche filed in 2009 an application which was related to a powder version of Valganciclovir, in order to grant exclusivity protection around the drug. The company also cut the retail price of its Valganciclovir hydrochloride drug by 35% in response to the central government's budget recommendation to help the patients in need.

The second application for the powder formulation by Roche was not appreciated by the generic companies such as Ranbaxy, Cipla, Bakul Pharma and Matrix Labs along with some patient organisations which filed a pre-grant opposition against the patent. Cipla's joint managing director at the time, Amar Lulla said: "We welcome Roche's decision to immediately pass on the custom duty cut to patients as it will reduce the prices to the patients, but the only thing we don't want is the exploitation of patients by creating monopoly through evergreening of patents." The legal battle went on for years and was at the centre of many authorities like Supreme Court, high courts and IPAB. In 2015, in a setback to the drug manufacturer, the IPO rejected the company's application to patent the powder formulation on the ground of lack of novelty. Deciding upon the efficacy of substance under the subject patent, the Controller observed that the new powder form of ganciclovir molecule has shown improvement in oral bioavailability than bis-valine ester of ganciclovir, whereas there was no support in the specification pertaining to efficacy. According to this, since no direct relation was shown for the improved bioavailability of new form of ganciclovir in the description with regard to significant difference in the efficacy, hence this new formulation was considered to be an equivalent substance. Thus, the Controller rules that the present patent was a '*mere use of a known process'* which was not patentable under Section 3(d), Patents Act. The revocation of it in 2015, thus, coincided with the deadline of the original patent expiry. Hence, Roche joined the list of other multinationals in failing to secure patents in India for major drugs.

[19] (Petitioners v. Union of India & F.Hoffmann-La Roche AG. Writ Petition No. 24904, 2008)

3.5. What happened next?

After losing its patent for "Gleevec," Novartis decided to retrieve from its plan on building a R&D centre in Hyderabad (India). The Swiss giant preferred to ‘move’ millions of dollars in planned investments away from India to other locations, primarily China. The U.S. industry trade group Pharmaceutical Research and Manufacturers of America, or PhRMA, valuated the decision of the Supreme Court and the Indian Patent Office as a reflection of a deteriorating environment for innovation in the country.

On the other side, Indian pharmaceuticals and medical experts weren’t surprised. In fact, this case cemented the role of local companies as big suppliers of inexpensive generics to India’s rapidly growing drugs market and also across the developing world.

India's Cipla Ltd, Sun Pharma Ltd and Natco Pharma Ltd, kept selling their generics of Gleevec in India at around *one-tenth of the price* of the branded drug. From the public health point of view, it definitely helped Indian patients who couldn’t previously afford to buy the branded drug. Gabble & Kohler (2014) analysed the timeline of the Novartis case from different perspectives. That case set an important precedent for the global pharmaceutical industry and ideally helped improve access to lifesaving medicines in the developing world. According to the authors, Novartis case illuminates how India is interpreting international law to fit domestic public health needs.

While, after the final decision for the Abraxis BioScience’ drug Paclitaxel, Natco Pharma, was free to supply the market with its generic Albupax. It was the first generic version of the international brand – Abraxane of Abraxis BioSciences, with sales of approximately US$375 million. It has been indigenously developed by Natco in India and was the first albumin bound Paclitaxel in nanoparticle to be developed in India. Each 100 mg vial of Albupax has been priced at Rs 11,500 (one fifth of the branded drug price). This drug had the potential of becoming the single largest brand amongst its basket of oncology products. But things changed. A few years later, in an unusual development, the Indian government stayed the suspension of Albupax manufacturing (product) licence by Natco Pharma Ltd. Natco’s manufacturing licence was suspended by the Drugs Controller General of India (DCGI) allegedly for not passing the test measuring endotoxin levels. This raised the sensibility also of the foreign markets regarding the efficacy of Indian drugs confirming somehow the reason behind the listing of India as one of the countries whose intellectual property rights regimes are of ‘concern’ to the US. While

Natco recalled all batches of Albupax from the market, other local companies Cipla Ltd, Panacea Biotec Ltd and Fresenius Kabi Oncology India Ltd (formerly Dabur Pharma Ltd) introduced their versions, lowering further the price of the drug.

For the Valvanciclovir drug, Cipla launched the low-cost version of the drug under the brand name Valcept which price was at Rs 245 per tablet, compared to Roche' s maximum retail price for Valcyte at over Rs 1,000. As per the Indian Patent Laws, a patent can be challenged within 12 months of the patent approval. In a new twist to the battle between domestic generic drug maker Cipla and Swiss drug major over the anti-infection drug Valganciclovir, the Bombay High Court restrained Cipla from using the trademark 'Valcept' for its copycat version of Valcyte, Roche's patented brand. Later on, Ranbaxy Laboratories Ltd, another generic major in the pharmaceutical industry, granted generic approval for valvanciclovir by the Indian Patent Office.

3.5.1. Entering the US market: The Sun Pharma and Novartis evergreening settlement

Going through the patent protection law in US in the first chapter, we learned about the ANDA applications that are managed by the FDA. This authority approves applications to market generic versions of brand-name drugs without repeating costly and duplicative clinical trials to establish safety and efficacy. In addition to the ANDA approval pathway, generic drug companies gained the ability to challenge patents in court prior to marketing as well as *180-day generic drug exclusivity.* The statute provides an incentive of 180 days of market exclusivity to the "first" generic applicant who challenges a listed patent by filing a paragraph IV certification and running the risk of having to defend a patent infringement suit. A paragraph IV certification begins a process in which the question of whether the listed patent is valid or will be infringed by the proposed generic product may be answered by the courts prior to the expiration of the patent. In some circumstances, an applicant who obtains 180-day exclusivity may be the sole marketer of a generic competitor to the innovator product for 180 days. Until an eligible ANDA applicant's 180-day exclusivity period has expired, FDA cannot approve subsequently submitted ANDAs for the same drug. Therefore, an ANDA applicant who is eligible for exclusivity is often in the position to delay all generic competition for the innovator product.

From our analysis based on various articles and also on the announcements of the pharmaceutical companies in their websites, some interesting facts were found following the three cases of study and the developments that followed. (Das, 2013)

Starting from Novartis, the decision to reject Novartis' patent "had global significance since India's generic drug industry, valued at approximately USD $26 billion, supplies much of the cheap medicine used in the developing world (Gabble & Kohler, 2014). But interesting steps occurred also in US pharma market. Novartis' initial US patent on imatinib was set to expire in May 2013. However, Novartis filed for a patent term restoration approval at the US FDA Office and with that imatinib's patent also received a paediatric exclusivity extension, which grants an additional 6 months of protection to pharmaceutical companies that respond to an FDA request to conduct a clinical trial in paediatric patients. As a result, the imatinib's patent was extended to July 2015. In addition, Novartis sought numerous additional patents on imatinib. The well-known secondary patents covered a different formulation of the active ingredient further extended its potential market exclusivity from July 2015 to November 2019 without offering additional clinical benefits.

Two months after the Supreme Court rejected Novartis' plea to declare its Gleevec patent valid, the Indian drug major Sun Pharma sued Novartis Pharmaceuticals Corp in the District Court of New Jersey. The Indian company wanted to introduce its generic of Gleevec (ANDA application under Par IV) also in USA market. Sun Pharma demanded the rights to launch a generic version of the cancer drug before the Novartis patent expires. The complaint challenged the crystal form patent for Gleevec, which would expire in 2019.

According to the US Patent Law, a generic drug applicant with a Para IV filing under the Hatch Waxman Act, is permitted to file a declaratory judgement suit against an innovator company if the ANDA applicant is not sued for infringing the patent within the 45-day period. Sun Pharma, which had made a Para IV filing for the drug in the US in 2006, claims Novartis missed its 45-day window to file an infringement suit after it was informed of Sun Pharma's application for generic ANDA in August 2007. As Novartis did not launch the expected infringement suit against Sun Pharma after it received a notice from Sun, the Indian drug maker filed for a declaratory judgment in the US court, urging it be allowed to market a generic version of Gleevec. In May 2014, Novartis Pharmaceuticals Corporation settled its litigation with the US subsidiary of Sun Pharmaceutical Industries relating to Novartis patents covering the use of certain polymorphic forms of Gleevec (imatinib mesylate), expiring in 2019.

Sun Pharma was the first Indian company to receive the US FDA approval for generic Imatinib Mesylate tablets. Sun Pharmaceutical Industries Ltd said it was allowed to launch a generic version of Novartis' leukaemia drug Gleevec in the United States on February 2016 under a settlement agreement between the two companies.

It was also given the first-to-file status carrying 180-day exclusivity in 2015 when the soon to be off-patent Gleevec saw sales of around $2.5 billion in the US market. This definitely hold

advantages for the Indian drug maker. Not only it was able to sell its generic in the Indian market but it guaranteed access also to one of the biggest markets in the world, USA. One might view this as a success of patent law, as Novartis was permitted to file for patents that the company argued were substantive, and a generic manufacturer was granted earlier access.

But the terms of the settlement agreement are otherwise confidential. Experts are worried that we had to do with another evergreening practice, pay-for-delay practice that occurred between the two companies. From one side, under Section 3(d) in India, the major generic manufacturer Sun Pharma got the right together with other pharma companies to develop their generics and supply the Indian market by gaining this way an important market share. And on the other hand, after India, it strategically applied for ANDA approval and got also the first-to file status carrying 180-day exclusivity in US, by challenging again the originator, Novartis. This time both parties reached a confidential settlement agreement which showed its effects later on. In fact, in 2016, this initial generic–branded duopoly does not lead to major price reductions. In the case of imatinib, Sun Pharma priced its generic product 30% below brand-name price. By comparison, in Canada, generic imatinib is sold for approximately 82% below brand-name price. This definitely might be part of the agreement between the two parties in order to preserve their 'powerful' duopoly.

Finally, although the imatinib active ingredient patent has expired, Novartis retained a secondary patent on the use of imatinib for the treatment of GIST and this patent expired only last year, in 2020.

3.5.2. Entering the US market: Competing for the privilege of the first-to-file generic.

Celgene acquired Abraxane with its $2.9 billion deal to buy Abraxis in 2010 and thanks to growing use as a therapy for pancreatic cancer, lung cancer, and breast cancer, Abraxane's sales topped $1 billion in 2018, with the number expected to continue to grow. Celgene should be able to count on Abraxane contributing to its top and bottom line in the U.S. until 2023 and in the EU until 2022.

In 2016, a year after the final decision of the Supreme Court in India, Glenmark Pharmaceuticals, another multinational pharmaceutical company based in Mumbai, entered into a strategic Development, License and Commercialization agreement with Particle Sciences Inc. to develop and market a generic version of Celgene's Abraxane product

As per the terms of the agreement, the company has obtained Global Exclusive Marketing and Distribution rights of the product upon commercialization. Particle Sciences is a US research-based company that would develop this product exclusively for Glenmark and therefore receive certain milestone payments during various stages of the product's development from the

company, including royalties on sales. Development of the product has been initiated for the USA market and the company filed the ANDA in 2019.

Glenmark is known for its strategy of identifying and exploring external development partnerships to supplement and accelerate the growth of its existing pipeline and portfolio.
On the other hand, Actavis, a subsidiary of Teva Pharmaceuticals was the first to file for ANDA approval of an Abraxane generic. Celgene started patent litigation with both companies for protecting its branded product. In 2018, Celgene reached an agreement with Actavis that terminated pending patent litigation over Abraxane. The settlement saw both parties file a consent judgment with the US District Court for the District of New Jersey to enjoin Actavis from selling a generic version of Abraxane until the patents expire. An *inter parties* review will also be terminated. Celgene provided Actavis with a licence supply the market with its generic form of Abraxane from March 31, 2022. Under which conditions? Those remain private between both companies. Glenmark on the other hand ended the development of the in-licensed complex generic of Abraxane in view of the extremely competitive landscape in the US. The Indian firm said it would rather focus on products where it is an *early entrant*. Just like Sun Pharma with the generic of Gleevec, alto this generic company aimed to be the first-to-file ANDA applicant. Two are the ways the situation might turn in these situations: either they go for out-of-court settlements with innovators (pay-for-delay settlements as strategies of evergreening) or try to win patent litigations so they can gain market exclusivity from 180-days up to 6 months according to the US Patent Law.
When both generics, Actavis and Glenmark declared their intention on challenging the originator, Celgene had to settle and allow one of them to the market. Their earlier entry is followed by important price reductions. As soon as they got the approval of their generics and terminate the patent litigation with originators, generic pharma companies usually start a heavy marketing on its generic to convince pharmacists and doctors on prescribing their generics to patients results in a more advantageous situation to them. This case shows the power of generic drug manufacturers on shortening the patent length of the branded drugs.

3.5.3. Entering the US market: another pay-for-delay settlement

While the Swiss company, was defending its right to grant a patent for valganciclovir in India, Indian generic companies were ‘ attacking’ its ongoing patent in US. Ranbaxy Laboratories Ltd was one of the opponents which filed a pre-grant opposition against the patent of Roche in India. In 2008, Ranbaxy applied to the US FDA to manufacture and market valganciclovir under the name Valcyte for the US market, claiming that it was a known compound, for which it has only

received tentative approval so far. The patent granted by Roche in this market would expiry in September 2015 and it protected the compound valganciclovir [HCl] in crystalline form, other pharmaceutical compositions containing the compound, and methods of using the compound to treat herpes simplex virus and infections.

Ranbaxy believed that in its First-to-File status on Valganciclovir tablets, thereby providing a potential of 180-days of marketing exclusivity, would offer a significant opportunity in the future. Roche immediately filed for patent litigation and the case went in front of the District Court of New Jersey. In September 2009, the Court rejected both Roche's bid for a judgment of patent infringement against Ranbaxy and Ranbaxy's request for a declaration that the patent-in-suit was invalid. Roche appealed the 2009 order, and Ranbaxy cross-appealed. The U.S. Court of Appeals for the Federal Circuit granted the parties' joint bid to send that matter back down to the district court for further proceedings consistent with the settlement agreement.

The parties stipulated that the asserted patent was valid and enforceable. Ranbaxy confirmed that its application for the approval of proposed generic was a technical act of infringement. would infringe the patent-at-issue. The deal allowed Ranbaxy to launch its generic product no later than March 2013, which means 2 years earlier that the originators patent expiry. Ranbaxy would have 180 days of market exclusivity.

The settlement's terms were confidential, just like in other cases, giving hints that Roche might have paid Ranbaxy to delay its generic’s entry in the US market.

IV.

Concluding Remarks

4.1. The trade-off of the patenting system.

The first chapter of this work introduced the importance of protecting the Intellectual Property Rights in order to have future innovation. Just like in any other industry, protecting the IPR and granting patenting rights is crucial to favour the introduction of new technological knowledge. A finding of the empirical literature is that if there is an increase in innovation due to patents, it is likely to be centred in the pharmaceutical, biotechnology, and medical instrument areas, and possibly specialty chemicals.

When considering the pharmaceutical industry, the need of granting patents is crucial in essential for giving the patent holder the right to exclude others from *making, using, selling, or importing* a patented invention. This, because of the specificity of such sector: here the patent is virtually the product itself and these products are really cheap to manufacture so without a patent protecting them, in a competitive market, the prices would be really affordable (see the case of generics). But in this situation, drug manufacturers would have no incentive on creating new technological inventions knowing that there will not be sufficient chances for them to recoup the high R&D costs. That's why Arrow and Nelson presented the problem of underinvestment specifically in basic research and pointed out that inventors' incentives to be inventive will suffer if they cannot appropriate the returns to their inventions A question was raised regarding the trade-off that the patenting system is associated with: What is best for the society*, more available knowledge in the future or less accessible knowledge in the present*?

From one hand, a patent in the pharma sector (and in any other sector) unables for a specific period of time other innovators to use the existing patented innovation as a basis of further developments that would provide new drugs or processes in the market. This leaves the other undertakings with less accessible knowledge in the present. Let's think at the example provided back on Chapter 1 regarding the hypothetical AstraPharma company. Other future originators had to wait until the patent expiry in order to be able to use the patented processes or drug molecules for building on future and sequential innovation. A trade-off situation is created, knowing also that not only the patent holder enjoys the privilege of setting a higher than competitive price of its product which results in a static inefficiency and a deadweight loss for the society, but also patent holder tries to extend this monopoly situation as long as he can

practicing evergreening. On the other hand, patent protection allows the originators to recoup their R&D investments and pursue other future innovation.

Much of the recent economic research on patents has been directed to attempting to answer this question and has found that the trade-off between a "patent monopoly" and "innovation incentive" is much more complex. So, finding an equilibrium is very difficult and no correct answer is currently available by the academia.

O'Donoghue, et al. (2004) considered for example the influence of the length-breadth trade-off in the sequential innovation. In this case, follow-on innovations can shorten the effective life of a patent, so length and breadth are interrelated rather than being two separate policy tools. They find that very broad but finite-lived patents improve innovation and diffusion but that long and narrow patents can lower R&D costs by encouraging effort toward larger innovative steps. (O'Donoghue, et al., 2004)

From all the literature and specific considerations made for the pharmaceutical sector in this work, we do acknowledge the essential need of granting patents and protecting IP rights for pharmaceutical products and processes, so I believe that 'sacrificing' knowledge in the present can be crucial for having more future innovation. On the other hand, authorities and regulations should be more attentive on banning to those unlawful practices such as evergreening that would break this equilibria. How? Possible solutions are presented in the next paragraph.

4.2. Evergreening in pharma: suggesting solutions.

Coming up with something the world has never seen requires a lot of energies. And when we refer to the pharmaceutical sector, it can take up many years. Patent clock starts much early in drug development. Most of the countries provide a 20-year exclusivity for a patented drug but considerable amount of this time is lost during the regulatory application and approval process. Sometimes, making some adjustments to something old, evergreen it and calling it new might be easier. Think about some simple acts in everyday life when by recovering a vintage dress from your grandmas' closet and matching it with just a pair of the latest trend earrings, you can call it a complete full new look. In simple words, pharmaceutical firms do the same with the soon to go off-patent drugs. They perform some new adjustments on some of the secondary characteristics of those drugs and file for further patent protection for those sometimes not-essential improvements. Takes less time, less effort and can brings them further benefits.

So, just like any other sector, it is natural for any innovator firm to resort to lawful and unlawful *practices* such as evergreening so as to recover the heavy costs incurred by them, but with time these practices have become too aggressive.

There are several official[20] and unofficial methods to extend term of a patent beyond 20 years. Unofficial methods include *altering or reformulating the existing compound* to obtain a new patent by utilising polymorphism, creating combinations, OTC switching, etc

The evergreening practices have been at the centre and main object of interest of this work. Chapter 1 fully described how actually pharmaceutical firms perform these strategies and which are the typical moves a company does to evergreen its patent. We provided real examples of evergreening in the pharma industry and it was easy to understand that most of the pharma giants play the card of evergreening for their blockbuster drugs.

So, the patent holder attempts to exploit the loopholes in patent laws and related regulatory processes in order to prolong their non-competitive position especially over blockbuster drugs. These firms file disguised or artful patents on previously patented invention just before the end of the term of the parent patent. (Kumar & Nanda, 2007)

Many have been the discussions regarding these practices on whether evergreening strategies are doing good or bad to the industry itself, to the competition in the market and how they are influencing the social welfare and public health. Experts and studies are divided in 2 extremely different sides: defenders and critics of evergreening in pharma.

In summary, critics of the innovator pharmaceutical industry argue that these incremental improvements to the pharmaceutical products/ processes behind the evergreening tactics are just a low-risk way of cashing in more money.

In reply those defending the industry have argued that the term is inherently pejorative. They observe that most technological advances occur incrementally and many improvement patents cover advances that are of considerable practical significance to patients and other consumers. In addition, patents on improvements do not impede the ability of competitors to market products that were covered by expired patents on original technologies.

This work doesn’t actually pick a side regarding evergreening. It is not the purpose of it to advance this debate but rather to consider and furnish the right solutions to the problem. Unfortunately, it is difficult to measure in terms of financials, the effect that these practices have but based on famous cases of strategic patenting in the pharma history we can say evergreening affects prices, litigation costs and the innovation level in the industry. Obtaining secondary patents through evergreening for not effective improvements unfairly shields a pharmaceutical product from generic or biosimilar competition, thereby resulting in higher prices. Also, the cost of litigation which is around 1.8 million doesn't help in challenging these

[20] Official methods include provisions by some regulatory bodies such as Data exclusivity, Orphan drug exclusivity, Paediatric exclusivity and the 180-day exclusivity in US, Supplementary protection certificate in EU countries,

patents. Small generic competitors cannot afford to do it. But on the same time, improvements can be made on every original invention. There are cases in pharma history when through evergreening pharma companies have eliminated the side effects of the original drug by improving it on terms of formulation, dosage etc. on it. And sometimes the value of a follow-on patent is comparable to or even might exceed that of a primary patent. So how can the problem of evergreening be directed?

It all stays in the provisions and regulations of patent protection. As already described in developed countries like USA and that of the European Union, the patent laws are too lenient to check ever-greening practices. Through the years it seems that pharmaceutical companies have forgotten their main role on contributing in healthcare and are focusing more on their business side, thinking all about profits. When it comes to evergreening, the reason these artful strategies can be performed are the loopholes in patents laws and regulations. Authorities should focus more on improving them and be more attentive to patent applications. With the Novartis case, India for example gave a clear and strong indication that it would not risk life of poor patients and the public health by permitting evergreening of drug patents. The judgment in Novartis case also gave a strong message to the world and the innovator firms that India will provide extended market monopoly to pharmaceutical companies only if a medicine is *genuinely shown to be innovative* and there is a significant enhancement in the efficacy. Even though defining the standards on how to prove this enhancement in efficacy might be precepted in different ways by different authorities, we believe that is key on preventing harmful evergreening strategies. On doing that literature and experts might help. Luckily there are many studies on these strategies that provide possible solutions to the phenomenon. More stricter controls also are required when approving and granting new patents and previous pharmaceutical scandals may help on preventing future ones. All these moves should be done for the same and essential objective: to bring patients innovative new therapies that help them to live longer, healthier lives.

4.3. Is Section 3(d) consistent with TRIPS?

In Chapter 3, the main attention was directed towards India and its relationship with patent protection laws in pharmaceuticals and how it manages the evergreening practices in such industry. Section 3(d) of India's Patent Act prevents the attempts of pharmaceutical companies who wish to seek evergreening of patents in India by filing patent on different attributes of the same drug to enjoy extended monopoly and delay of the availability of cheap generic versions. Various threats and veiled attacks are mounted on the Indian Patent system by United States and European Union to remove Section 3(d) claiming that it discriminates western pharma

companies and is not consistent with TRIPS Agreement. After the Novartis case judgements, the situation got very heated. The Swiss drug company accused Indian Government and the Indian Patent Act for being unreasonable towards the protection of innovation in the industry suggesting especially that Section 3(d) does not comply with the essential regulations of TRIPS. The effect was the same also for the other 2 cases treated in the previous chapter. Big pharma claimed that granting a patent protection in India was not consistent with the already established standards of the international Agreement, TRIPS and Section 3(d) is discriminatory towards the foreign western pharma companies.

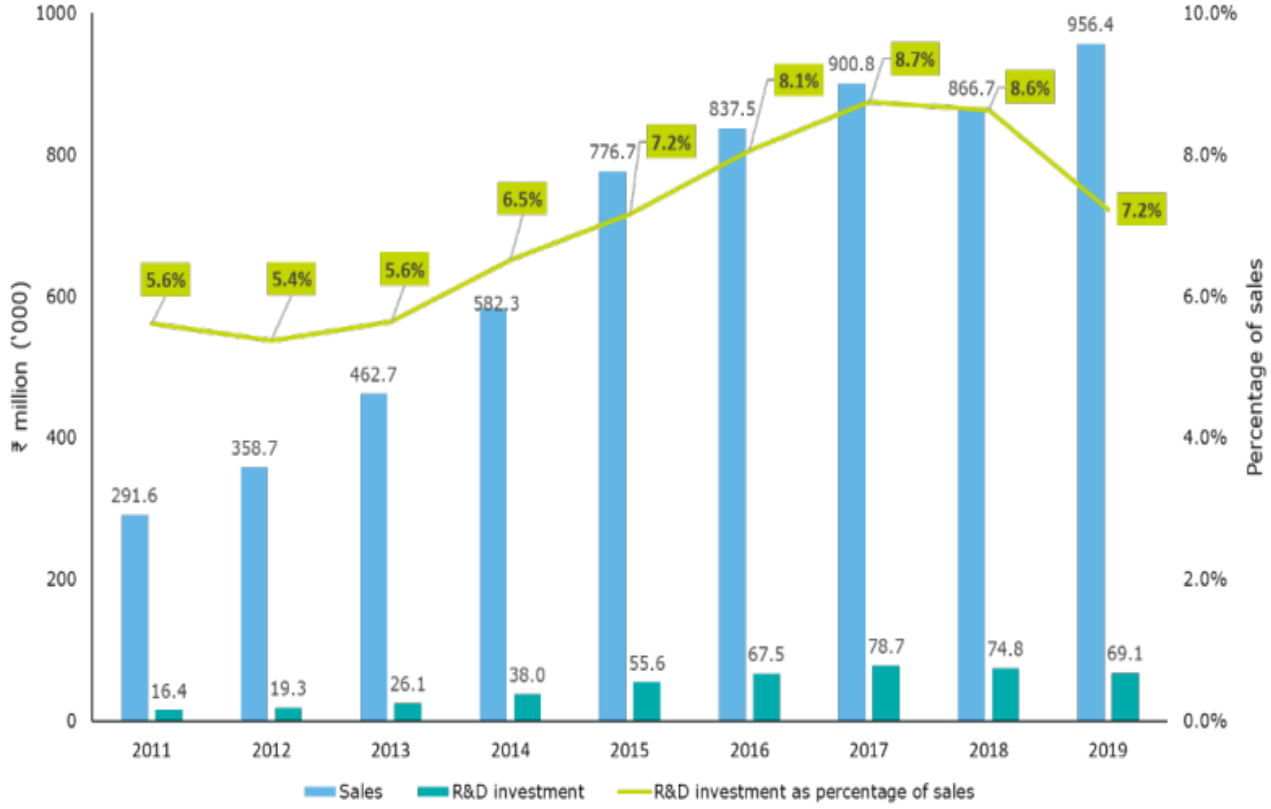
Many have been the studies that have tried to compare various policy regimes in the world and analysing the Indian regulations in this light. Many different interpretations were given in the context of the Novartis case for example regarding what type of standards Section 3(d) actually establishes. Correa (2010) analysed this case starting from the main concept of TRIPS. As previously mentioned, when introduced the main international patent law in Chapter 1, the Agreement allows to all WTO members the flexibility on defining what is an 'invention' for the purposes of their patent law. Hence, different WTO members can adopt different concepts in accordance to their national policies. According to Correa (2010), the policy space left by the TRIPS Agreement allows national laws to define what inventions are patentable and which are not. In particular, the TRIPS does not specify the standard of 'non obviousness' or 'inventive step'. So, given this important flexibility, WTO members can also adopt the patentability criteria to avoid in this case evergreening of pharmaceutical patents. For India, Section 3(d) is the provision for preventing these tactics and is fully compliant on what TRIPS allows to all WTO members. The author agrees that Section 3(d) is perfectly compatible with the TRIPS Agreement and also enshrines the right policy approach in dealing with pharmaceutical patents: protection should be granted when genuine inventions are made and rejected when patent applicants just aim to create barriers to generic competition by patenting minor insignificant modifications. While for the discriminatory hypothesis against western pharma, the author concluded that this provision is not discriminatory in terms of *Article 27.1 of TRIPS* as long as it doesn't create neither different nor additional requirements other than those specified in the said article. (Correa, 2010)

4.4. India towards specialty medicines

The Indian pharmaceutical industry has been facing a transition from being nowhere on the global pharma map in 1970 to playing key role in delivering high-quality and affordable generic drugs worldwide. In the previous chapters, we looked at the factors behind its evolution and

highlighted some of the recent domestic and international challenges and trends which have resulted in a period of more volatile growth.

Figure 6: Yearly trends of Pharma sales and R&D investments



Source: Deloitte analysis of the Annual reports of top five Indian pharma companies (by revenue)

The IQVIA Institute (2019) studies the approaches that Indian pharma companies are working to establish sustainable revenue streams and cost leadership strategies. A trend that caught our eye is the continuous shift towards specialty medicines. In fact, in response to the erosion of generic drugs prices in the US and Europe, generic drug manufacturers in India are exiting drug portfolios where margins are deemed unsustainable and focusing on developing differentiated complex generics of specialty medicines. Shifting towards complex generics and specialty drugs has required companies to increase their R&D investment. When we analysed the 3 case studies in Chapter 3, it was easy to notice that all three of them had specialty drugs at their centre: Iminatib against cancer, Valganciclovir against HIV/AIDS and Abraxane for treating different types of cancer.

This shift in focus is primarily due to the fact that complex generics are harder to develop, face less competition and command higher margins than generics. Indian pharma companies also aim to be the *first-to-file and first-to-market complex generics* especially in US market, to gain a competitive advantage.

To confirm this trend, we can recall for example Sun Pharma's strategy towards being the first generic company to provide the US market with its version of iminatib. Sun Pharma was the first-to-file generic of iminatib drug sold by Novartis under the brand name Gleevec so the Indian company gained the first to market exclusivity for its generic. Not only the company entered in a evergreening settlement with the major pharma Novartis, delaying its entry until established but also gained the privilege of being the only generic for 180-days in the market. It created duopoly situation with the originator Novartis which led to only a small reduction of the drug price (only 30% in US compared to nearly 70% in Canada). Practicing still a high price for its generic brought enormous profits to the Indian generic company. So, this definitely explains why Indian generics are 'abandoning' simple molecules that require no costs in R&D sold cheaper price and focusing on more complex ones that bring in more profits.

4.5. Section 3(d). To prevent or to promote?

Section 3(d) of India's Patent Act prevents the attempts of pharmaceutical companies who wish to seek evergreening of patents in India by filing patent on different attributes of the same drug to enjoy extended monopoly and delay of the availability of cheap generic versions. This would certainly facilitate early entry of generic medicines into the market and the impact would be felt not only in India but also across other countries that depend on Indian generic medicines. Consequentially, threats and veiled attacks are mounted on the Indian Patent system by United States and European Union to remove Section 3(d). In fact, while looking at the three case studies (and not only), the denial of granting patent protection by the Indian Patent Law naturally allowed free space to the Indian generic pharma to supply the market with cheaper generics. Being specialty drugs, as these medicines would treat different types of cancer and HIV/AIDS, and having the possibility of offering generic versions at one-tenth or one-fifth of the branded drug price was definitely a victory for the patients in need but also for the country's Patent Law which had at the centre of its objectives, protecting the healthcare of its population. Section 3(d) was the determinant on the final decisions of the Supreme Court of India for the three case studies. On one hand, Indian authorities claimed to have prevented strategies of evergreening in pharmaceuticals and that the entry of generics was inevitable into the market. After understanding the impact it had on this market, we raise questions regarding the real effect of the Section 3(d) in terms of evergreening in pharmaceuticals outside India, specifically in the US market.

Is this provision 'fighting' evergreening by filling patent challenges to the western pharmaceutical companies not only in the country but also outside it? As we've seen in the meantime or

shortly after the final decision of the SC of India regarding the case of Novartis, Abraxis Bioscience and Roche, Indian generics filed ANDAs for their generics approval challenging under Paragraph 4 of US Patent Law the current patents granted to the innovators and claiming that they were based on previously known compounds. These generic firms gained time in developing their generics in India for moving then in international markets such as US.

The Indian drug manufacturers aimed for the first-to-file position of generic. This would guarantee them according to the eventual Court decision 180-days up to 6 months of market exclusivity of their generic, blocking this way the other generics entry, and gaining good profits. One may think that their ANDA approvals according to the law would end in patent litigation from the patent owner. And that is true. Novartis for example sued Sun Pharma for infringing its patent. The suit went along for around 3 years with extremely high litigation costs up to $1,8 million. Why would Indian generics run the risk of getting sued in the US by originators? Firstly, in case of approval of their ANDAs as the first-to-file generic bring them huge profits as we have to do with generics of important specialty drugs. Secondly, court trials most of the time end with private settlements between the originator and the generic drug manufacturer creating this way a situation of duopoly in the market. These settlements can be pay-for-delay agreements (evergreening) in which the originator, in this case Novartis, pays huge amounts of money in order to convince the generic to postpone its entry and then license it by giving it the exclusivity shortly before the patent expiration to sell its generic drug.

Introduced in Chapter 1, these private settlements are just evergreening tactics performed by pharmaceutical companies to extend their non-competitive position.

Are Indian generic manufacturers seeing this opportunity of demanding the patent removal of specialty medicines under Section 3(d) in order to base their long-term strategy for entering the US market?

Finally, we close this work raising some questions regarding the eventual opposite effect that Section 3(d) might have on promoting other evergreening strategies in the US market of pharmaceuticals.

Is this provision creating a boomerang effect by increasing rather than fighting the evergreening practices (i.e., pay-for-delay settlements) between the Indian generics and the big western pharma in US? Should the US authorities consider these specific strategies and interfere in the ANDA approvals under Para IV?

We do believe that these and other questions should be object of interest for further studies on secondary patenting and evergreening practices.

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