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Course of Markets, Regulations and Law

The Paying-Twice and The Price Regulation in The Pharmaceutical Industry: Sovaldi and SARS-CoV-2 Vaccines Cases

Prof. Giuseppe Colangelo
SUPERVISOR

Prof. Luca Arnaudo
CO-SUPERVISOR

ID No. 726751
CANDIDATE

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Introduction

Since the end of the World War II, pharmaceutical industry has acquired a prominent and important role inside the communities and society in general. The continuous and incessant ageing of the population of developed countries, the outbreaks of epidemics and pandemics – Ebola, Polioviruses, MERS, SARS, Influenza A and H virus, and Covid-19 – and the achievement in innovation for the cure of different diseases have pushed the industry towards innovation, change, and breakthrough discoveries: Chlorpromazine, Poliovax, Capoten, Prozac, Saquinavir, Lipitor (1997), Herceptin (1998), Rapamune (1999), Humira (2002), Sovaldi (2013) Keytruda (2014), Kymriah (2017), Luxturna (2017), Comirnaty (2020). Those drugs have been made the history of pharmacology through their innovation and efficiency, helping thousands of millions of people surviving and living better lives.

However, in a world where profit, revenues, costs, shareholders and stakeholders are of a capital importance, the space for equity, equality, fairness and justice is day-after-day shrinking. This is the reason that have pushed us for investigating on the pharmaceutical industry: a sector that has given – and still does – a lot to societies, but that in certain times and for certain cases exploits its position to pursue capitalistic values and market arrivisme. The 'paying-twice' critique has been in place since the first launched drug with public funds investments, and – since then – has been addressed in the literature. During the discussion of the Bayh-Dole Act at the US Senate in the mid-80s, Sen. Long said:

> "[…] It is dismaying, therefore, to find that S. 414 provides for contractors, in this case small business firms, universities and nonprofit *(sic)* organizations, to receive gifts of ownership of taxpayer-financed research, and according to S. 414's chief sponsor, this is to be only a first step. […] There is […] absolutely no reason why the taxpayer should be forced to subsidize a private monopoly and have to pay twice: first for the research and development and then through monopoly prices (Mr. Long, Us Senate, 1980)."[2]

The preoccupations of Senator Long were not premature as someone might think: the Us taxpayers, as well as Italian, British, German, Sweden, etc. ones have been subjected to a Brobdingnagian expenditure in pharmaceutical products, medical devices and therapies. Therefore, the topic of this Thesis will focus on the

I am beholden to prof. Giuseppe Colangelo and prof. Luca Arnaudo for their precious guidance and their insights. I am especially indebted to my family, Nicoletta, Alfonso and Carlotta, for their advice and relentless encouragement throughout the years, together with my wingman Flora Trieshi. I am grateful to Nicola Ranieri Da Re, Nicolò Sammartini, Gabriele Di Panfilo and Alfredo Menghini for their presence. I thank Leonardo D'Amico for his encouragements since the day we met, Amadou Diallo, Lodovica Capovilla, Matteo Francescato, Corrado Conta, Federico Faccioli, Adriana Trieshi, Carlo Liviero, Giovanni Ravetta, Beatrice Zilio, and many others that have crossed my path, for their insightful comments and the valuable discussions.

[2] Us Senate 1980

'paying-twice' dilemma and the pricing strategies of two examples that outline the importance and the heavy situation that arise from the 'paying-twice'.

The dissertation will be divvy in four chapters. The first chapter will focus on the pharmaceutical industry, the global, Us and Italian markets and the situation of the sector and of the society during the recent outbreak of Covid-19. Finally, it will explain the role of the regulatory authorities and their procedures for the evaluation of drugs and generics.

The second chapter, instead, will be divvy in two parts: the first part will address the Intellectual Property Rights situations in the world, focusing on the Bayh-Dole Act and the Professor's Privilege systems, ending with a review of literature on the differences between these two. The second part will be focus on the remaining part of the pharmaceutical industry: we will try to address the debate on the scientific research as a public good, the meaning of innovation in the industry and how it is defined by the regulatory authorities, the pricing techniques that are applied in the pharmaceutical industry between companies and regulatory agencies and the 'paying-twice' critique, with a review of literature and brief explanation on why has to be addressed by the governments.

Moreover, the third chapter will be treating two real cases where the 'paying-twice' arise: the Sovaldi Case and the SARS-CoV-2 vaccines (Comirnaty and Vaxzevria), covering the history of these drugs, the main events, their funding, the pricing strategies and their impact on the world.

Finally, the last chapter will address two possible solutions for the 'paying-twice' dilemma, one centred on the reform on IPRs regimes and the other on the pricing side.

Chapter I

Pharmaceutical Industry and Regulation in the Market

In this chapter, we will introduce the pharmaceutical industry, its composition, and its functioning. The industry plays a vital role in the world, distributing drug and therapies, and increasing the life-expectancy of humans through a continuing and strong innovation. We will briefly describe the history of the industry together with a few breakthroughs, and we will outline the regulation procedure in order to introduce a drug in a market.

1.1 Pharmaceutical Industry

Pharmaceutical industry is a fundamental sector in every society. It provides communities with pharmaceutical products: "substance*[s]* or complex of substances which is administered to man or to animals in order to prevent, diagnose, alleviate or cure a disease, to relieve a symptom, or to modify bodily function in some way". [3]

We can trace the origins of the pharmaceutical sector to two sources: one is the business development of local apothecaries, that enlarged their scope and started to produce in bigger scale; the other is the shifting in scope of different chemical companies which saw medical applications in most of their products. The application of new pharmaceutical technology, together with the discovery of new treatments, led to the creation of a settled and more robust sector between the 1920s and 1930s. With these new dynamics, different pharmaceutical companies began to grow in lot of European countries and in the United States of America.[4] Altogether, governments facilitated the industry growth through legislative and economical interventions, trying to improve the quality and the safety of the commercialized drugs.

However, the advances in the industry led to an increasingly urgency of a strict market regulation, in controlling the safety of the products and the ownership of the patents. From the 1970s, the industry started to expand, "becoming a mega-industry"[5]; horizontal and vertical integration pushed the emergence of large companies with different partnerships with small biotechnology firms. With the rise of a sort of stagnation in innovation and of different health global challenges – HIV/AIDS, among them – the world starts to see the different problematic associated to the pharmaceutical industry as the pricing controversy of most of the products in the market and the consequent affordability issues for the population (especially in those countries where the healthcare system was not universal).

[3] Dukes 2006
[4] Wang 2009
[5] Wang, 36.

In the Nineties, pharmaceutical industry experienced a new advance towards the globalization of operations, with a significant push in vertical and horizontal integration. Together with this new trend, governments started to fund and create new bodies in order to research new means and help achieving an innovation boom. In the USA, the federal government created the National Institute of Health (later, NIH) and initiated the funding of the "academia, which – played – an increasing role in the basic research stage of drug development."[6] Through the new millennium, the industry became more concentrated and profitable, with more than 200 major companies. The changing of paradigm in research, especially thanks to a boost in technology and the proliferation of new challenging diseases (SARS-CoV-1, SARS-CoV-2 and MERS-CoV, among them) "rendered *[to]* this industry even more opportunities than before."[7]

The main aspect of the industry is its bounded relationship with the health care system. Formally, the relationship itself does not pose any threat to the industry; however, the economic and social mechanisms underlying health care systems (WS, later WS) are the real weak points of 'this union'.

The debate around the formation and composition of the health care system is in place since its creation. Briefly, since the conception of the WS[8], it is possible to individuate four models of WS: the Otto von Bismarck's model (or social-democratic model), the liberal model, the conservative model, and the Mediterranean model (theorised by Esping-Andersen[9] et al). Nevertheless, the debate is not centred on the existence of these model, but on the rightness of the intervention of the State on the economy, namely – in this case – on the health care system. Indeed, in the social economic literature, it is possible to see several arguments against or in favour the interventions in the economy. The reason of this vast literature lives on the counterposed problem of why the State have to intervene in the self-regulation mechanisms of the market; namely why the State has to intervene in cases where there are failures in the market. Hence, the models early cited represent different approaches to the same problem.

These types of WS can be summarised explaining the two extreme position. One is the social-democratic welfare model (and partially also the Mediterranean model) which "supports the vision of an active central government that provides virtually all social services throughout the economy".[10] On the other side of the 'spectrum', there is the liberal perspective which holds that the government should intervene only if and when the market system performs imperfectly. However, the point where failures undermine the market is up to discussion: namely, when these market imperfections come alive, together with the debate on how to solve

[6] Wang 2009, 37
[7] Wang 2009, 38
[8] Historically speaking, the creation of a structured welfare system could be linked with the creation of the so-called workhouses (Act for the Relief of the Poor, 1388), literally houses where poor people could live exchanging work as provision of service. This type of relief for poor where also subsidized by the Catholic Church before, and by the Protestant Church after the English Reformation. Regarding this part, it is possible to better deepen with *Slack, Paul. 1995. The English Poor Law, 1531-1782. 1st Cambridge University Press ed. New Studies in Economic and Social History. Cambridge; New York: Cambridge University Press.*
[9] *For an in-depth analysis of the matter see*, *Esping-Andersen, Gosta. 1999. Social Foundations of Post-industrial Economies. Oxford University Press, and Distaso, Guglielmo. 'I sistemi di soccorso extra-ospedaliero in Italia e Inghilterra: un'analisi costo-efficienza.' Università Cattolica del Sacro Cuore, 2019 (Chapter I).*
[10] Management Sciences for Health. 2012. Ch. 10-10.2.

them, the response has to come from the Government, through a political decision. Indeed, the vast possible dominium of solutions are economically inconvertible *per se*: the only debate is on the consequences that the solutions bring to the society.

It is now clear that pharmaceutical industry is not an independent market with a clear path from the producer of raw material to the customers. Indeed, in this path there are a lot of different entities that are at the same time dependant from those upstream, but also independent from each other.

Therefore, the boundaries of the industry are definitely broad. The environment is not the same of any other manufacturing industry: the usual limits of any manufacturing sector are broadened by the elevated social responsibility (SR) that the industry has on communities and on healthcare systems. Moreover, this high social responsibility, that is not so uncommon in other industry, is more intense and more concentrated: it highlights a double-face nature of pharmaceutical. The main objective of a firm in the capitalistic system is the maximization of the profit and the costs minimization. This vision collides with the social importance of pharmaceutical products, together with main objective of the healthcare system, that is the minimization of the cost for the maximization of the output of the "production".

The early called double-face of the industry gives rise to a divergence of intents. Communities and Governments have – usually – one mission that is the maximization of the population health together with the respect of self-imposed budget constraints. Regarding the firms' problems, pharmaceutical companies have one only objective – as we already seen – and that is the maximization of the investment on innovation of pharmaceutical products and the subsequent maximization of profit. Therefore, the industry is dominated by a continuous unbalance between two fundamental actors.

Linkages between pharmaceutical industry and healthcare systems are a lot; however, this topic will be treated in depth in next sections and in Chapter II. For now, it is useful to underline the existence of dependency between different actors of the economy: on one side, we have the regulatory bodies that are responsible for protecting the customers, regulating the market, and ensuring the safety of the pharmaceutical products; on the other side, the pharmaceutical companies play a fundamental role in innovation and development of drugs.

1.1.1 Pharmaceutical Product Life-Cycle and the Phases of Development

In preparation for next sections and chapters, it is useful to underline the product life-cycle of a pharmaceutical drug and its development phases. We should point out that the activities and requirements around the regulatory aspects of the cycle will be treated in the next sections.

The life-cycle of a pharmaceutical product is fairly different from a generic product (in the sense of consumer goods, not patented products, or common products). Indeed, the life-cycle of a drug starts far from its marketisation. As it is possible to see from figure 1.1, the product originates from an R&D stage, chosen from thousands of different candidates: it goes through a clinical trial (as we will see in the following part of the section), it receives a Market Authorization (after an MA application) and then, it is launched onto the market.

During the first phases of the life of the product, it has a market exclusivity and when the patent associated to the product expires, it gradually decreases its market share due to the introduction of generic drugs, that are copies of the patented drug, with the same effects, efficiency, and often same methods of administration. Usually, the prices of patented drug are high (cfr. Chapter III), but they significantly decrease when generics are release in the market since the competitive advantages of generics are low prices and the quasi-absence of R&D and regulatory costs.

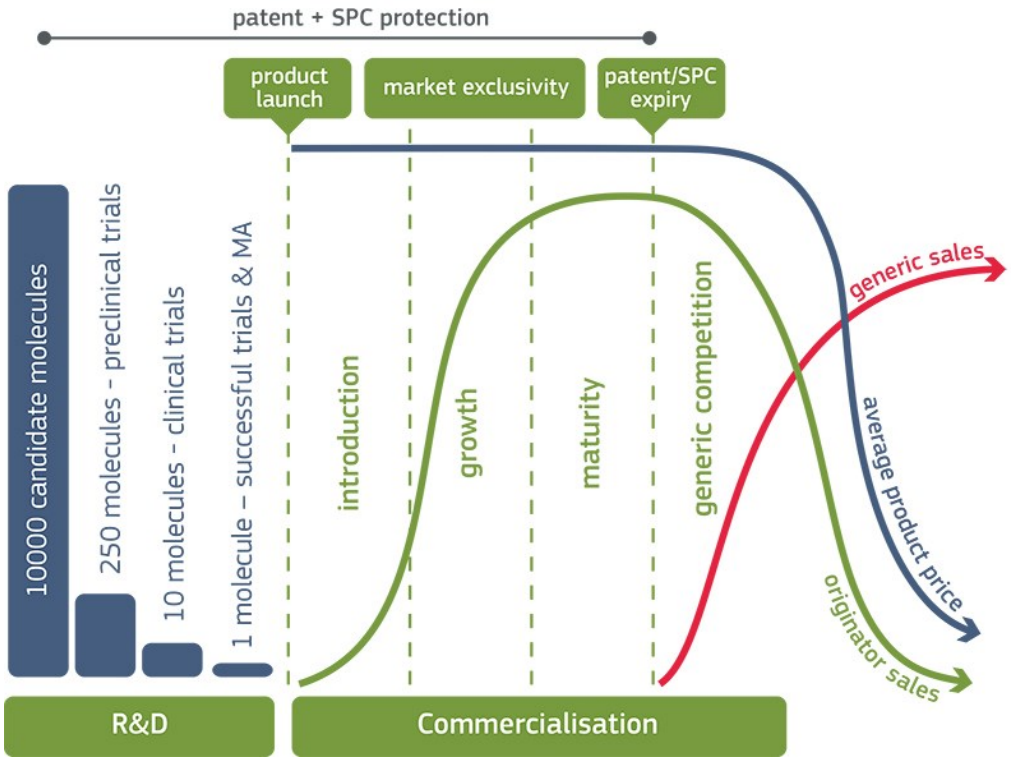

Figure 1.1: Pharmaceutical product life-cycle. Source: European Commission; Market, Regulations and Law Lecture Notes - Colangelo, 2019.

Generally, the product cycle of a drug passes different stages where different type of professionals, equipment and skills are needed. Broadly, the cycle is composed by the pre-clinical phase (or non-clinical phase), the initial registration of the patents, the clinical trials, and the start of the processes for the production of the composite or of the drug.

As a matter of fact, we can divide the pre-clinical phase in two stages: the drug discovery processes and the pre-clinical development. The first is composed by the identification of a drug target and of the candidate compound through different activities (in vivo efficacy, toxicology experimentation, etc. The drug discovery phase is the start of a long race with different and high risks that will end with the marketing of the drug. The latter, instead, is structured in different activities, from the active pharmaceutical ingredient (API) preparation to safety and pharmacokinetics studies.[11] These activities have as output the filing of an Investigational New Drug Application which contains the general investigation plan and brochure, the chemistry, manufacturing,

[11] Steinmetz and Spack 2009.

and control information, the pharmacology and toxicology information, and the previous (if any) human experience with the investigational drug.[12]

After the pre-clinical phase, it starts the investigational registration of the new drug with the filing of the INDA to the regulatory authorities; together with it, the company has to attach a regulation of the clinical trial and file the eCTD (in EU; electronic Common Technical Document), or other technical documents where it is stored every information regarding quality, safety, and efficiency of the new drug. This phase ends with a risk management plan that identifies and assesses the risk linked to the manufacturing and distribution of the product, together with the quality product assessment risks.

With the drafting of the risk management plan and correlated quality risk management plan, it ends the first round of registration at the regulation authorities, and it marks the start of the clinical trials phases.

Clinical trial phases are the core of the development of a drug, and they involve a huge amount of time and resources. There are four different stages of clinical trial. Phase 0, introduced by the US Food and Drug Administration (FDA) in 2006[13], also known as 'exploratory IND', is meant to understand whether the forecasted action of the compound in clinical trialling can be observed in humans, to provide information on the pharmacokinetics, and, especially, to help selecting "the most promising lead product from a group of candidates design to interact with a particular therapeutic target in humans."[14] Usually, this type of clinical trial is conducted with a small group of people (10 to 15 people) in order to have a more controlled space.

Figure 1.2: Drug Product Cycle; our elaboration.

[12] Gad 2007.
[13] 'Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies' 2006.
[14] Steinmetz and Spack 2009.

With phase I, the trial "attempts to estimate tolerability and characterize pharmacokinetics and pharmacodynamics"[15] of the drug. These studies provide an initial assessment of the drug on healthy volunteers or patients who have not been able to heal with already in-market drugs. Phase II starts when the dose range has been set, evaluating the biological effects of the composite and the efficacy. These studies are performed with the help of different statistics and by the use of different groups of people in the trial (100-300 participants). The last two phases – III and IV – are performed in order to assess the efficacy of the drug with multiple and different group of people: usually the range goes from 300 to 3000 participants, but it really depends on the drug tested (or vaccine) and the scope of it (cancer drugs have a smaller pool of candidates compared to SARS-CoV-2 vaccines). With these phases, it starts the long and tortuous way to marketize the drug. Truthfully, the phase IV is also called post-marketing surveillance or pharmacovigilance, and it is shown in the figure 1.1 at the end of the product cycle: its objectives are to monitor the long-term effects of the drug and its efficacy in order to check any safety issues for the drug already in market. Therefore, it is not so simple to collocate it in a timeline since it is a continuous process.

The clinical trial phases are terminated with the phase IV, which actually – as we have already seen – never ends. However, when phase III is completed, the company does not have the authorisation to distribute the drug: it has to submit to regulatory agencies (FDA, EMA or local agencies, such as AIFA, BFARM, EOF, etc.) a Marketing Authorisation (for EU) or an NDA (for USA). Essentially, it is a license to marketize a pharmaceutical product; the process starts before the clinical trial, and it ends with the phase III when all data are collected and analysed. With the filing of the last document for the MAA and the approval process (Marketing Authorisation Approval) the firm can start the production of the drug.

During the production stage, the company has to organize and manage the complex structure of procurement, production and distribution of raw material, semi-finished materials, and pharmaceutical products, in order to meet the market demand. There are precise requirements for the manufacturing of drugs: compliance with local, national, and international law and standards, specific equipment (capsule filling machines, x-ray inspection systems, tablet punches, etc). Moreover, throughout the entire process, the level of complexity in managing the various manufacturing phases is very high and the quality checks are strictly performed in order to distribute efficient drugs. This stage in the development and production of a drug ends with the pharmaceutical product packed and shipped.

Simultaneously, a tracing phase begins involving the management of the inventory, the transportation and distribution of the goods and the pharmacovigilance of the drug. Pharmacovigilance, as stated above, is a key process in the drug-product-cycle: indeed, phase III of the clinical trials collects data from a pool of different people; however, although the process is statistically significant and representative of the general population, can fail to assess every different aspect of human interaction with the drug in developing. Pharmacovigilance has, therefore, the duty to assess the efficiency/efficacy and the safety of the drug in the medium-long run.

[15] Friedman, Furberg, and DeMets 2010, Ch. 1, 6.

Where the data show a decrease in safety or efficacy/efficiency of the drug, will be company's duties to reassess the drug and take the right and conscious actions to ratify the drug.

Truthfully, the product-cycle has no end, as said before. There are three outcomes of this possible never ending process: the company can decide to better develop the drug, changing the formulation of the drug in order to increase safety, efficacy, or efficiency (or for other objectives that will be much clear with the section on the regulation process of pharmaceutical products [see 1.4]), or decide/being forced to withdraw the drug from the market for causing great risks for the health of population; lastly, the company can exploit its patented for the lawful granted time by the patent and profit from the manufacturing and selling of it.

1.2 An Economic Analysis of Pharmaceutical Industry

As we already seen, pharmaceutical sector is fundamental in every country for its purpose and its role in the healthcare system. However, this industry has not the same composition and area of expertise in every geographic area.

With the new millennium, the global market experienced a major concentration and a boost in the profits. In the last decade, the use of pharmaceutical products has globally increase for different reasons. On one hand, the composition of the population has drastically changed: indeed, in 2011 the world population reached 7 billion people and throughout the entire decade grew until the 7.7 billion people in 2020 (at a 1.1 growth rate in 2020).[16] On the other, the improvement in treatment of the so called non-communicable diseases – that is a disease that is not transmissible from one person to another – has highly pushed the profitability of the market, clearly demonstrating "the value of medicines in addressing the needs of patients, prescribers and health systems around the world".[17]

In order to better understand the role of the industry in the global economies, it is useful to characterise the market more in depth. Indeed, we can divvy the pharmaceutical market into three main categories of firms: one regroups the conventional side of the market where large companies produce conventional pharmaceutical products (such as the Humira [AbbVie], Eliquis [BMS/Pfizer], etc.); another one regroups the biotechnology firms, that is those companies that mix biology and technology in order to create products for the treatment of specific diseases (among them we can find Novo Nordisk A/S, Regeneron, etc); the third group represents those firms and businesses that cannot find an adequate position in the groups cited above. The outputs of these firms can vary from each other, and, now more than ever, the pharmaceutical products are much more differentiate than in the past. Overall, we can individuate four different categories of outputs: biological/biosimilars products, generic drugs, over-the-counter drugs, and the traditional Chinese medicines (that hold a significant share in the Chinese market and, for the size of it, also in the global market).

[16] USA and Central Intelligence Agency 2020.
[17] IQVIA 2020, 3.

Regarding the sizing of the firms operating in the industry, we can see a distribution similar to other sectors. Large multinational companies (LMCs) can be cursorily seen as the protagonist of the industry: however, in an article published by Lincker et al. in Nature Reviews,[18] small and medium companies (SMEs) are the real heroes in the situation. According to Lincker et al., between 2010 and 2012, "94 MAAs […] containing an NAS […] received a positive opinion from the CHMP"[19] (the EMA's Committee for Medicinal Products for Human Use), among them 41 were requested by SMEs and 59 by LMCs: the particularity of the industry is, however, the number of originators of NAS in the industry. Among the 94 MAAs, 48 come from SMEs, 28 from LMCs, and 24 from academic, public bodies, PPPs, and from private-private collaborations.

Although the considered data are shown in a tight time-window, the behaviour shown in the article is significant: SMEs, public bodies, academic bodies, and collaborations between privates are the engine of the industry. Once the NAS is discover and registered, LMCs usually acquire the patent and rights for the marketing of the products, or directly acquire the small company originator of the NAS (in 5 cases out of 18 studied by Lincker et al.). The reason underlying these affirmations can be retrieved in the large funding necessary for the clinical phase of the trials for the marketing of a pharmaceutical product: large companies have the ability and the power to focus on the most prominent NASs, leaving to SMEs those that cannot be patented or possibly granted in the future a MAAs. In history and the economy, there are plenty of examples of these passages between SMEs and LMCs: one above all, the Gilead case that is also useful for the discussion in the chapter II. In 2011, indeed, Gilead acquired Pharmasset (originator of PSI-7977 or Sovaldi – a hepatitis C drug) at a price of 11.2 billion of US Dollar, after the NIH and the US taxpayers granted 2.460.171 US Dollar of funding for the development of Sovaldi to Pharmasset. [20]

Therefore, it is clear the role-pattern in the industry: small companies and private/academic/public bodies discover NASs, patenting them. At that point, they have different roadmaps to follow: some companies try to sell the rights to medium and large enterprises or directly try to be incorporated in the LMCs (by direct or indirect M&A actions). Others, instead, try to finance the clinical phases and marketing of the products through different escamotages, IPOs among them, or through a reverse-takeover (friendly takeover by a shell company that can go public on the market), as IMV experienced in 2009.[21]

[18] Lincker et al. 2014
[19] Lincker et al. 2014.
[20] Silver and Hyman 2020
[21] Korets-Smith and Riaz 2010

Regarding the geographical distribution of pharmaceutical firms worldwide, United States and the Asia-Pacific area are the most firm-dense zones where companies are located, alongside with the European market (figure 1.3). Historically, China is producing some of the strongest growth every year, while European countries are smothering also due to the spending culture and the prevalent type of health care system.

The dynamics of the industry are not so dissimilar to those of other markets. Hence, the scope analysis is centred on the manufacturing actors as players, while hospitals, pharmacies, health insurance providers and governmental healthcare services play the role of buyers.

1.2.1 The Global Market

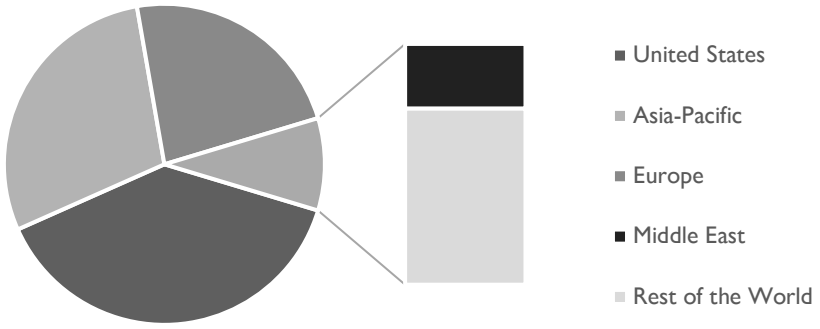

Figure 1.3: Geographic distribution of market share in pharmaceutical industry; Source: MarketLine

Nowadays, the global market is populated by more than 200 large companies which generate an enormous turnover. Indeed, in 2001 the global pharmaceutical industry had total revenues equal to 390.2 billion of US Dollars, while in 2019 the industry reached an outstanding amount of 1,250.4 billion of US Dollars.[22] The revenues compound annual growth rate (CAGR) for the global pharmaceutical market between 2015 and 2019 was 3.6%. Nevertheless, the geographic spread of these revenues is different. According with IQVIA[23] (figure 1.4), the distribution of the total global pharmaceutical market sales is predominant in the USA with a slight increase from 2014 to 2019; the other markets have an equal percentage of global share, with Europe and emerging markets slightly equivalent. According with the IMS, the future largest segment will be in the emerging countries such as BRICS (Brazil, Russia, India, China, and South Africa), Mexico, Poland, Indonesia, etc. The reasons behind this increase can be individuated in better reforms for the health care systems, in the growth of the population and in the increase of economic performances of these countries.[24]

[22] Statista 2020, 8.
[23] Statista 2020, 10. Data from IQVIA (Midas Quantum); 2014 to Q3 2019
[24] Yadav and Smith 2014

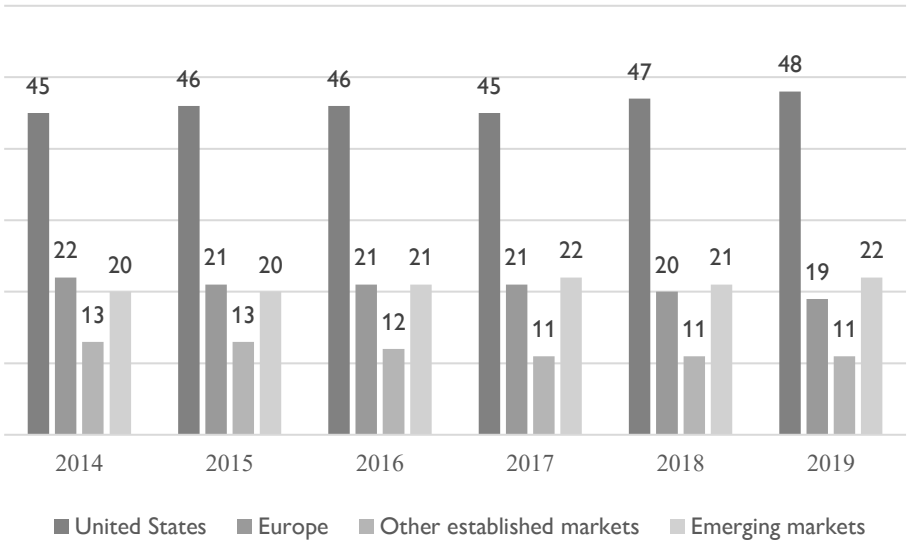

Figure 1.4: Pharmaceutical sales distribution worldwide (in percentage); IQVIA

In order to deeply characterise the pharmaceutical industry, it is necessary to apply the Porter's Five Forces Model, theorised in "How Competitive Forces Shapes Strategy".[25] The model focuses its scope on five forces that together are present in the industry. In this section we are going to deepen these forces: competitive rivalry (or degree of rivalry), threats of new entrants, bargaining power of suppliers, bargaining power of customers, threat of substitutes.

The degree of rivalry gets hold of different forms in the market, as lowering prices, improving offered services, and launching new products. It is determined by the diverse nature of the pharmaceutical outputs of the manufacturing firms that compete in the market: indeed, the produced products can be divvy in patented drugs and generic drugs. Regarding the first, the competition around this type of product is mainly based on innovation in specific illness-fields and on the number of research on those biological/biosimilar products.[26] The main competition drivers are innovation, intellectual properties, and product patents, and these are also those characteristics that influence the market share of each firm operating in the industry. Essentially, the operational competition is based solely on R&D activities: the company that acquire faster and more efficiently a specific solution for a specific problem acquires a competitive advantage. Regarding, instead, the competition around the 'non-patented' or generic drugs, the drivers are more similar to consumer products than medicines: indeed, these products are usually price sensitive; moreover, the area of distribution of these pharmaceutical outputs is usually locally limited to few countries for each generic[27], and therefore the rivalry.

The second Porter's force is centred on the bargaining power that "suppliers can exert […] on participant in an industry by raising prices or reducing the quality of purchased goods and services".[28] In the pharmaceutical industry at large, the bargaining power of suppliers is increasingly influencing whereas there is not a

[25] Porter 1979.
[26] Nedelcheva and Filipova 2021.
[27] IQVIA 2020, 3.
[28] Nedelcheva and Filipova 2021, 5.

counterpart in the supply agreements or there are not any other alternative solutions. In other words, whereas the supplied product cannot be substituted, the suppliers' power is enormous.

There are different types of suppliers in the pharmaceutical supply chain. At the initial phase, suppliers are mainly focused on providing skills and competencies in order to create a biological composition: in this stage – we have seen – different actors are involved, especially academic and private bodies, and the bargaining power is not so high, due to the size of the customers and the relative power to influence the exchange. The next stage in the supply chain is centred on suppliers holding patents and IPRs on future pharmaceutical products: in these cases, the bargaining powers is high due to their ability to raise the prices of the selling products and, therefore, influence the market. At the manufacturing phase, instead, the suppliers have low bargaining power, due to their role of chemical compounds providers and their high presence in the market. Regarding this point, we should notice, however, that providers of raw material in manufacturing processes had have a high bargaining power during SARS-CoV-2 pandemic, due to the scarce availability of resources. To conclude, the last phase – the distribution stage –both sides have the same level of bargaining power: on one side, State, regulatory professionals and NHS have a high bargaining power due to their ability to change regulatory framework, influence prices and blocking the access in the market; on the other side, pharmaceutical companies can deny the availability of specific pharmaceutical products, inhibit the drugs on a specific market, or, in case of high-demand drugs (nutrients, vaccines[29], orphan drugs) increase the selling prices.

The third Porter's force is built on the same logic functioning of the suppliers' bargaining power, focusing instead on the demand side. Indeed, "customers influence competition by gaining more value by influencing lower prices, demanding better quality or greater service at the expense of industry profitability."[30] As well as for the suppliers' side, there are different types of customers in the market. Patients (also view as the last-mile customer) are not capable to exercise a tight and structure bargaining power for patented products due the lack of representation (there are customers associations that can lobby and push towards a specific direction, but it is strangely rare and not economical). Instead, when the pharmaceutical products are not patented (generics) customers do have a bargaining power in the form of price sensitivity and low-switching costs.

Another type of customers is represented by the State: a lot of different countries have a public founded or a public management of pharmaceutical products procuring, and, therefore, they act as customers for the distribution-mile of the supply chain of pharmaceutical industry. In this case, the bargaining power is higher than patients' one, due to the State's ability to influence and change regulations around pharmaceutical distribution (especially for patented products), and due to the size of the entities involved. We should also notice that it is a common practice in healthcare management of pharmaceutical products to diversify the

[29] See next section for an in-depth analysis of Covid-19 vaccines.
[30] Desislava, Assena and Pencheva. 2016

supplier of certain drugs and devices in order to differentiate the risk of shortages: therefore, governments and hospitals can bargain more due to their supply-chain structure.

New competitors give to the industry "new capacity, the desire to gain market share, […] substantial resources" [31] and a push towards an increase in intra-industry innovation: however, if there are not barriers at the entrance of the market, can pluck market shares. As stated by Porter, there are six sources of barriers to entry: economies of scale, product differentiation, capital requirements, cost disadvantages independent of size (compulsory fixed costs), access to distribution channels, and government policy. Regarding the latter, Governs and regulatory agencies play an important role as barriers to the entry, due to the strict regulations for the preservation of life and health. At the same time, economies of scale pose a hard threat to new entrants due to their presence, through vertical integration policies and horizontal integration, and, therefore, the creation of a huge market of *too-big-to-fail* companies with a globalise network of partnership and a globalise supply chain. Despite the recent economic crisis, above all the 2007 crisis and the Covid-19 pandemic, the globalisation of the pharmaceutical industry is still intact and, on the contrary, give to the market a push towards a bigger expansion, with the insert of huge stream of liquidity. Yet importantly, "pharmaceutical industry, as well as other manufacturing industry, tends to transform to oligopolies".[32]

The last Porter's force regards the threat that poses a new and equally exchangeable product traded in the market. Substitutes have a variety of characteristics that can impact positively or negatively the market. The basic logic around the threat of substitutes is that "the more attractive the price-performance-trade-off offered by substitute products, the firmer the lid placed on the industry's profit potential".[33] Therefore, generally, substitutes arise in those industries where the switching costs between certain products are low. In pharmaceutical industry, substitutes are generic drugs: this kind of drugs is mainly characterised by the absence of a patent, and therefore, they are legally reproducible in specific markets: as above stated, the switching input is based on the price of the generics compared to the original drug. Moreover, a substitute for an original pharmaceutical product can emerge using different technologies or different means of delivering the active substance.

The global pharmaceutical industry is populated by different companies, public and private research institutes, and biotechnology firms. We have already seen how the industry is composed and the role of each type of firm; however, it is still needed an examination of the competitive scene.

The global market is fairly consolidated and, as we have seen in early sections, composed by different actors: LMC, SMEs, academic bodies, private foundations, and research entities. Regarding the intra-market competition, the pharmaceutical industry has a huge number of companies. However, as it is possible to see from figure 1.5 and 1.6, the so-called 'Big Pharma' are a limited number of companies: Roche, Novartis,

[31] Porter. 1979, 3.
[32] Korets-Smith and Riaz 2010
[33] Porter. 1979, 8

Pfizer, Merck & Co, Bristol Myers Squibb, Johnson & Johnson; all together, they spend around 50 billion US Dollars in R&D and they sell around 250 billion US Dollars in prescription drugs.

Roche (F. Hoffman – La Roche AG) is a healthcare company based in Switzerland, focusing its activities on two branches: one is the pharmaceutical production of cancer treatments, virus diseases drugs, and metabolic diseases (among all, Tecentriq, Hemlibra, Ocrevus, Actemra/RoActemra, and Parjeta[34]), the other branches is the diagnostic one, focusing on clinical chemistry & immunoassays, molecular diagnostic, tissue diagnostics, point of care diagnostics, and haematology & haemostasis (among all, Ventana E600, Cobas e602, Cobas c502, Accu-chek)[35]. The company is leading per market share (5.5%, see figure 1.5).

Instead, Johnson & Johnson is a healthcare company that develops, manufactures, and sells consumer pharmaceutical products and devices, focusing its activities in specific areas of treatment such as immunology, oncology, neuroscience, infectious diseases, and vaccines (Stelara, Darzalex, Imbruvica, Remicade, etc.).

Again, Novartis, as J&J and Roche, is a healthcare company focusing on discovery, manufacturing, and marketing of patented and generic drugs: it provides treatments drugs for cancer, cardiovascular diseases, neurological disorders, ophthalmic and respiratory diseases, among others.

Pfizer, however, is not completely a healthcare company: its activities umbrella spaces from pharmaceutical products to biotechnology products, with a focus on human drugs for inflammations, immunology, neuroscience, and pain management, as well as orphan drugs and rare disease drugs. Together with Pfizer, also Merck & Co, a US-Germany company based, has a much broader scope, focusing on research activities, manufacturing, and marketing of different disease area (oncology, vaccines, infectious disease, and cardio-metabolic disorders). Finally, Bristol Myers Squibb has the same scope of Merck, focusing on haematology, fibrosis, immunoscience and oncology.

Hence, these companies together have $1/3$ of the total global market in market share (30.7%, as in table 1.6), representing a huge force to fight against in scaling the market for other company.

[34] Roche 2020, 116.
[35] Roche 2020, 118.

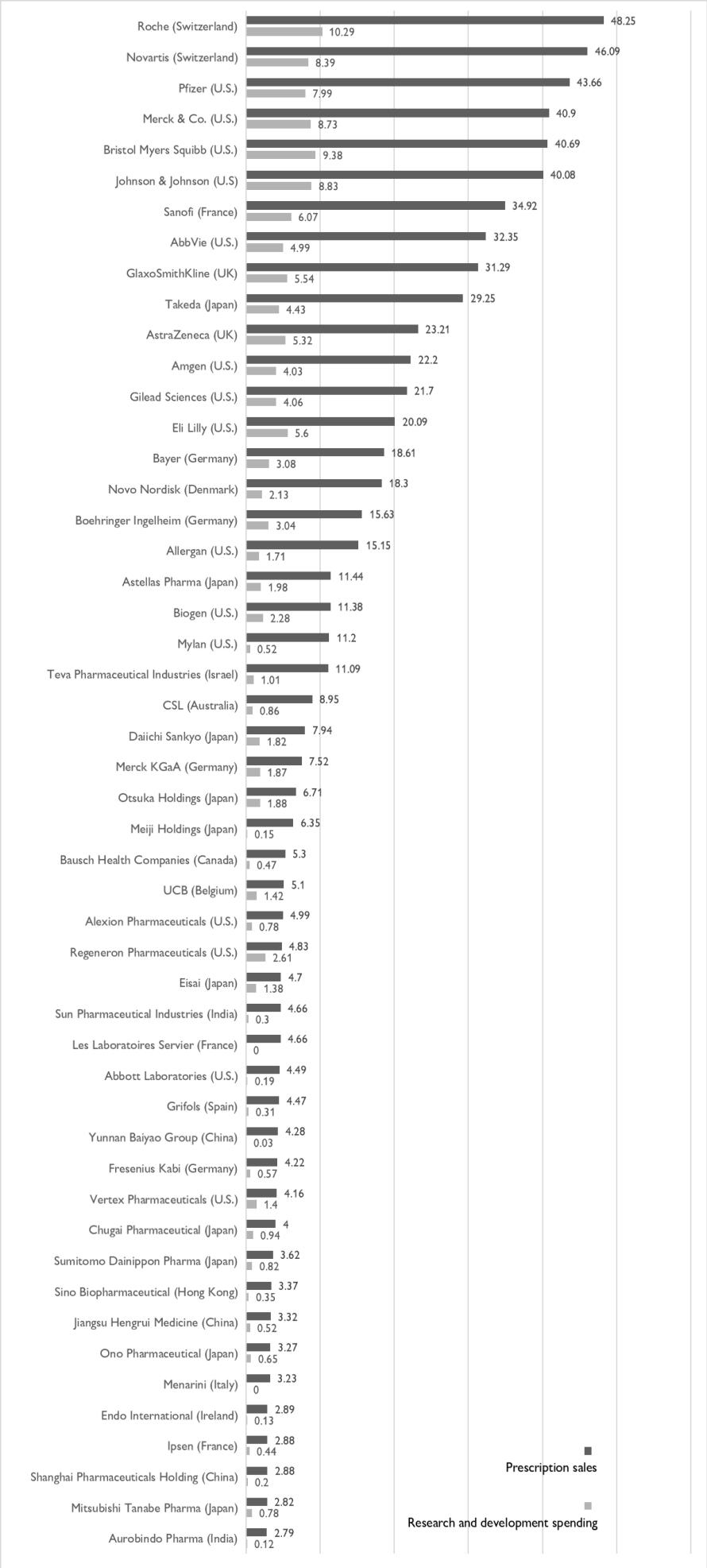

Figure 1.5: Pharmaceutical Companies per Prescription Sales and R&D Spending (in billion US Dollars). Source: Statista, 2020.

In this context, it is observable a common strategy alongside the market, that is focusing on heavy investment in R&D and in M&A. For example, Pfizer have 95 in-progress projects in clinical R&D and owns and licenses several of Us and foreign patents; as Pfizer, Bayer – another multinational pharmaceutical company – focuses its R&D activities on several area of scope, including consumer health, crop science, developing new molecules, technologies, and business models, employing around 7800 employers[36]. At the same time, Bristol Myers Squibb – during the last decade – has expanded its company's borders, including new small and medium firms, such as Celgene (2019), IMF Therapeutics (2017), Cardioxyl (2015), Forbius and Myokardia in 2020.

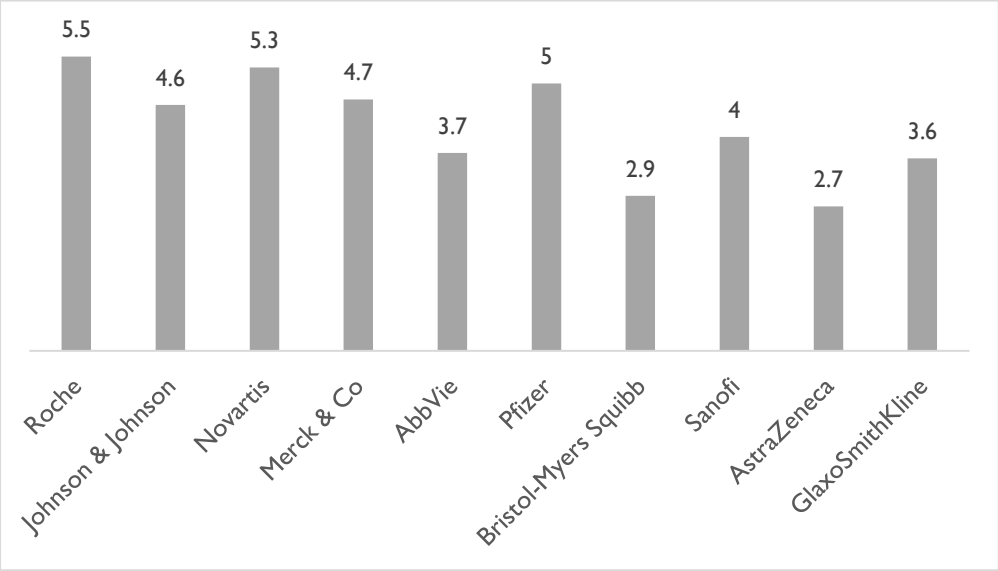

Figure 1.6: Pharmaceutical Companies by Market Share in % for 2019; We should notice that the data are not up to date and therefore may not describe the situation with the Covid-19 Pandemic ongoing. Source: Statista, 2020.

1.2.2 The Us Market

The United States of America is a particular market regarding several aspects of the pharmaceutical industry: it is the one most profitable market in the world (48% of the global sales happen in the us). A summary of the essence of the market can be find in these words: "the health care delivery system in the united states is described by some as the best in the world. For those who are uninsured or underinsured, however, it is described as the worst in the world."[37] The market has been growing steadily since the seventy, reaching in 2013 2.9 trillion US Dollars in health care expenditure (roughly, 9.255 us$ per capita). As we already seen, Us debate on nationalizing the health care system has been in place since the early XX century: instead of having a single system, the USA have a mix of public sector and private sector programmes (based, mainly on insurance programmes).

Regarding the Us pharmaceutical deliver system, there are different ways in delivering pharmaceutical substances: hospitals usually use unit based system, tracking the drugs delivered through bar code and double checks; local shop and wholesaler can be designated as point of distribution of generics and patented drugs,

[36] MarketLine. 2020 (I)
[37] Scott 2016, 1

and customers can purchase drugs directly from the pharmaceutical companies; community pharmacies act as point of selling of different communities along the Us territories, however in the last decades "the impetus for pharmacies *has been* to reduce inventory, increase prescription volume, and thus generating a higher turnover rate"[38]. Therefore, the environment is pushing toward a much more capitalistic vision of the selling of pharmaceutical products, without the interventions of the State or the Federal Administration.

Economically speaking, the US market has the biggest market share for pharmaceutical products globally: throughout the entire country, the most sell products are relative to oncology area, diabetes related illnesses, respiratory diseases, and HIV/AIDS.

If we apply the Porter's five forces model on the Us pharmaceutical industry, the deviation from what we already presented in the last section is small. Main differences can be found in buyer power: indeed, bargaining power of buyers is strengthened by the development of oligopsony and by the free pricing regimes. We should notice that the Patient Protection and Affordable Care Act – also known as Obamacare – is still under severe pressure from Us Congress, causing the Us healthcare apparatus to move from a value-based pricing system to a formulation of prices based on the health outcomes of drugs.

1.2.3 The Italian Market

Italian NHS, together with few other countries, is a universal and "free-to-access" healthcare system. This aspect puts the Italian market in a particular position compared to others around the globe.

If we look at the performances of the Italian market, it appears obvious the underperformed outputs that yearly pharmaceutical environment lives in: the reason behind this fall in growth can be find back to the financial crisis of 2008. Since then, Italian Government, together with the Italian Regional Health System have been under a strict review by European Union, using austerity measures to reduce public debt and inefficiencies in the system: only in 2010, the IT-NHS funding has been cut of 22.2 billion of Us Dollar, causing a drugs price drop by 1.2%.[39] The Italian sector had a total revenues of 25,1 billion U Dollar in 2019 with a revenues CAGR of 0% between 2015 and 2019 (in order to give context on this statement, French market has a revenues CAGR of -1.5% in the same period, while Germany a 0.6%). Since the collapse of financial system in 2008 and the real economy crisis of 2012, the use of generics has begun increasing: [40] indeed, the turnover of generics in Italy was 3.9 billion of Euro in 2018; since 2014, the generics average growth rate per year is totally increase of 33.1%, with an average yearly increase of 7.4% (slightly more than the patented drugs sub-industry).

At the same time, Italy has an assessed and strong background in clinical development (vaccines area, plasma protein therapies, advanced therapies, orphan drugs and rare diseases): indeed, according to MarketLine, 1/5 of Europe's clinical trials is conducted in Italy with a turnover of 0.7 billion of Euro.

[38] Scott 2016, 8.
[39] MarketLine 2020 (II)
[40] Nomisma and Egualia 2020.

The pharmaceutical delivery system in Italy is enormously different compared to the Us one. Firstly, the Italian NHS is public funded and accessible to every citizen no regards to ethnicity, wealth status or religious creeds (as stated in art. 32 of Italian Constitution): this aspect reflects also on the drugs delivery system in Italy. Italian drugs prices are much lower compared to the Us counterparts,[41] and the distribution is regulated by the State through different means. Intra-hospital distribution is conducted through hospital pharmacies (the so called *farmacie ospedaliere*), where specific treatment drugs are distributed: drugs delivered through these points of sale are rare diseases drugs, orphan drugs, class A drugs and those drugs listed in the PHT list.[42] The cost for the customer is totally or partially charged to the NHS, depending on the customer condition: usually the hospital pharmacies are used by discharged patients in need of specific treatments or by those patients under treatment for rare diseases or cancer related diseases. Together with the hospital pharmacies, along the Italian territory there are public and private pharmacies and drug store (*parafarmacie*). The former are pharmacies where are distributed prescribed drugs, OTC drugs and WPO drugs (without prescription obligation, or in Italian *SOP*, "*senza obbligo di prescrizione"*), while in the latter, State's regulations require drug store to sell only OTC and SOP.

As we already state early in the section, the pharmaceutical industry in Italy is markedly dissimilar to the global and Us one, also for what concern the forces in play. Italian market accounts for the 10.3% of the European pharmaceutical market value, at the same level of United Kingdom: compared to other markets, Italy has not LMCs and big corporations, however it has different intermediate size firms and smaller firms. This facet can be trace back to the incumbent presence of Large Multinational Corporations, such as Pfizer, J&J, Novartis, etc. Therefore, the competition scene is populated by Pfizer with 7.9% of market share, followed by Menarini (3.9%), Chiesi Farmaceutica SpA (1.1%), Recordati (1.1%) and others with less market stakes (86.1%).[43] The presence of these abroad incumbents, together with small generics company battling for each drug approval makes the rivalry condition very strong. At the same time, the threats of new entrants are low due to the strict regulations forcibly applied in the market and due to the different regulation on the patents and intellectual property protection regimes that lower the likelihood of new entrants. According to MarketLine, "entering the Italian market is made harder by the 50% reduction drug are discounted by when used in a hospital. Doctors – continues MarketLine – are also banned (*sic*) from prescribing a brand name and must instead use the chemical formula name".[44] Another regulation barrier is the usage of restrictive formularies that limit the utilization of specific drugs to the specific treatment or disease: this facet causes "potential market for non-formulary drugs to be smaller than the size of the therapeutic class market." [45] Therefore, it is safe to state that the threats of new entrants are quite weak, if not absent.

[41] *Regarding this point, the formulation of prices of drugs and relative impacts on the NHS systems are deepened in the last section of this chapter (cfr. 1.6).*
[42] Regulated through the article 1, comma 426 of Law 27/12/2013, published in Gazzetta Ufficiale n. 147 (GU n.302 of 27/12/2013 - S. O. n. 87).
[43] MarketLine 2020 (II)
[44] MarketLine 2020 (II), pg. 16.
[45] MarketLine 2020 (II).

At the same time, the threat of substitutes is considered high due to an increasing trend in the use of homeopathy drugs (according to OmeoImprese, 16% of Italian customers use homeopathy products at least once per year)[46] and due to the use of biosimilar (follow on biologics) and generics, for the same reason just discussed above.

1.3 SARS-CoV-2 and Pharmaceutical Industry.

In the late 2002, an atypical pneumonia case has been reported in the Guangdong region, Southern China province. The cause of this symptom has been linked to a new virus, the SARS-CoV (later SARS-CoV-1), a severe acute respiratory syndrome coronavirus, that causes a severe acute respiratory syndrome (respiratory symptoms such as cough, dyspnoea, and pneumonia). The outbreak of this virus reached 29 countries and infected more than 8000 people around the globe, causing 774 deaths. The virus spread mostly in Asian countries – with China and Hong Kong (at the time, in serious economic and governmental transformation due to the passage from an UK Protectorate to a Chinese territory) the most hit by the infectious disease. Europe, instead, responded in different ways and it was able to contain the spread of the virus: in order to give a comparison China had 5327 cases and 349 deaths, while Europe (Italy, Sweden, Romania, Germany, Ireland, France, Spain, and Switzerland) had 33 cases and 1 death. The reason for this less spreading of SARS-CoV-1 is not the topic of this section, however, we surely can state that the less globalization has favoured Europe and spared it from a much more spread of the virus.

Later, WHO's and independent studies have been proven that the origin of the SARS-CoV-1 was to be linked with a spill-over from mammals to humans[47]: moreover, according to Li

> "it is highly likely that there are more SARS-related coronaviruses to be discovered in bats. Indeed, our positive serological findings in the cave-dwelling fruit bat *Rousettus leschenaulti* indicate that infection by a related virus could occur in fruit bats as well, albeit at a much lower frequency (Li, 2005)"[48]

Indeed, in 2019 a Chinese doctor, practicing medicine in Wuhan (China), reported several cases of atypical pneumonias in his region. In the late 2019, specifically on the 27th of December, the Wuhan Central Hospital release a statement around the presence in the hospital of "a new kind of coronavirus", after assembling a quasi-completed viral genome of a similar strain of Bat SARS. The first international message of a new outbreak of a new virus has been published by FluTrackers (a web-forum that track changes in population health), stating that an outbreak of Chinese SARS has been communicated by the China Central Television.[49]

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[46] OmeoImprese. n.d. 'Omeopatia in Italia'. Accessed 24 April 2021. *Disclaimer: although the data presented in this essay are considered corrected according with different sources, including a non-verified news post of an ISTAT survey on utilization of homeopathic drugs in Italy, there is no source attached to the statements in this blog. Moreover, the data is cited by MarketLine in MarketLine 2020 (II), 16.*

[47] Li 2005

[48] Li 2005*, 678.*

[49] 'China - Original COVID-19 Coronavirus News Thread: Weeks 1 - 4 (December 30, 2019 - January 25, 2020)' n.d.

It is only on the 31st of December 2019 that the Wuhan Municipal Health Commission releases an official statement around the presence of vast clusters of pneumonia in the region.

On the 9th of January 2020, China CDC stated that a novel coronavirus (named 2019-nCoV) "had been detected as the causative agent for 15 of the 59 cases of pneumonia"[50]. In the later January 2020, the first cases of imported 2019-nCov have been assessed in France, Germany, and, later, in Italy. On 11th of February, the International Committee on Taxonomy of Viruses adopted the official name of SARS-CoV-2, in order to avoid confusion with SARS-CoV and discrimination towards Chinese people (the 2019-nCoV was often called 'Chinese Virus' by the Us President Trump). It is only on the 11th of March that WHO, together with CDC, declare the 2019-nCoV outbreak a pandemic, after Italian Prime Minister Giuseppe Conte's second worldwide lockdown imposition.

At this time, it is not possible to assume where, when, and how the SARS-CoV-2 officially originated; however, there are different research in medical literature that theorise the SARS-CoV-2 as a spill-over from a mammal to a human, like SARS-CoV-1.

SARS-CoV-2 (and its consequences, *id est* the Covid-19 disease) has been and still is responsible for various lockdowns (in order to contain the spread of the virus) around the globe, causing different crisis (especially economic and social crisis).

In order to understand the magnitude of the consequences of SARS-CoV-2 on the market, and on the pharmaceutical industry structure and practices, it is useful to underline the situation before the hit of the pandemic. Prior to the outbreak, the pharmaceutical industry was promising: indeed, the market – as we already seen in the previous section – was growing at a pace of 4.6%[51]. At the same time, the global GDP for the 2019 was increasing compared to 2018 at 2.8% pace[52]. In table 1.7, it is possible to see the revenues trend of the pharmaceutical industry together with the sales of retail products worldwide prior and during the outbreak of SARS-CoV-2: while retail sectors (line, in 1.7) suffered an enormous decrease in sales during 2020, pharmaceutical industry in US, Italy and Germany were slightly economically attacked by the outbreak. Surprisingly, Germany had not any decrease in revenues since the outbreak, on the contrary German pharmaceutical industry kept increasing its revenues, with a changed growth rate (2019: 3.99%; 2020:

[50] ECDC. 2020, 2.
[51] MarketLine. 2020
[52] Statista (II) 2021

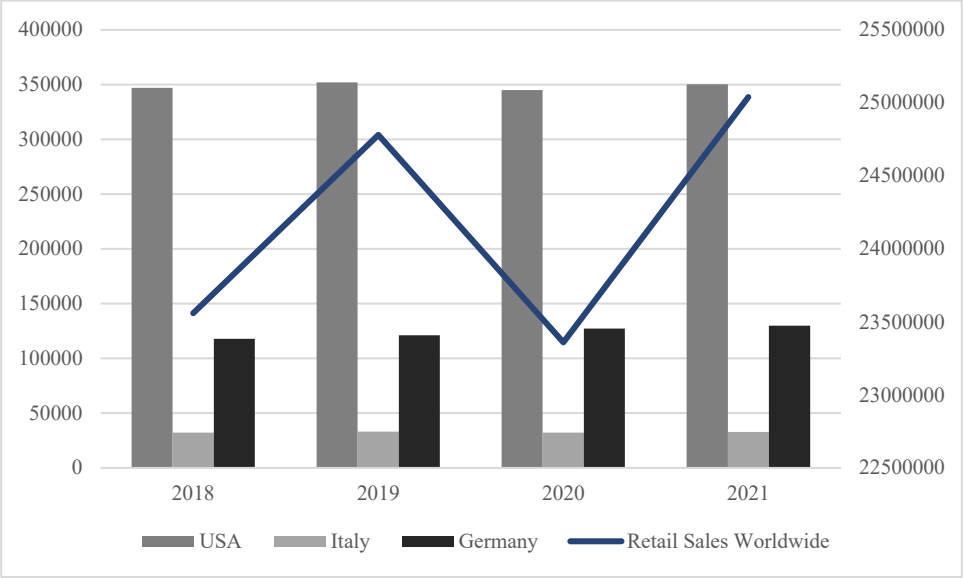

Figure 1.7: Comparison between US, Italian and Germany pharmaceutical industry revenues and worldwide retail sales from 2018 to 2021 (expected). Our elaboration. Source: Statista

2.10%).[53] Italian pharmaceutical industry, together with the US one, suffered instead a light decrease in aggregated revenues: macroeconomic causes, such as a decrease in consumption, and surely a less availability of raw material (especially in the first phases of the pandemic) have led to an insignificant reduction in revenues which have been quickly recovered in 2021. Since March to the end of June, different countries have been in shortage of basic medical devices and instruments: N95 masks, O_2 tanks and O_2 masks, API, pharmaceutical products (especially, drugs related to pulmonary diseases). Therefore, pharmaceutical and health industry have begun to transform and readapt their supply chains accordingly, in order to meet the incessant demand and to distribute lacking products.

With the SARS-CoV-2 pandemic, west countries began to rush for the research of new means to cure the disease (Covid-19) and to find ways to prevent the spread of the virus; hence, the focus was put on the development of new vaccines against the SARS-CoV-2, together with the creation of health policies ensuring distancing, compulsory masks wearing, and a communication pounding on hands hygiene (vehicle of transmission with breath droplets).

As we already state, the pandemic is having a huge impact on the economic and social situation of the entire world and the discover of new variants and mutations from the first observed SARS-CoV-2 virus is worrying most of the countries and pharmaceutical companies which have to cope with the continuous changing of the environment.

US Reactions. In the early phase of the pandemic, different countries, especially USA and Europe countries, began to research new means to fight the Coronavirus in order to minimize the effects of the pandemic through the funding of new research. US Government (Trump's Administration) in March 2020 published a Public

[53] Statista (III). 2020.

Law named CARES Act,[54] in order to, among many other reforms, support the pharmaceutical industry and incentivise the research of new vaccines or cures. With the CARES Act, the Govern commenced the so-called Operation Warp Speed, removing different barriers for the creation and management of public-private partnership and funding;[55] moreover, it decided to use a particular body of the Department of Health and Health Service (later, HHS), the Biomedical Advanced Research and Development Authority (later, BARDA) under the authority of the Office of the Assistant Secretary for Preparedness and Response (that is under the HHS Secretary, later, ASPR). Under Trump's Administration, BARDA Director doctor Rick Bright was removed from his tenure (for different reasons, among all, political ones), enrolling Gary Disbrow, PhD as acting director (then confirmed in November 2020).[56] BARDA is mainly a body inside the ASPR Office that manage the development, procurement, and distribution of medical countermeasures against biological, biochemical, nuclear, and radiological threats. It also maintains the stockpiles of resources for the Strategic National Stockpile.

As we have already stated, CARES Act removed 'barriers for the innovation' bringing new public-private partnership, using funds allocated by law from the H.R.748 through the supervision of the US Department of Defence (later, DoD). Title III, subtitle A, part III of CARES Act "amends the Public Health Service Act to remove a cap on 'other transaction authority' […] to allow BARDA to more easily and rapidly collaborate with the private sector on research and development of qualified countermeasures or qualified pandemic or epidemic products."[57] Again, Division B, Title I and Title VIII ensure the allocation of different categories of emergency funds to respond to COVID-19, including development, and purchase of necessary medical products.

Therefore, BARDA, together with DoD, enhanced a funding campaign to pharmaceutical companies in order to develop and produce different vaccine. [58] 10 Billion Us Dollar have been distributed to different entities including AstraZeneca, Moderna, Novavax, Johnson&Johnson and others, following the scheme in table 1.1.

The decision of funding numerous and diverse private company comes with a lot of critiques. The fundamental point on which these are based on will be discussed in the following chapters: for now, it is useful to underline the main points. In normal times, the US administration uses the so called National Institute of Health (later on, NIH) as point of contact and mean for funding private partnerships with public funds. According with CARES Act, BARDA received 3.5 billion US Dollars for the development of medical countermeasures, together with the access to the 27 billion Us Dollar that HHS received for the same purpose. The main critique around this point is on the utilization of public money gifted to pharmaceutical companies to develop and

[54] 116th United States Congress 2020
[55] White&Case LLP 2020
[56] Shear and Haberman 2020
[57] White&Case LLP 2020.
[58] Bloomberg.com 2020; Stacey and Kuchler 2020.

Grantee	Medical Technology	Date of awarding	Amount granted (in US Dollar)	Notes
Johnson&Johnson	Viral vector	5th August 2020	1 billion	ASPR-BARDA with US ACC, DoD 2020
AstraZeneca - University of Oxford, Vaccitech and IRBM	Adenovirus viral vector	21st May 2020	1.2 billion	ASPR-BARDA with DoD (II) 2020
Moderna	mRNA	11th August 2020	1.53	ASPR-BARDA with HHS 2020
Novavax	Recombinant spike protection nanoparticle with adjuvant	7th July 2020	1.6 billion for manufacturing and distribution	ASPR-BARDA with DOD (I) 2020
Merck and IAVI	Antiviral drug	15th April 2020	0.03 billion	Terminated by Merck for inadequate response
Sanofi and GSK	Protein with adjuvant	31st July 2020	2.1 billion	Still ongoing

Table 1.1: Distribution of funding for Covid-19 Vaccines and Therapies; see notes for sources.

manufacture a vaccine against Covid-19, while different public funded research bodies and foundation could have used the same amount of funds to develop a vaccine that could be 'owned by the public'.

This critique came especially from a group of Us-International researchers from University of Pittsburgh (Pennsylvania, USA). Indeed, in 2003, Andrea Gambotto together with many other academics discovered a formulation that could be the perfect candidate for the SARS-CoV-1 vaccine (SARS); although still in pre-clinical phase, with the outbreak of the first SARS-CoV-2, UPitt researchers began to develop a new formulation (based on the already discover one from the SARS-CoV-1) for the fighting of Covid-19, with a cheaper and more practical vehicle of distribution (microneedles array patches).[59] However, back to 2003 the NIH, together with the Bush's Administration, refused to sponsor such vaccine for two main reason: the urgency of funding of the Iraqi war and the no economic output that such a funding could have been showed in 2003 (SARS pandemic was much less severe and under control during those times). According to various sources,[60] during Covid-19 pandemic Pittsburgh laboratories began again to look for this mean as vaccine, receiving from NIH and Trump Administration no funding whatsoever: hence, the pool of scientists started to remake the entire process of authorization in Italy in order to receive the authorization for the clinical trials and, possibly the MAA, for a future vaccine (with different vehicle of transmission: a nasal spray).

European Response. The old continent response to the SARS-CoV-2 Pandemic has been fairly hectic: the first countries to register Covid-19 cases acted in different ways.[61] Italy decided to initiate a total lockdown, impeding the free circulation of people, France instead decided to retard the start of a lockdown (mid-March 2020[62]), Germany turned the decision toward its regional parliament (*Landesparlamenten*), which only 5

[59] Kim et al. 2020
[60] Zito 2020; Tornago 2021; Kim et al. 2020.
[61] Roser et al. 2020.
[62] Or et al. 2021

Länder decided to impose a sort of lockdown. Overall, the response to the European Covid-19 pandemic threat was inadequate considering the risk of spreading of the viruses: truthfully, however, the information around the mechanism of spreading and infectious of SARS-CoV-2 were at that time insufficient to turn them to real and effective actions.

Hence, the European Union began to fund diverse and significant research and development of new means for prevent and fight the SARS-CoV-2 and Covid-19 spreading. Through a modification of EU Reg. n. 2014/282 (EU Reg. n. 2020/1043), the Union decided to specifically turn the mission of Horizon 2020 (2014-2020 programme) in order to sustain and support new research on SARS-CoV-2 fighting. In January 2020, the EU Commission launched an emergency call for the awarding of 48.2 million Euro; among the projects awarded, three different projects have been funded in order to develop a Covid-19 vaccine: OpenCorona, Prevent-nCoV and BioNTech (Biopharmaceutical New Technologies). The first one is a project led by Karolinska Institutet, together with other research institutes and the Italian Pharmaceutical small enterprise Igea Pharma SpA aiming to find a vaccine that can act also as therapy for SARS-CoV-2 disease; the second one was a project aiming to use proprietary technology to develop a novel and scalable vaccine combining the virus-like particles (or VLP) and an antigen (project led by Kobenhavns Universitet, and other German and Dutch institutes); the latter is performed trough the combination of two different financing methods: one is a loan agreement signed between BioNTech and the EIB (European Investment Bank) and the other one is a financing of 30 million Euro from the European Fund for Strategic Investments (EFSI) via Horizon 2020.[63]

With more progresses on the SARS-CoV-2 fight and the outbreak of new variants and mutations, in the early 2021, EU Commission started to fund[64] research on countermeasure to Coronavirus variants, funding the "HERA Incubator", mobilising 30 million from Horizon 2020 and Horizon Europe; at the same time, EU Commission decided to join the VACCELERATE Network and fund it with 12 million Euro in order to establish a network spanning 21 countries and EMA, in order to test vaccine efficacy, efficiency and safety on different age and health status groups.

Ultimately, European Union did not behave as USA: they decided to not collectively sponsor or fund important private pharmaceutical companies' projects[65], delegating the possibility to single member states. Other than the projects cited above, indeed, nothing has been literally funded: instead, EU Commission decided to purchase in advance certain number of vaccines in order to allot them to every member according with a certain proportion. For example, Germany decided to fund with 445 million Euro the pharmaceutical company Pfizer-BioNTech[66], while at the same time IRBM gave the possibility to the Italian Govern to sponsor a part

[63] EU Commission 2020 (website)
[64] Fleming and Peel 2021
[65] *While in aggregate view this stands truth, European Union has sponsored in a way the development of the Oxford-AstraZeneca Vaccines. For this see §3.2.*
[66] Griffin and Armstrong 2020

of the development of the AstraZeneca vaccine (requiring 70 million Euro) and, therefore, acquiring the intellectual property of the vaccine, however Prime Minister Conte refused to act accordingly.

Italian response. The European Union Commission decided to collectively fund different projects for developing Covid-19 vaccines and cures. Different single member-states decide, instead, to fund the development and production of diverse pharmaceutical products and vaccines for fighting the Coronavirus. Italian Conte's Government decided to sponsor the development of two Covid-19 vaccines: GRAd-Cov-2 and Covid-eVax. The former developed by Reithera, and Lazzaro Spallanzani National Institute for Infectious Diseases is based on adenovirus viral vector technology, in phase 3 at the time writing,[67] while the latter is based on antigen-coding DNA sequencing, and it is developed by Takis and Rottapharm Biotech.

To conclude, pharmaceutical industry during the outbreak and the following Covid-19 pandemic have had a huge flow of funding and an immense aid from Regulatory Agencies which, obviously, authorized and implemented an expedite path for the marketisation of new drugs. Therefore, it safely to state that the Covid-19, without considering social impacts, has greatly benefited the industry.

1.4 Pharmaceutical Regulation Systems

Pharmaceutical regulation is defined as "the combination of legal, administrative, and technical measures that governments take to ensure the safety, efficacy, and quality of medicines, as well as the relevance and accuracy of product information".[68] Therefore, we can define the regulatory authority as that body entitles to develop and enforce pharmaceutical legislation and regulations: main tasks are linked with quality, safety and efficacy assess of drugs, and the accuracy of product information.[69]

Far from recalling the entire Theory of Regulation, it is useful to frame the reason why regulation authorities are needed in the market. Campbell citing Pigou states "that the pursuit of self-interest which motivates economic action can readily take unwelcome forms, such as mere appropriation by violence or deceit, and accepted without much argument the necessity of a legal framework which channelled self-interest into the beneficent form of exchange as an essential condition of market order."[70] In these words, it is possible to see the deeper motivation of regulation existence: in order to outcome the failures of the self-regulation of the markets (and of the actors in the markets), it is ineluctable to funnel the possible negative results on a social and beneficial paths. More operatively, the economic reasons for the existence of a regulatory agencies can essentially be linked to two failures of the market: the imperfect or absence of informative symmetry, and the patents and insurance-related moral hazard for price and reimbursement regulation.

[67] InvItalia 2020.
[68] Al-Worafi 2020, 21.
[69] WHO 1999.
[70] Campbell 2018.

The main motivation of creating a regulatory authority in a country could be originated from the need of assessing and controlling the efficacy and safety of pharmaceutical products on the market. Since the first authorities, the frameworks around the pharmaceutical regulation have evolved in favour of a more globalise and standardized legislation. Nowadays, the processes of registering and marketizing a medical product are fairly similar: the differences presented in the following section are mainly based on different strategic vision of market. Indeed, Europe, together with its member-states, apply standardized procedures, keeping the independence of certain decisions to the national regulatory agencies; while, USA has only one regulatory agency – Food and Drug Administration – which decides, assesses, and controls on pharmaceutical products for every state of the Federation.

The scope of a regulatory authority does not end with the 'efficacy and safety' control of drugs, it also focuses its activities on drug marketing legislation, drug development framework, quality controls, pharmacovigilance after marketization of drugs, and price setting.

In the following section we will outline the different processes of drug approval for FDA and EMA, with a focus on AIFA (Italian authority).

1.4.1 United States Regulation System: Food and Drug Administration

The United States body that assesses the quality, safety and efficacy of drugs is the Food and Drug Administration (later, FDA). The authority was founded in 1906 with the Pure Food And Drugs Act in order to control the interstates distribution of drugs, and regulated and publish the 'addictive or dangerous' components of drugs in the market. Throughout the decades, the US Legislator enhance and enlarge the regulations around the two main scopes of FDA, from regulating the packaging of pharmaceutical products, controlling the distribution of possible abuse drugs, regulating the composing of certain food products, to improving the generics market and the competition inside the pharmaceutical industry. Indeed, in 1984 the Drug Price Competition and Patent Term Restoration Act (also known as Hatch-Waxman Act) was approved by the US Congress, expediting "the availability of less costly generic drugs by permitting FDA to approve applications to market generic versions of brand-name drugs without repeating the research done to prove them safe and effective".[71]

Since the Hatch-Waxman Act, the pipeline of approving and distributing a new drug has changed towards a split between on-patented drugs and generic drugs. Nowadays, the chain of approving is fairly complicated by the different means of marketisation. Without deepening the patent side of the processes, we can outline three different pipelines of approving a drug, differentiated by the status of the drug itself.

The pharmaceutical company with a new candidate drug has to file an INDA, or Investigational New Drug Application, in which it will include the preclinical testing, the manufacturing information, the investigator

[71] FDA Office of the Commissioner 2021

information, clinical trial protocols and other commitments. The INDA is compulsory for every drug candidate: it has to be filed in the preclinical phase of trials when the drug is still *in vitro*-experimental phase or *in vivo*. There is no filing need in this phase, but companies have to follow the good laboratories practices submitted by FDA and US Federal Government (Code of Federal Regulation, Ch. I, subchapter A, part 58).

There are two types of INDA depending on the use of the drug. The first is the commercial INDA, an application usually filed by a for-profit company with the intentions of obtaining a marketization approval in the future. The other one is the non-commercial INDA, generally reserved for drug for research purposes or for obtain a future approval for an unapproved drug. There are three categories of non-commercial INDA: the first is an Investigator IND usually submitted by a physician that starts a study of an unapproved drug or of new population target (such as different disease than the illness that is hit by the approved drug), the responsibilities for the drug are under the sponsor as per 21 CFR Part 312.3; the second is an Emergency Use IND, also known as compassionate use or single-patient INDs, these let FDA grant the use of an experimental drug in an emergency situation (it was recurrent during the first phases of Covid-19 pandemic). Finally, the last is the Treatment IND that is filed for those drugs that can cure life-threatening diseases and for those drugs still in the final phase of clinical trial.

After filing the INDA and completing the three phases of clinical trials, the company can file an NDA with every information collected. The Federal Food, Drug and Cosmetic Act approved in 1999, describes thoroughly the documents that have to be filed for an NDA. Section 505 [21 USC 355], let. b.1.A, n.i to viii, states that the NDA has to contain the full reports of investigation "which have been made to show whether such drug is safe for use and whether such drug is effective in use"[72], a full list of components and composition, full description of use of the drug and methods of administration, samples of the candidate drug and the patent number of the drug. Regarding the patent side, we will address the topic in the next chapter: however, section 505 (b)(2)(A) states that NDA can also be filed in those situations where certain information is not available or does not exist (such as patents numbers, expired patents, or infringing patents). Section 505, (b)(2)(B) also address the scenario where the NDA is related to a drug whose active ingredients, dosage form, strength route, labelling, quality, and performance are identical to a pre-existence approved product.

Section 505 (b)(2)(B) lays the foundations of the ANDA that is the Abbreviated New Drug Applications, reserved for those drugs with expiring patents which are going to be marketized as generic drugs. After the filing of an NDA, the FDA has the right to approved or issue a notice of denial of approval within 180 days. We should notice that FDA does not have to approved or deny the approval in 180 days: indeed, there are two overlapping periods of 180 days where the first is called "review clock", that begins with the submission of the NDA (if there not any issues regarding the composition of the application and, if so, it is published after 60 days from the filing) and ends with an "action letter" (see next paragraph). The second 180 days window is referred as the "filing clock": "this time period begins 60 days after FDA's receipt of the application unless

[72] FDCA, sec. 505 (b)(1)(A)(i).

the agency determines that the application is facially deficient and should not be filed. Such a determination is called a refuse-to-file (RTF) action. The agency must either approve the application or issue a notice of an opportunity for hearing by the expiration of the 180-day filing clock."[73] In total, the FDA has 240 days for process an NDA, (60 for rejects the NDA for procedural defects and 180 for the issue of a "action letter"), but is fairly common that the applicant files supplemental information that extends the time window of the NDA approval.

After 240 days, FDA issues an "action letter" that can be an approval letter, an approvable letter, or a not-approvable letter. The first indicates a positive outcome of the NDA; the second one is issued for those drugs that met the requirements but have minor deficiencies (23 CFR 314.110). In this case the applicant can file a resubmission or amendment, withdraw the application, request a hearing for deepen the decision, or agree and take more time for choose which actions are best suited for the process. The non-approvable letter is prescribed by 21 CFR, 314.120 (a) and the applicant can response amending the NDA, withdrawing it, or requesting a hearing as per above.

As cited above, Section 505(B)(2) of Food, Drug and Cosmetic Care Act prescribes that some NDA cannot rely on data provided by the applicant: the main difference with the 505(b)(1) NDA is that the investigation were "not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted."[74] A 505(b)(2) application must contain a patent certification that states that the patent has expired, or that the applicant is willing to delay the approval until the patent is expired, invalid, unenforceable, or not infringed. The filer of this application has the duty to notify the patent holder and the applicant that the patent is invalid or not infringed. The notification, however, can lead to a lawsuit for patent infringements which may delay the approval process up to 30 months.

Lastly, FDCA sec. 505(j) prescribes the creation of the Abbreviated New Drug Application, ANDA later on: ANDAs are NDAs for generic drug that are not provided to contain the same regulations and data provided for 505(b)(1) application. ANDA has to be filed only for those copies of drugs already approved by the agency, contained in the listed drug (Orange book, see later on). Within the limit of FDCA, 505(j)(2)(A)(i)-(viii), an ANDA has to hold information about the already drug approved and the numbers of active ingredients contained in the listed drug and generic drug, the information of the route of administration, dosing, strength of the generic drug, information "show that the new drug is bioequivalent to the listed drug referred to […], information to show that the other active ingredients of the new drugs are the same as the active ingredients of a listed drug or of a drug which does not meet the requirement of section 321(p) [*of FDCA*]"[75], information that ensure the equivalence between labelling of listed drug and generic drug, together with those information for 505(A)(2) of FDCA.

[73] McInnes 2011, 5
[74] FDCA, 505(b)(2)
[75] FDCA, 505(j)(2)(A)(iii)

Companies filing ANDA does not have to file an INDA: indeed, ANDAs can be considered as a single application, does not prescribe a preclinical investigation or a clinical trial (with the filing of the INDA). However, the applicant has to ensure and specify the bioequivalence or similarity with the listed drug is referring in the application. In a specific case, FDA can waive the requirement of demonstration of bioequivalence, and that is when the dosing prescribe by the generic and the listed drug is through injection or oral administration because the bioequivalence is self-evident. The process of approval for ANDAs is the same for NDAs, FDA can deny the application within 60 days for procedural defects, and 180 days for the 'action letter'.

With the approval, FDA inscribe the drug in the Approved Drug Products with Therapeutic Equivalence Evaluation, also called Orange Book for the cover colour of the hard-copy version and of the introduction page of the website.

After issuing the acceptance of the NDA, FDA does not end its role in the process. Indeed, if the applicant wants to change any conditions of the accepted NDA has to file a new supplemental application to FDA in order to get the approval for the changes. At the same time, FDA performs manufacturer inspections in order to ensure the respect of the Good Manufacture Practices and it also regulates the advertisements and promotion of pharmaceutical products. Finally, it performs pharmacovigilance duties in order to ensure the quality and safety of the marketed listed drugs and generic drugs.

We finally should point out that NDA applicants have an exclusivity window, during which no company can file an ANDA for the generic use of a patented drug: this is set by the Hatch-Waxman Act in order to resolve the reverse engineering of generic pharmaceutical companies that hit patented drug and exploit them without any R&D costs. We can say that the measure is a sort of 'equalizer' of the market.

1.4.2 European Union Regulation System: European Medicines Authority

The European Union regulation system is in a unique situation: contrary to the United States of America, European Union is not a federalisation of states, it has not any supranational bodies that can rule for every aspect of the lives of European citizens, and therefore, has precise borders of ruling. The Treaty of Lisbon has established the contents which the European Union, together with its legislative and regulative bodies, can act on.

In this context, since the first treaties for the establishment of the Union, the pharmaceutical industry has been in the centre of different and complicated reform which aimed to found a cooperation between state-members on the regulation and protection of public and animal health, while ensuring the free circulation of medicines, according with the Treaty on free movement of people, goods, and money.

Indeed, the Council Directive 65/65/EEC (OJ No L.147, 09/06/1975) laid down what it is still the EMA framework. Since the 1975, the activities of member-states were aiming to a systematisation and

institutionalization of different directives and procedures common to HTC bodies across the European Union. The outcome of this long and thoughtful process led to the creation of the European Medicines Evaluation Agency, created with the Council Regulation (EEC) N. 2309/93 on 22 July 1993 (Oj N. L214, 24/08/1993) along with other three directives on existing human and veterinary medicinal product legislation. The operational activities of EMEA only started in 1995 with its headquarters based in Canary Wharf, London. [76]

The institution had as precursor of the Scientific Committee the former Committee for Proprietary Medicinal Products and Committee for Veterinary Medicinal Products. Throughout the experiences of EMEA, the management Board and the European Union concluded that the participation of the national competent authorities of the member-states were and still is fundamental. Indeed, contrary to the FDA, EMEA, now EMA, is a decentralised scientific agency with the mission of performing technical and scientific tasks that help the EU institutions. According to European Union[77], "[EMA] protects and promotes human and animal health by evaluating and monitoring medicines within the European Union (EU) and the European Economic Area (EEA)".[78]

Being a decentralised agency, EMA does not entirely substitutes the activities that national authorities are entitled to perform. Indeed, the European agency performs human and veterinary pharmaceutical evaluations for the member states in the context of approving the marketizations in the European market. However, there are specific drug class that are mandatory to be evaluated by the EMA: rare diseases drugs, HIV, cancer, neurodegenerative disorders, diabetes, auto-immune diseases, viral diseases, biotechnology drugs and those drugs that focus on gene therapy and monoclonal antibodies. For other class of drugs, the manufacturer or patent holder has the right and possibility to apply for the market authorization (MA) within the EEA, and therefore being able to market the drug in every European country, or he can apply to the national authority, limiting the sphere of marketisation within the State where it is applying to.

Therefore, it is possible to summarize the EMA activities regarding regulating pharmaceutical pathways, saying that EMA is entitled to perform a 'centralised procedure' where companies apply with one application, going through a single evaluation and a single authorisation. While national authorities are entitled to a mutual recognition procedure by validating previously granted approvals, a decentralised procedure where the company applies for a specific authorization in a specific country and the regulatory agency applies the approval in every country of the Union, or a national authorization: indeed, pharmaceutical companies have the right to apply for a MA to a single national authority and then asking for the recognition in all member-states, or for economic, legal and strategic opportunities can only apply for the national market.

The EMA's regulatory approval process is fairly different from the FDA's one: being a decentralised scientific agency, as already stated, its powers and rights are comparatively mere than the FDA's. Indeed, in order to

[76] EMEA 1996,
[77] EU 2016 - website
[78] EU 2016 - website.

acquire a Market Authorization, the applicant has to undergo several and thorough procedures for assessing the quality, safety, and efficacy of drugs under scrutiny.

As a matter of fact, EMA performs duties linked with different phases of drug research and development. While it is not authorized to compel companies to research specific drugs or treatments, it publicises areas where the need of new breakthroughs in medicine are urgent. However, EMA can give scientific advice such as guidance and direction in R&D processes. The reasons behind the providing of scientific advice are mainly for generating robust and complete studies and data in order to give patients quick access to the drug.[79]

The regulatory pathway is as follow. After the preclinical phase of development of a drug, the drug applicant (for-profit company or academia or research institute) submits a CTA – Clinical Trial Application – to the competent National Regulatory Authority (for Italy, AIFA) in order to conduct the three phases of clinical trial (for the contents of the CTA, see next subsection). In any case, EMA has the duty to ensure that the good clinical practice is applied across the EEA in accordance with the requirements set by the Annex 1 of the Directive 2001/38/EC: the Directive states that clinical trial have to comply with European legislation on the matter (Directive 2001/20/EC) and with the ethical principles (International Good Clinical Practice and Declaration of Helsinki). [80] We should point out that according with Chiodin et al., the CTAs and the IND (cfr. 1.4.1) are fairly similar regarding the number of documents to file in order to have a clinical trial approved: however, the CTAs "contain fewer documents than INDs, requiring less preparation time"[81] and "do not carry potential risks for clinical hold like INDs do". [82]

During the pre-submission phase, to the applicant is given the opportunity to be guided by EMA in order to ensure legal and regulatory compliance of requirements for MAA: this guidance is conducted by different expert of different areas for exploring every aspect of the candidate drug, from quality to risk management. In accordance with the Law N. 0083 of 16th November 2001[83], the MAA has to contain various documents and information as stated in Annex I of the above cited Law, art. 2.1-.7 such as active substance, manufacturing information, characterisation, microbiological attributes, clinical overview where clinical findings are shown together with non-clinical information (pharmacology, pharmacokinetics, and toxicology). During this phase, the applicant has to file a document stating the official date of MAA submission (a letter of intent request): the CHMP and the PRAC, according with the letter of intent, appoint rapporteurs to conduct the following scientific assessments. Besides, in this pre-phase, the applicant has the right to request a pre-submission meeting in order to be guided in the process and to enable themselves to be in line with legal and regulatory requirements. After the pre-submission phase, pharmaceutical companies willing to market a drug have to

[79] EMA 2019; Van Wilder et al. 2015
[80] EMA 2019
[81] Chiodin et al. 2019
[82] Chiodin et al. 2019
[83] European Union Parliament 2001

respect the date set by the letter of intent (send before to EMA). Indeed, the applicant at the set date has to file an electronic Common Technical Document (eCTD): with this filing, the application pathway officially starts.

After the MAA filing, EMA performs a technical validation of the application, making sure that all essential requirements are met by the application. If EMA finds any missing information, the applicant has the possibility to supply them by a set date.

Considered the information in the eCTD, the CHMP starts the evaluation of the MAA together with the PRAC and the CAT (if needed). At this stage, the rapporteurs of the just cited Committees have the right for requesting an inspection of the manufacturing site, of the non-clinical and clinical study, and of the pharmacovigilance process performed by the pharmaceutical company. At the same time, members of the PRAC have the duty to assess the company risk management plan filed in the eCTD. After these inspections, the CHMP, PRAC and CAT members assess the reports and file a list of questions to be submitted later to the applicant. With this list, every member of the Committees, together with the rapporteurs and co-rapporteurs meet in a peer review meeting, addressing every doubt, problematic and concern on the drug in scope. The outcome of this meeting is a single report that comprise an overview of every assessment performed up to that day.

Therefore, after 120 days from the submission, there is the first clock stop: the evaluation is paused allowing the applicant to address and respond to the questions filed by EMA. This phase, averagely, takes from three to six months.

After the applicant's response of EMA's list of questions, the second part of the assessment can start. The active evaluation clock can restart: the rapporteur and co-rapporteur evaluate the applicant's answers, updating the report and the analysis of the drug. The CHMP reviews the updated assessment together with PRAC. In this occasion, PRAC has the right to ask to the applicant the planned conduct of safety after authorisation. Comments from PRAC and CHMP are collected and transformed in a consolidated and integrated assessment report that will discuss together with the applicant later in the evaluation pathway. Generally, this report contains a new list of questions, called list of outstanding issues.

If a list of new questions is formed, the active evaluation is again stopped (second-clock stop) while the applicant prepares the response to these issues. The applicant has from one to three months to address the problematic expressed by EMA.

After the second clock stop, both the applicant and the CHMP can ask for an oral explanation about the application and its linked issues. Usually, CHMP organised this type of meeting when EMA has major objections about the drug on scope. Once the responses are satisfied, the CHMP assesses the revised information together with the PRAC relation on the risk plan of the applicant. By the day 210 of the active evaluation process, CHMP adopts a final decision on the MAA: the committee makes then the

recommendation on whether the drug has to be market or not, also agreeing on the product information and labelling of the drug.

At this stage, if the applicant is not satisfied by the final decision of EMA, can request a re-examination of the CHMP's opinion, stating on which ground they are appealing the decision by day 15 from the file of the final decision. In this case, the rapporteur and co-rapporteur are changed and in 60 days the CHMP has to adopts a new final opinion.

These brief excursus of the regulatory process of approval of an MAA is reserved only for the centralised procedure (as we have already seen): the centralised procedure have been indeed created in order to enable rapidly the marketing of a drug in the European Union Market. With the aim to give a graphical perspective of the timing of the centralised procedure, it is advisable to see the figure 1.8 that describes two pathways: one (A) is related to the standard assessment and the other (B) the accelerated assessment that reduces the total time by 60 days of active evaluation (that is, not considering the two clock stops).[84] We should notice for clarify every aspect that figure 1.8 is related to ATMP (advance therapy medical product), but the procedures are the same for every type of drugs and medical product.

1.4.3 Italian Regulation System: Agenzia Italiana del Farmaco

The Italian Regulation Authority is the Agenzia Italiana del Farmaco (literal transl. Italian Agency of Pharmaceutical products; later on, AIFA). AIFA is instituted with the Decree n. 245 of 20th September 2004 that outlines the functions, duties and responsibilities, and organization layout of the Authority[85]. Before the

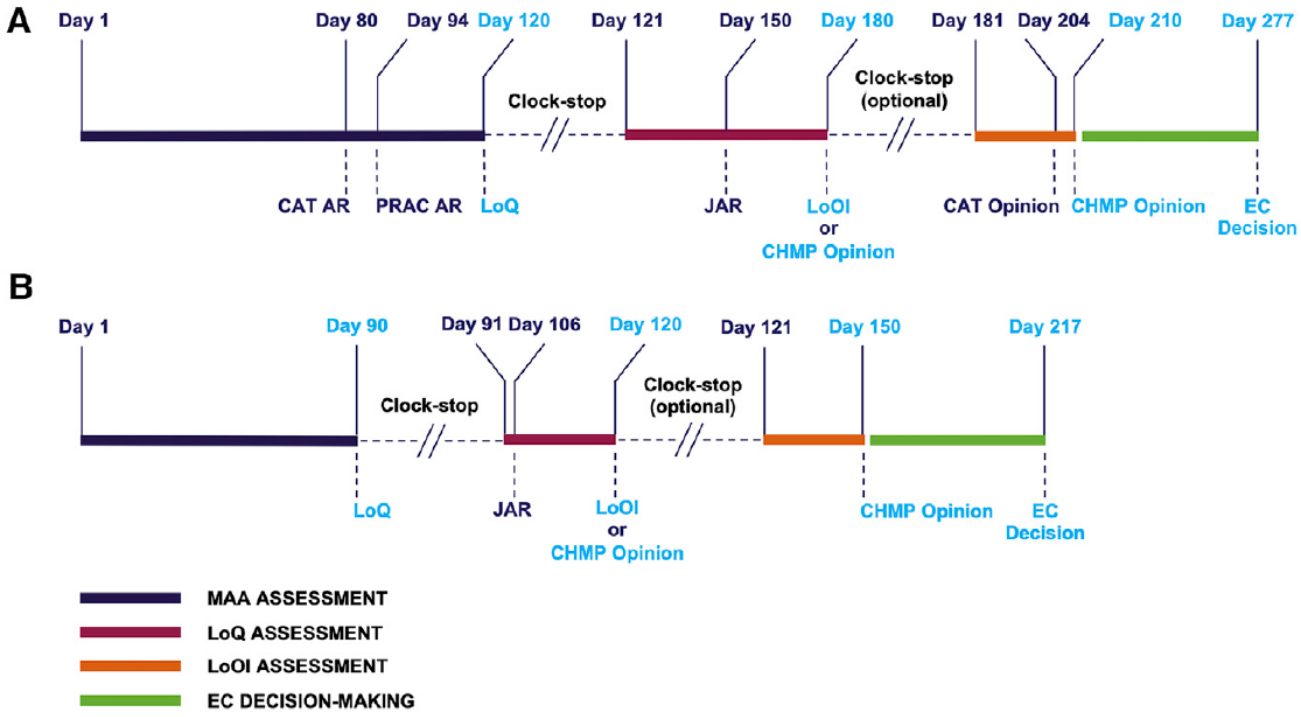

Figure 1.8: Timeline of MAAs according with centralised procedure. Source: Detela and Lodge 2019

[84] Detela and Lodge 2019
[85] Parlamento Italiano, 20th September 2004

foundations of AIFA, the regulation activities were performed by the ISS (Istituto Superiore di Sanità, already called ISP [Istituto di Salute Pubblica], founded in 1925 by the Fascist Regime).

AIFA is entitled by different Decrees and Statutes to perform three procedures: one is the decentralised procedure, the other one is the mutual recognition procedure and, lastly, the national authorization. In this paragraph, we will see all three procedures, keeping in mind that some process can be similar to each other. The first and the second are regulated by national and supranational regulations: among all, the main directive comes from the 'Notice to Applicants. Volume 2A. Procedures for Marketing Authorisation' published in 2016 by EMA.[86] Instead, for what concern the national authorisation, AIFA has to follow the Legislative Decree n.219 of 24th April 2006.[87]

Decentralised Procedure. The decentralised procedure, as already stated, is that procedure allowing the applicant to request the marketisation of a drug non-included in the mandatory scope of the centralised procedure (cfr. 1.4.2) to a Member State that will allow the marketisation to all the European Union. Generally, the applicant may file such type of application to one or more Member States in case its drug has not already acquired an MAA. The decentralised procedure consists of six steps: the pre-procedural step, the validation phase, two assessment stops, the discussion at the CMDh (if needed) and the National Step.[88] In the pre-application stage, the future applicant should inform the National Authority considered (later on, RMS – Reference Member State) that they are willing to file an application under the decentralised procedure. As for the centralised procedure, it is advisable that the applicant reach the RMS in order to ask for guidance in the procedure, while following the rules that the RMS imposes. Throughout the entire process, the RMS together with the Concerned Member States (later on, CMS) are assisted by the CMDh (Co-ordination group for Mutual Recognition and Decentralised Procedures). Once the pre-procedural step is completed, the applicant can file an application to the RMS and to the designated CMS, ensuring that the documents and the presented data are the same both in the RMS application and CMS application. The validation period starts at the time of receival of the submission of the dossier and lasts 14 days: in this phase the RMS has the duty to validate and circulate the 'RMS validation checklist for human medicinal product in Decentralisation Procedure' (DCP) to the CMSs and to the applicant. Whereas the RMS is in doubt to legal ground on the validity, can ask the CMDh advise. Once the validation phase is completed, the RMS can initiate the two assessment steps. The first step consists of 120 days of active evaluation during which the RMS has the duty to prepare the Draft Assessment Report and comments on draft SmPc, PL and draft labelling documents. The RMS forwards the PrAP (Preliminary Assessment Report) to the CMSs and the applicant within 70 days of active evaluation phase. By day 100 CMSs have to communicate their comments on the PrAP to the RMS, other CMSs and to the applicant. If consensus is reached, the RMS prepare the Final Assessment Report and at day 105 closes the procedure, continuing with the national procedure. However, if no consensus is reached, the RMS send a Request for

[86] HFS Directorate-General EMA 2016
[87] Parlamento Italiano 2006
[88] CMDh - EMA 2020

Supplementary Information (RSI). At day 105, there is the first clock stop of active evaluation: the applicant has 3 months to respond to the list of question prepared by the RMS together with the CMSs.

After the applicant has submitted the response to the list of questions, the RMS can restart the window of active evaluation, getting into the assessment step II. This new step lasts at most 90 days, however if the consensus between RMS and CMSs are reached before the last deadline, it can be interrupted. The RMS has the duty to conclude whether the product is approvable, drafting an AR, a final SmPC/PL, and the labelling documents to the CMSs. Between day 145 and 150, the RMS has to consult with the CMSs around the comments raised in the early phases, if consensus is reached the procedure is closed and it can follow the national procedure; if consensus is not reached, the RMS notifies the issues to the applicant, requesting additional information. At day 210, the RMS has to conclude the procedure with or an approval or a deny of marketisation. In case there are disagreements among the parties, the RMS refers the case to the CMDh: according with the article 29 (1 - 6) of Dir. 2001/83/EC this revision can last at most 60 days during which the CMDh, with the RMS and CMSs has to come to a final decision. If the consensus is reached, the RMS records the agreement, closing the procedure at day 270 after CMS have approved the FAR, SmPC, PL and labelling documents. If no consensus is reached at the level of CMDh, then the RMS notify the outcome to EMA that will start a new procedure according with articles 32, 33, and 34 of Dir. 2001/83/EC. Those Member States that have approved the FAR, the SmPc, PL and labelling documents, shall continue to the national authorisation without waiting for the outcome to the procedure stated in art. 32 of Dir. 2001/83/EC.

The last step for the decentralisation procedure is the National Step. European Union – and EMA, particularly – obliges the MS regulation authorities to adopt a national decision within 30 days after the closing of the RMS procedure. In case the procedure ends with a deny of marketisation, the Member States need to take a final decision at national level, unless the applicant withdraws the application. [89]

Mutual Recognition. Contrary to the decentralised procedure, the mutual recognition procedure aims to recognise already marketized drug in all Member States. The procedure can be started by the authorisation holder (the pharmaceutical company) or by the Member State(s) according with the article 28 of Dir. 2001/83/EC. The mutual recognition procedure is composed by six steps, involving the MS, CMSs and the CMDh.

The procedure is not too distant from the decentralised procedure; however, the main obstacle for the pharmaceutical company is to reach a common agreement between every Member States. The applicant has to apply to the competent authorities of every MSs, stating that submission is identical to the one accepted by the RMS and by CMSs. The procedure lasts 90 days, and if a consensus is reached the holder can marketize the drug in every Member States after each national authorisation procedure; if not, the holder can appeal to the CMDh that will take the matter and in 60 days communicate a Final Assessment.

[89] Parlamento Italiano 2006.

National Authorisation Procedure. Regarding the national authorisation, the rules are similar across the European Union, however for simplification, we will outline the Italian normative for the marketisation national authorisation procedure.

The Italian procedure are performed according with the articles 8 to 13 and 29 to 40 of the Decreto Legge n. 219 of 24th April 2006. The procedure is started by the applicant submitting the application to AIFA: the filing has to contain the active substance denomination, manufacturing information, characterisation, microbiological attributes, clinical overview where clinical findings are shown together with non-clinical information (pharmacology, pharmacokinetics, and toxicology), together with the risk management plan. [90] If AIFA assesses that the drug application has already been filed to other MS or to EMA, the national authorisation procedure does not apply, and the application is refused not being conform to the art. 8 of the already cited Decreto Legge. Where the requirements are met, AIFA, according with the article 29 of DL 219/2006, has 210 days to assess and inform the applicant about the outcome of the procedure. If there is no consensus in the AIFA's Commissione Consultiva Tecnico Scientifico (AIFA's Technical-scientific Advisory Board) – the committee aiming to assess the safety, efficacy, and efficiency of the drug in application – the applicant can appeal to AIFA that will decide in 90 days from the appealing notification.

With this chapter, we have seen the fundamentals of the pharmaceutical sector, from the history to the regulation functioning of the market. It is now important to focus on the legal side of the matter of this Thesis. Therefore, the next chapter will focus on the Intellectual Property Rights (IPR) regimes and, especially, on two different system of regulation of patents property: the Bayh-Dole Act and the Professor's Privilege.

[90] Decreto Legge 219/2006 (*see note 88):* art. 8, comma 3, let. a to s.

Chapter II

IPR Regimes, Innovation, Drugs and Prices: USA versus Italy

This chapter is divided in two parts: one is focused on the IPRs regimes and its exploitation in the world, the other on the innovation and pricing sides of the pharmaceutical industry.

Part I: Intellectual Property Rights Regimes: Bayh-Dole Act and Professor's Privilege

The focus of this Part is more legal than economical. Indeed, in the scope of this thesis, it is useful to outline the two Intellectual Property Rights regimes which are present in these days: in particular, the Bayh-Dole Act and the Professor's Privilege. These two IPRs system have been and still are debate in the scientific and economical literature. Therefore, the Part will explain the basis of patent legislations in common law (USA) and civil law (Italy) and then addresses the literature debate on the Bayh-Dole Act and Professor's Privilege.

2.1 Systems of Intellectual Property Rights

Intellectual property is an abstract proprietary interest addressing the intangible, that is the creation of the mind that has been embodied. There are different forms of Intellectual Property (later, IP): copyrights that protect artistic and literary works; patents, pertaining to pragmatic innovations; trademarks, protecting commercial symbols. The focus of this thesis will be the more pragmatic form of intellectual property, that is the patent.

We can define 'patents' with Schechter and Thomas's words: "patents provide exclusive rights to inventors of new, useful and nonobvious inventions. The patent law concerns hard technologies, including chemical, electrical and mechanical products and processes, as well as other pragmatic innovations in fields ranging from biotechnology to business methods." [91] Throughout international laws, there is no definition of *invention*, but it is correct to define it as 'solution of a technical problem', in order to counterpose it with the concept of discovery. Indeed, the invention "applies the natural laws in order to satisfy human needs: and for satisfying them with a serialized (technical) industrial production."[92]

However, we should point out that IP is an "umbrella term": indeed, there are different fields of law embracing IP that can be regrouped under a single term. We pointed out above that IP addresses the intangible, contrary to other forms of proprietary interests, but the law insists nonetheless on the tangible nature of the object protected by IP laws: copyrights must be fixed in tangible form to be protected, patent law requires that the

[91] Schechter and Thomas 2003, Ch. I, pg. 26.
[92] Cetra and Cian, 2017, Ch. XVII, 281. *Translated from:* "*l'invenzione applica queste leggi naturali per soddisfare bisogni umani: e per soddisfarli attraverso una produzione industriale (tecnica) serializzata*".

inventions be reduced to practice, and trademarks have to be used in the marketplace. Therefore, "intellectual property rights are […] allowed for the embodiment of that idea in a particular work of authorship, invention or commercial symbol".[93]

Moreover, IP confers the right to exclude others from exploiting the intangible subject. Taking for example a patent, the *right to exclude* does not give the right to the owner to marketize the subject of the patent: it protects only the invention from others.

Another aspect of the IP is that the exhaustion of rights: IP, indeed, are subject to the exhaustion. Therefore, broadly speaking, the IP ceases its dominance after the first sale of the patented or copyrighted object: that is for example, a boat owner has the possibility to sell its used sailboat to another future owner without the fear of being sued for patent infringement.

Another important aspect of the IP law is its territoriality: world nations have yet to legislate on a common and unified regime governing the IP rights. The consequence of this enormous legal vacuum is the lack of global protection, whereas there are international agreements that comprise the international IP regime: such as the Berne Convention, the Paris Convention, together with the TRIPS Agreement (WTO on Trade-Related Aspects of IPR). Regarding European Union and Europe as a continent (with its political area of influence), we should point out the existence of the Convention on the Grant of European Patents (EPC), that created the European Patent Office (EPO).

In order to patent an invention, the invention must be novelty, non-obvious and have a utility. The Italian corpus juris adds to these the concept of industriality. Regarding the US law, 35 U.S. Code, section 101, 102, 103 describe the requirements for an invention to be recognized and patented. §Section 101 states that "whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor […]."[94] However, this invention has to be novel (according to §Section 102) and non-obvious (§Section 103): it means that the invention has to not be already known publicly (even those are not patented, but known from the public: *Netscape Communication Corp Versus Konrad* is example of this situation); moreover, the invention has to be non-obvious, that is that the invention must not be accessibly invented by "[…] a person having ordinary skill in the art to which the claimed invention pertains".[95] The Italian Legislative *corpus* adds the concept of industriality (defined in the art. 49 of Codice di Proprietà Industriale, and also in the art. 57 of EPC) that for the Us Laws is inherent in the §Section 101 of the 35 USC: mainly, it prescribes that the invention is in place "whereas the object may be manufactured in any industry […]".[96]

[93] Schechter and Thomas 2003, Ch. I, pg. 28.
[94] 35 USC § Section 101.
[95] 35 USC § Section 103.
[96] art. 49, Codice di Proprietà Industriale; Cetra and Cian, 2017.

Regarding the scope of this thesis, it is useful to outline the general assumptions and jurisprudence around the patenting of biotechnology inventions. As Schechter and Thomas stated, in the field of biotechnology, "the most significant restriction is that a 'product of nature' – a naturally occurring substance discovered in the wild – may not be patented *per se*"[97]. Indeed, there are two ruling that can be defined as controversial: one is *Funk Brothers Seed Co. Versus Kalo Innoculant* Supreme Court's rule in 1948 which stated that new means of using product of nature cannot be patented because the patent itself was around "the discovery of some of the handiwork of nature"[98]; the ruling staged a new path in Us jurisprudence where the patentability based on laws of nature are exceptionally debatable. The other ruling is *Morton Versus New York Eye Infirmary* around the use of ether as anaesthetic. The New York Circuit Court acknowledged the importance of the discovery but "for the specification presents nothing new except the effect produced by well-known agents, administered in well-known ways on well-known subjects. This new or additional effect is not produced by any new instrument by which the agent is administered, nor by any different application of it to the body of the patient. It is simply produced by increasing the quantity of the vapor inhaled".[99] Essentially, the Court ruled that the patent was based on a discovery and not on an invention – although it specifically states that the discovery is ground-breaking – voiding the patent. Contrary to common law, in civil law statute are predominated: indeed, in the Italian law system the 'product of nature' could be patented providing the ability of the filer to manufacture the product as per the art. 81-*quater*, co. 1, let. *d*, CPI.[100] As noted by Cetra and Cian, the Italian jurisprudence around the 'product of nature' has changed throughout the decades. Indeed, initially the commodification of technology in specific industry – such as the medical and pharmaceutical sectors – was not allowed, but it was overpassed *de jure condito* by a trustful legislative "on profit expectations in the research and development market orient*[ing]* investments towards satisfying demand in these sectors as well".[101]

This brief discussion on the definition, jurisprudence, and legislative status of IP rights, especially patents, will serve in the next sections in order to understand the two predominant systems of Intellectual Property Rights regimes (later, IPR regimes). The first one is based on the Bayh-Dole Act, a bill passed in 1980 in the USA that introduced a new era in the IPR regimes; while the second one is the Professor's Privilege that still hold today in a few countries.

[97] Schechter and Thomas 2003, Ch. XIV, pg. 376.
[98] Schechter and Thomas 2003, Ch XIV, pg. 376.
[99] Morton V. New York Eye Infirmary, 1862.
[100] *Article 81-quater, co. 1, let. d states that "an invention relating to an element isolated from the human body or produced otherwise, through a technical process, even if its structure is identical to that of a natural element, provided that its function and industrial applications are concretely indicated and described. A technical process is understood as that which only human beings are capable of carrying out and that nature by itself is not able to perform".*
[101] Cetra and Cian, 2017, Ch. XVII, pg. 283. Original: *"le aspettative di profitto nel mercato della ricerca e sviluppo orientino gli investimenti verso la soddisfazione della domanda anche in questi settori".*

2.1.1 Granting Institution in USA and Italy

Before start to analyse the BDA and PP regimes, it is useful to briefly explain from where and how the grants are distributed both in USA and Italy.

US public granting system for medical and bio-pharmaceutical research is performed by a single institution, under the authority of the US Department of Health and Human Services (US-HHS), named National Institutes of Health (later, NIH). The public body aims at conducting and supporting biomedical and behavioural research, as well as research training and health information dissemination. The NIH is composed by the Office of the Director (OD) and 27 components (19 institutes, 4 research centres, the National Library of Medicine, and 3 other centres of central services). The OD contributes to the organisation in setting the policy and strategy and in coordinating the programs and the activities. The institute is annually funded by the US Congress, that separately assess each centre appropriations. The authority of the NIH is derived by the Public Health Service act of 1944 (42 USC § Section 201 to § 300hh-11: Section 301 of PHS Act gives to the Us-HHS Secretary permanent and broad authority to conduct and sponsor research.

The NIH's budget is created from four sources: the majority originated from the annual Labor-HHS-Education appropriation (Labor-HHS-ED), with a small amount from the Superfund-related environmental work form the Interior, Environment and Related Agencies appropriation. These two sources together form the discretionary budget. The other sources originated from different National Institutions, such as the budget from the Type 1 Diabetes Initiative appropriation (in 2006 based on the P.L. 107-360). At the same time, the NIH and the Public Health Service agencies are subject to a 'budget tap' called the PHS Program Evaluation Transfer. In order to give an example of the weight of the NIH's budget, in 2007 the OD requested to the Us Congress an annual budget equal to 28.487 billion US Dollars. Regarding the usage of this budget, the NIH in 2006 has used 52% of its budget on Research Project Grants, while 10% on the Intramural Research and 10% on R&D contracts. [102]

Therefore, the NIH is responsible for federal granting research and development, carrying this role in a manner that not only facilitate research but also performs so in a cost-effectively way. Generally, the grants are conceded to organizations that are domestic, foreign, public or private, for profit or NGO.

The Italian system of public funding is fairly different from the USA. In Italy, research is mainly performed by higher education institutions and other public agencies, as well as business companies and NGOs. The source of the funding is public and there are two major originating points: the central government and the regional governments, with a small percentage of EU framework programmes funding.

Therefore, in Italy we have 4 major categories of institutions performing basic or apply research: 98 public, private universities and polytechnics funded by the Ministero dell'Università e della Ricerca (MUR); 14 research organizations observed by MUR (CNR, ENEA, INAF, INGV, ASI, etc), there are also other

[102] Smith, 2007.

institutions funded by other Departments, like ISS funded by the Ministry of Health; business enterprises and associations, foundations and other bodies not for profit.

As already said above, the major public funder is the Ministero dell'Università e della Ricerca which distributes the funding via public calls. Besides central government, regional bodies and central administration agencies play a role in funding the scientific research in Italy, aiming to develop better research in specific areas and cultivating interactions among universities.

2.2 Bayh-Dole Act: Literature Review

The Patent and Trademark Law Amendments Act, also known as Bayh-Dole Act (Pub. L. 95-517, December 12, 1980), is an Act sponsored by two US Senators – Birch Bayh (D) and Bod Dole (R) – that modified the legislation on federal government-funded research: specifically, it modified 35 USC Chapter 18, §Section 200-212, amending the Patent Act of 1790, of 1836, of 1922, and of 1952. The Bayh-Dole Act was created with one objective, that is "to use the patent system to promote the utilization of inventions arising from federally supported research or development".[103] §Section 200 of the 35 US Code states indeed that:

> "It is the policy and objective of the Congress to use the patent system to promote the utilization of inventions arising from federally supported research or development; to encourage maximum participation of small business firms in federally supported research and development efforts; to promote collaboration between commercial concerns and nonprofit organizations, including universities; to ensure that inventions made by nonprofit organizations and small business firms are used in a manner to promote free competition and enterprise without unduly encumbering future research and discovery; to promote the commercialization and public availability of inventions made in the United States by United States industry and labor; to ensure that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions; and to minimize the costs of administering policies in this area" (35 US Code § Section 200).

The scope of intervention of the Bayh-Dole Act (later, BDA) was to transfer the IPRs from the granting agency to universities that received federal funding for researching. The complete change in policy was aimed to increase and simplify the relationship between granting agencies and non-profit organisations/small-firms, and to increase the competitiveness of the US industries (as stated in §Section 200). Moreover, §Section 203 of the 35 US Code adds a march-in clause held by the Federal Agency granting funds. The section states that the Federal Administration has the right "to require the contractor, an assignee or exclusive licensee of a subject invention to grant a nonexclusive, partially exclusive, or exclusive license in any field of use to responsible applicant or applicants […] or […] to grant such a license itself".[104] The Section continues stating the scenarios

[103] 35 USC § Section 200
[104] 35 USC §Section 203, let. a.

where the Federal Administration can retain the right of licensing of the grantee: one of the most debated numbers of the section is the second, which states:

> "(2) action is necessary to alleviate health or safety needs which are not reasonably satisfied by the contractor, assignee, or their licensees" (35 USC §Section 203, let. a num. 2).

The debate around it raised with the Trump Administration that saw the march-in rights as a method of imposing pricing control of pharmaceutical products. Therefore, the NIST (Department of Commerce's National Institution of Science and Technology) has proposed a specific rule in order to solve the political and regulatory impasse: essentially, the Department ruled-out the possibility to apply march-in rights exclusively in case of pricing decisions of the contractor. The rule was meant to "give assurances to investors and prospective licensees that the federal government needs more than just price control as a reason to exercise its march-in rights". [105] The debate is still ongoing with the Biden's Administration, but it seems – at the time writing – to be resolved in favour of the vision of the NIST.

The BDA has been – and nowadays still is – in the centre of a wide scientific debate. Since its conception, the Act has been criticised and supported by different actors. The aim of the bill proposed by senators Bayh and Dole was to simplify the bureaucratic process of obtaining a patent from a federal granted invention: indeed, at that time, there was a wide pool of unlicensed, unpatented, and uncommercialised discoveries (federally granted) that were unused by the market. Therefore, "the goal of the act was to provide universities with a financial incentive to tap this pool".[106] The detractors of this act focused its criticisms on the shift of research-core of different universities: indeed, a majority of them pursued applied research instead of focus on basic research (much less profitable). Henderson et al, together with Coupe, demonstrated that the BDA has generated a major shift in focus of universities which tend to behave like commercial firms, applying at the same pace to patents.[107] However, other economists counterposed this theory with different papers stating that the shift took place well before the approval of the BDA: indeed, Mowery et al. and Stokes showed as UCLA and Stanford "accelerated in the 1970s in tandem with the rise of biomedical and pharmaceutical research".[108]

Besides, Rafferty, in accordance with different studies,[109] stated that "the view that Bayh-Dole Act has led universities to alter R&D activities is an argument about the incentive to commit resources to basic research. Licensing and patenting data are arguably good measures of research output, but not necessarily good measures of research inputs".[110] He added also that the literature seems to investigate with an 'implicit theoretical model' that universities behave better with incentive structured by the Federal Administration: "in this implicit model, universities pursue their publicly mandated goals of expanding scientific knowledge and

[105] Morley and Behar 2021, pg. 1; Morley and Behar, 2021.
[106] Rafferty 2008, pg. 29.
[107] Henderson et al. 1998; Coupè 2003.
[108] Rafferty, 2008, pg. 30; Mowery et al. 2001; Stokes, 1997.
[109] Jensen and Thursby, 2001; Mowery and Ziedonis, 2002.
[110] Rafferty, 2008, pg. 30.

educating students while simultaneously maximising the revenues".[111] The universities' financial model is, therefore, enriched by states incentives that helps developing discoveries and inventions (applied research), that can patented and then sold or retained, financing their own specific goals.

Of different opinion a much newer paper, published by J.G. Thursby and M. C. Thursby in 2011. They explain a different view of the consequences of the Bayh-Dole Act: the research is based on a unique database of faculty research at eight major Us universities over the years immediately after the approval of the BDA until 1999. The study shows that the BDA has increased basic research effort alongside an increase in applied effort.[112]

In conclusion, there is another view of a few observers which shows that the BDA fostered a monopoly like "system deterring the dissemination of knowledge and having marginal or insignificant effects on patenting and academic entrepreneurship".[113]

Putting aside the different views of different observers, universities and college institutions with the approval of the BDA were – in a way – forced to institute the Technology Licensing Offices (or TLOs). The arise of this new department in the organisation chart of the education institutions were mainly a consequence of the BDA itself: as proved by Mowerty et al., only 14% of the TLOs were created before the approval, while more than 44% were institutionalised in the Nineties.[114]

To summarise, there are three different positions regarding the consequences of the BDA on the universities and college institutions. Some observers claim that the reform on the 35 US Code promoted a surge in innovation, others more sceptical show that the BDA concurred together with other reform to an improving in commercialisation of discoveries and invention powered by federal granting; lastly, a few observers see the BDA as a system deterring the distribution of knowledge.

2.3 Professor's Privilege: Literature Review

As we are going to see in the next section, the Bayh-Dole Act was 'globalised' and adopted by different and numerous countries as policy for increasing innovation in their universities ranks. However, two countries decided that the BDA was not the proper and rightful policy and adopted another method in administering the patent policies: the Professor's Privilege.

The Professor's Privilege is – at the time writing – a policy adopted only by Italy and Sweden. Let takes as example the Italian Legislation. Professor's Privilege is embodied in the art. 65 of the Codice di Proprietà Industriale (Code of Industrial Property; later on, CPI). The art. 65 states that

[111] Rafferty, 2008, pg. 30.
[112] Thursby and Thursby 2011, pg. 1083.
[113] Astebro et al., 2019, pg. 7.
[114] Åstebro et al. 2019.

> "when the employment relationship exists between the researcher and a university or a public agency whose institutional purposes includes research, the researcher shall be the sole owner of the rights resulting from the patentable invention of which she is the author. In the event of multiple authors employed in a university, public administrations, or public agencies the rights resulting from the invention shall belong to all of the inventors in equal parts, unless otherwise agreed. The inventor shall file the patent application and notify the agency of that action" (art. 65, comma 1, CPI)[115]

Art. 65 acts in derogation of the art. 64 of the same Code: indeed, it states that the rights of use of an invention made by a subject who have a labour agreement or is employee of an entity are held by the employer and not by the employee, except the right to be recognise as author of the invention.

The art. 65 CPI does not end with the first comma: indeed, commas 3 and 4 regulate the situation in which the inventor does not exploit the invention. After 5 years, universities or PAs have the right to retain the invention and exploit it or let exploit it by third parties: this right is not exclusive and free of charge.

Historically speaking, the setting of a much more compelled code of industrial property was celebrated by the academic world: since, before the actuation of the Code, the Legislator did not provide a unique code, but instead a much wider single Statutes, that compelled, have formed the code of industrial propriety. With the D.lgs n. 30 of the 10/02/2005, the Legislator finally made them in a single code. However, in the draft, the Legislator provided a change in IP rights moving from the PP to a much more accepted system based on BDA: the draft never came to light and was changed in favour of the PP. The ratio behind this decision was to incentive professors and researchers to industrially exploit their invention, in this way choosing applied research than basic research: where basic research was far from an industrialization.[116]

Again, although never clearly stated, the rationale of the rule may be traced back to the attempt to shift the economic incentive to market from a subject plagued by bureaucratic and organizational inefficiencies (the university) to the individual researcher, deemed more flexible and sensitive to the incentive, completely ignoring the problems related to transaction cost.[117] The crucial point that the Legislator – willingly or unwillingly ignored – was the actual scenario where the inventions may be traced back to a collaboration relationship between researchers or professors and private industries. At the same time, art. 65 of the CPI – as seen above – asserts that the IP right of the invention in case of the presence of researchers is held by the research alone and not the co-author (in this scenario the private company). The Legislator decided to produce an ambiguous comma – art. 65, co. 5, D. Lgs. n.30 of 10/02/2005 later CPI – that divides the ownership of the invention between the university and the private company.

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[115] Translation from CPI art. 65: *"quando il rapporto di lavoro intercorre con un università o con una pubblica amministrazione avente tra i suoi scopi istituzionali finalità di ricerca, il ricercatore è titolare esclusivo dei diritti derivanti dall'invenzione brevettabile di cui è autore. In caso di più autori, dipendenti delle università, delle pubbliche amministrazioni predette ovvero di altre pubbliche amministrazioni, i diritti derivanti dall'invenzione appartengono a tutti in parti uguali, salvo diversa pattuizione. L'inventore presenta la domanda di brevetto e ne dà comunicazione all'amministrazione"*.

[116] Lissoni et al. 2004.

[117] Malva et al. 2007.

Therefore, in the Italian legislation there is a dual system that is taken into action depending on which actor is funding the research. This duality is a unicum in the world, but there is no evidence of a delay in innovation for the Italian system since there is no comparison term with the ongoing situation at the same condition.

Truthfully, CESPRI-Università Bocconi[118] has tried to calculate and show the weight of this policy in the Italian innovation system. The research showed that most of the patents are held by private companies, while academic patents are produced in a bunch of universities (especially small universities such as Sant'Anna and San Raffaele). In Lissoni et al.'s views, the ratio for improving the PP was to incentive the academic world in profit from patents and inventions, but this possibility does not have a grip with reality since the Italian TLOs do not have positive revenues.

In 2013, Lissoni et al. again investigate the reality of the market finding that between 1996 and 2007 the "share of academic patenting over total patenting at the EPO has declined, conditional on the typical characteristics of academic patents and on the evolution over time of the Italian R&D system".[119] The economists conclude that "the introduction of the professor privilege has neither encouraged academic patenting nor favoured individual ownership. In fact, it has been effectively neutralized by universities, through the introduction of IP statutes. This deposes against the transformative potential of the privilege, in a context in which universities exploit their autonomy to increase their control over their faculty and resources".[120]

To conclude, different observers see the PP as a concurrent in the initial boost of patenting, but later in the decades, the PP shows the real entity, concurring to a decrease in invention made by universities, whereas the majority of the patents are held by enterprises or mixed relationship private-universities.

2.4 Literature Review on the differences of the IPRs regimes

As afore discussed, USA "pioneered a systemic change where IPRs, traditionally held by the granting agency, were transferred to universities provided that research had been granted federal funds".[121] This new system came to place with the BDA aimed at increase competitiveness of US innovation industry. At the same time, in Europe, the Humboldt tradition still persisted, focusing on basic research and limited links with private sectors: in this scenario, the PP continued to be prevalent in most of the European countries.

As we already saw, there are two huge differences between these two systems: with the BDA the control rights are held by the research entity (universities, colleges) while with the PP, the control rights are held by the researcher conducting the research. Moreover, with BDA the university has *de jure* the ownership of the IPRs, while under the PP, the university has not control on the IPRs.

At the end of the XX century and while the BDA effects were starting to be thoroughly discussed in the policy making and academic worlds, a conspicuous number of countries decided to introduce policy and legislations

[118] Lissoni et al. 2007.
[119] Lissoni et al. 2013, pg. 22.
[120] Lissoni et al. 2013, pg 22.
[121] Astebro et al. 2019, pg. 5.

similar to the BDA: the goal with this decision was to increase the competitiveness of the academic and innovation sector of those countries.

This globalization of a policy, such as the BDA, were put in practice in Germany, Belgium, Denmark, Japan, Norway, Finland and China. However, in Germany, the increase in competitiveness have never shown: indeed, different studies[122] have shown that the number of university invention has remained unchanged or decreased. At the same time, in Denmark the data has shown a 14% reduction in patenting made by biotech firms. The worst case is Norway which have been subjected to a 50% decline "in the rate of new venture creation and patenting by university-based researchers after the reform and the quality of university start-ups and patents also appears to have declined".[123]

We should – however – point out that the causes of this decline in patents and inventions could be not completely caused by the regime itself. As mentioned in Darmsgaard and Thursby (2013), the relative advantage of the regimes depends on the opportunity-cost of time, the skill-set of the TLOs and "tacitness of the technology"[124], as well as on search costs and inventors' preferences and technology. Some models[125] have demonstrated that the probability of success in marketisation of an invention is higher with the PP than with the BDA, as "the inventor's effort level is not contractible, and the inventor has a lower take-home share under BDA". [126] Truthfully, the same observers stated that the presence of a general investment complementary between inventors' efforts and university aid may counteract this effect: in this counteracting effect, the TLOs play a vital role as they can bid the price of the IP, but it is still unclear if the TLOs have this business skill in series.

Again, we also should point out that the groups of inventors "who are discouraged from engaging in firm formation through the introduction of BDA should be those whose expected returns are in the lower tail of distribution".[127] Therefore, the average expected return of realized academic spin-offs under BDA rather than under PP should be higher. Under BDA universities are incentivized to support academic spin-offs since they can increase their chances of success: this induces the over entry into the academic entrepreneurship, causing lower return and even negative average rates of return.

Pointing towards PP, we should underline the minor presence of studies on the effects of PP on academic entrepreneurship: the main cause of this under-presence in scientific literature is mainly triggered by the less countries applying this type of IPRs regime. Therefore, we can see that two works[128] have found that with BDA regime "increased royalty shares to faculty decrease the rate of academic entrepreneurship"[129]. At the

[122] Von Proff et al. 2012; Czarnitzki et al. 2015.
[123] Astebro et al. 2019, pg. 7.
[124] Astebro et al. 2019, pg. 8.
[125] Darmsgaard and Thursby 2013; Hvide and Jones 2015.
[126] Astebro et al. 2019, pg. 8.
[127] Astebro et al 2019, pg. 9.
[128] Di Gregorio and Shane, 2003; Markman et al. 2009.
[129] Astebro et al. 2019, pg. 10.

same time, other observers have not found neither a correlation of the decrease in the rate of academic entrepreneurship nor correlated significant effects.

Åstebro et al. have compared two countries – USA and Sweden – where, respectively, BDA and PP are applied. In their findings, different incentives for pushing university employees to become entrepreneurs have been used in order to accelerate the entry of inventions on the markets and in order to quicker create social rates of returns. Those incentives, however, put too much emphasis on "general stimulus of academics since in both countries there is selection from the bottom of the ability distribution […] encourage*(ing)* over entry of marginal projects".[130] Therefore, they deduce that incentivise academics in becoming full-time entrepreneurs is not the right recipe. Regarding the literature debate on the IPRs regimes, Åstebro et al. conclude that, according with different studies[131], change of IP regimes in USA should increase the academic entrepreneurship by only 4.5%, a change "hardly seems worth the effort"[132]

To sum up, it safely to say that there is no empirical evidence against or in favour on one of these two IPRs regimes. The only way to capture and describe which IPR is best suited for the academic world should be observing a country that changed the IPR regime from a BDA regime to a PP regime or vice versa and then, capture the change. At the time writing, nor Italy nor Sweden have on the policy plate a change in regime, and therefore it cannot be correctly estimated the weight of these regimes on the academic entrepreneurship structures.

Part II: Innovation, Drugs and Prices: USA versus Italy

2.5 Innovation and Pharmaceutical Industry

Innovation is the key to keep alive the industries. We can define innovation as "the multi-stage process whereby organizations transform ideas into new/improved products, service or processes, in order to advance, compete and differentiate themselves successfully in their marketplace".[133] Therefore, innovation is a process involving different actors across all social spectrum with the aim to change, improve or renew lives, processes, products, services, etc.

The innovation in the health sector, as well as in the pharmaceutical industry, is becoming progressively vital: indeed, in the last century – and still nowadays – on one hand, the population is massively growing at a huge pace, and on the other one, the western population is increasingly becoming older, especially thanks to the innovation in the health sector and to the increase in the quality of life. However, globally, the access to pharmaceutical or health assistance is not always assured: governments and hospitals with increasingly accesses to the health systems are facing arises in costs both operational and related to human labour force. In

[130] Astebro et al. 2019, pg. 25.
[131] Lowe 2006; Farnstrand-Damsgaard and Thursby, 2013.
[132] Astebro et al., 2019, pg. 24.
[133] Baregheh, Rowley, and Sambrook 2009, 1334.

this scenario, the pharmaceutical innovation and heath care innovation play an essential role in order to maximise the effort and minimize the costs of access and applications of health.[134] If we want to characterize the forces that drive the innovation, it comes in aid Achilladelis and Antonakis[135] with their driving force for innovation: scientific and technological advances, raw materials, market demand, competition, societal needs, government legislation, company scientific, technological and market specialization (as per in figure 2.1).

As we already saw in chapter I, the pharmaceutical industry is a heterogeneous industry with different actors with diverse characteristics. However, each actor plays an essential role in the innovation chain of the sector: first of all, every firm tends to innovate in a specific branch of the sector, bringing to the world new sets of services, products or solutions; moreover, foundations, research labs, universities, polytechnics and colleges carry out basic and applied research, in order to promptly pushing the industries towards a continuous innovation. In this context, we think it is useful to report the words of Edward M. Scolnick, the former president of Merck Research Labs that pronounced in his Medallist Address to the Industrial Research Institute in 1990:

> "Successful management of industrial research is dependent on rapid access to the latest discoveries in academic laboratories, the ability to recognize the importance of a given discovery, the ability to integrate the information into research programs within an industrial laboratory, and the ability to focus effort to allow maximum chance that the idea will bear practical fruit. It is vital for an industrial laboratory to have its own cutting edge basic research program at early stages of newly evolving fields (Scolnick 1990)".

Therefore, basic research in the pharmaceutical field of innovation is the key to offer to society instruments to gain and develop new means of cure, services and products. We already saw the literature on the debate on

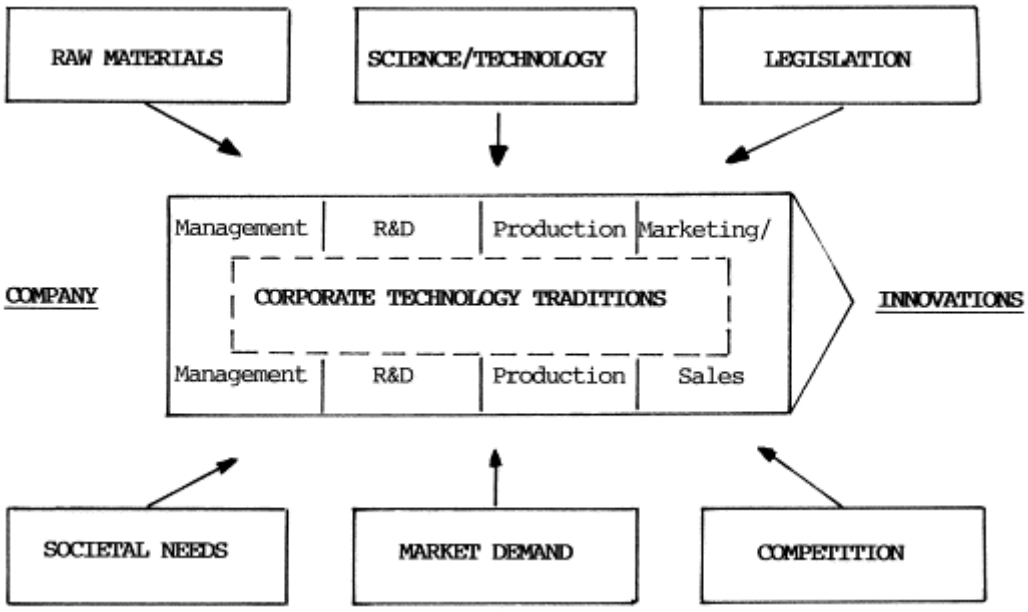


Figure 2.1: Forces driving Technology Innovation. Source: Achilladelis, Basil, and Nicholas Antonakis

[134] Aldieri et al. 2020
[135] Achilladelis and Antonakis 2001

the application of basic research in academics: indeed, with the BDA, some observers[136] capture the shift in academic research trends from basic research to applied research. The reason behind this shift were essentially of economic nature: indeed, NIH were more favourable to distribute grants to applied research (more profitable) than basic research (less profitable).[137]

To pull round the core, different observers[138] believe academic research to be the fuel of technological change and opportunism. In the field of empirical literature, Jaffe[139] captured the increase contribution of academic research in shaping and producing of corporate patents over time. Therefore, innovation is pushed by basic academic research that provide a foundation of knowledge which creates new opportunities in the field. Toole, for example, provides an example on ACE inhibitors: indeed, Captopril is the best case that links public basic research and pharmaceutical innovation. The drug prevents high blood pressure by inhibiting the conversion of angiotensin I to angiotensin III. The discovery of this NME (New Molecular Entity) may date back to 1934 to a public study that – however – was published only in the mid1950. At the same time, in 1965 a public study was published in Brazil where scientists discovered a natural snake substance that acted as lowering blood pressure substance. In the early Seventies, Squibb's R&D Department took these two public research, synthesise the first ACE inhibitor. As state by Toole, and Cockburn and Henderson[140], different drug discovery is characterized by public and private interaction research.

Regarding innovation and pharmaceutical market, we believe it is useful to present a model developed by Acemoglu and Linn in 2004[141] explaining how the market size in pharmaceutical industry influences innovation. In their 'Market Size In Innovation: Theory And Evidence From The Pharmaceutical Industry', Acemoglu and Linn link the market size to the innovation in a curious way: once developed a base model that explains the preference of consumers in the pharmaceutical market and the behaviour of the market in relation with the firm with best technology, they address the various problems of the pharmaceutical innovation chain including generics/non-generics formulation diatribe and delayed in approval of pharma; once capture the reality through the model, they apply it with FDA, NAMCS and OECD data. Without going deep in the maths of the model, the paper investigates the entry response of new molecules in the pharmaceutical market and its linkages with innovation and potential market size: the Acemoglu and Linn's result indicates that "a 1 percent increase in the potential market size for a drug category leads to approximately 4-6 percent growth in the entry of new drugs approved by the FDA".[142] These findings provides the evidence needed to demonstrate the chase of R&D and technological change towards much more profitable branches of the market.

[136] Henderson et al. 1998; Coupè 2003.
[137] *For the in-depth analysis of the debate, see section 2.2.*
[138] Griliches 1979; Griliches 1991; Klevorick et al. 1995; Toole, 2012.
[139] Jaffe, 1989
[140] Cockburn and Henderson, 1998.
[141] Acemoglu and Linn, 2004
[142] Acemoglu and Linn, 2004, 36.

The importance of this paper is unquestionable: the major consequences of these findings are generally linked to rare-diseases market behaviour and third-world-diseases market (such as malaria or Ebola or even avian influenza), where for-profit firms are less incentives to research on due to its limited market size. Therefore, to sum up, Acemoglu and Linn demonstrated that the sub-market size of the pharmaceutical market is an important value in order to decide in which direction move the pharmaceutical innovation, while they also found no evidence that NIH investments incentive the intra-industry innovation. What is not captured in the paper is the choice-discriminant: indeed, they have not been able to address if the choice in R&D is based on historically trends or future predictions or mixed preferences; the only finding is related to the evidence that 2004 market size and 5-10 year predictions in market size had a strong effect on entry ratio in the sub-market for new drugs: however, it does not prove in which direction the market looks in order to make a R&D choice.

The no-evidence of a systemic aid from NIH into the pharmaceutical industry is fairly disturbing: as stated by Toole,[143] there are two main reasons. The first one is mainly literature related, where it is inconsistent with numerous findings of different observers both qualitative and quantitative.

> "Second, it calls into question the contribution of public investments into biomedical research. The NIH is the largest public enterprise to supporting biomedical research performed by universities and other not-for-profit research institutions. New drugs innovation should be one of the important channels for reaping the benefits of these enormous public investments in biomedical research (Toole 2012)."

To counter-demonstrate the basis of the affirmations of Acemoglu and Linn, Toole analysed the possibility of technological change thanks to public investments in biomedical markets, using NIH data from 1955 to 1996. Trough statistical analysis, "NIH funded basic research, potential market size, and industry R&D all have economically and statistically significant effects on the entry of new drugs" transforming a 1 percent increase in basic research into a 1.8 percent increase in number of new molecular entities after a non-indifferent time lag.[144] For a typical NME, the lag between public investment and application in the industry is 17 to 44 years: this gap has been identified as enabling discoveries time. However, Toole, together with other observers, has found no causation in relationships between advances in public research and industry NME innovation. Indeed, "it is important to keep in mind that the discovery stage of NME innovation […] is an interdependent, complementary and often complex bi-directional process involving scientists in both academic and industrial laboratories". [145]

Coming back to the chain of innovation in the pharmaceutical industry, it appears obvious the process of developing NME. As already stated in the previous chapter, the industry relies a lot on SME and private/public labs in order to develop NMEs. The reason hides behind the long and cost-intensive process that a discovery

[143] Toole 2012, 2.
[144] Toole 2012, 2.
[145] Toole 2012, 10

of new entities has. The large companies than acquire knowledge, skills and the discovery in order to begin the regulation and clinical pathway that ends with the marketization.

2.6 Is Science a public good or a private good?

We have just seen that the debate on the pharmaceutical innovation is complex and has been going on since the last century. What we saw is a small sample of an ongoing and long literature debate: however, we think it is useful, in order to better understand following topics and reasonings, focus on the definition of pharmaceutical discovery with public funding, namely are pharmaceutical NMEs under BDA or PP public goods or private goods?

Before answering this question, we should address the definition and differences between public good and private good. Contrary to universal believes, a public good is not similar to "public service": indeed, in the economics theories "a good is technically defined as 'public' if and only if it is (a) not strictly rivalrous in consumption and (b) not strictly excludable".[146] The letter (a) is deemed in a technological way, namely there are different goods that physically cannot be used simultaneously by numerous people. The second letter is conditional to the existing property rights regimes that establish who is entitled to exclude the good from others. The confusion around this topic surely comes from the simplification acted in different economics course, especially in Bachelor level courses, that wants the market to provide private goods and governments to provide public goods.

One of the first authors laying the basis for the concept of public good is Adam Smith in his 'The Wealth Nations' in 1776[147]: indeed, he stated that

> "The third and last duty of the sovereign is that of erecting and maintaining those public institutions and those public works, which, though they may be in the highest degree advantageous to a great society, are, however, of such a nature, that the profit could never repay the expense to any individual or small number of individuals, and for which it cannot be expected that an individual or small number of individuals should erect or maintain (Smith, 1776)".

In the public good debate, there are numerous contributions made by different economists, among them Machlup, Olson, Musgrave, Buchanan and Samuelson. Certain goods allow multiple and simultaneously users to consume without reducing it from another consumer. As instance, Mankiw[148] provides tornado siren as example: indeed

> "public good are neither excludable nor rival. That is, people cannot be prevented from using a public good, and one person's use of a public good does not reduce another person's ability to use it. For example, a tornado siren in a small town is a public good. Once the siren sounds, it is impossible to

[146] Safner 2021, 18.
[147] Smith, 1776.
[148] Mankiw 2004, 225.

prevent any single person from hearing it. Moreover, when one person gets the benefits of the warning, he does nor reduce the benefit to anyone (Mankiw, 2004)"

There are other examples of public good, some economists and authors describe it through the national defence example, or with the flood control system, street lighting, air, water, Internet, knowledge, and scientific knowledge. In the older literature on this theme, public goods – that are non-excludible and non-rival – have been linked as sources of market failure (especially, for Public Finance economists), which – of course – require the intervention of the State. Recent debates have exceptionally found that there are cases where "a particular actor has an incentive to provide a public good irrespective of the free-riding behavior *(sic)* of other beneficiaries".[149] Another characteristic of public goods is that they produce external effects (or externalities), both positive and negative: Pigou in 1920 saw the externalities as by-product of economic activities and the government task must be the appropriation of these externalities.

Innovation, focus of this chapter, may however force a revaluation of the characterisation of public goods, "which had hitherto been regarded as universally accessible and non-diminishable, has been rendered potentially excludable".[150]

Placing aside for a moment 'the innovation debate', we should also address the definition of private good. Private goods are in contrast with public goods and are those that are rivalrous, diminishable and excludable, therefore scarce. Nicholson defines them as product that "yields positive benefits to people".[151] They produce externalities as well as the public goods, both negative and positive. Therefore, we can individuate 4 types of goods as per in figure 2.2.

Focusing on the innovation side of the question, is knowledge (in this thesis, innovation[152]) a public good or a private good? In order to answer, we must make a compulsory introduction and – in a sense – a spoiler of the question itself: there is no answer, or in other way, innovation is both a public good and a private good. Although the non-end of the debate on the characterisation of innovation as good, it useful to investigate it in a deeper way.

As we already stated few lines above, technological change, and in a way innovation, force us to reconsider the definition of public good. Héritier in his Public Goods: International highlights a case which recentres the debate on the matter: broadcasting; indeed, broadcasting is a technological change, hence an innovation, that used to be accessible to anyone without limiting other consumers. However, the progress on technological branches of the market has pushed this innovation towards a private good definition in se, instead of keeping it as public good. Namely, the transaction costs associated with broadcasting pushed the market to limit the

[149] Héritier 2001, 12350.
[150] Héritier 2001, 12351.
[151] Nicholson, 2004.
[152] *We should also open another debate on the definition of knowledge and its links with innovation. For simplifying, innovation and knowledge will be considered linked. For better understanding, see Chen et al. 2004; Cardinal et al. 2001; Herkema, 2003; Gloet and Terziovski, 2004.*

access of it to a small number of people, blocking *de facto* the access of consumers to the service. The consequences of this shift have been read by Héritier as a shift in definition of public good: indeed, he says "the definition of what constitutes a public good and what does not, may not necessarily be determined by 'objective' characteristics, but instead by political and social definition".[153] The point here is tremendous: the debate on the definition of public good versus private good has to be geographically limited in accordance with local political and social believes; in other words, 'capitalistic' countries may see universal healthcare as a private good and thus do not provide free cover to all citizens, while 'socialist'[154] countries can weight free and universal care as a public good, and therefore act accordingly. At the same time, Hèritier continues

> "policy makers in one society may decide that its provision should be left entirely to the buying power of the individual through the market. Hence, what constitutes a public good or common-pool resource can be answered either in terms of analytic economic criteria or in terms of a process of social and political definition. Once a good has been identified as a public good or a common-pool resource, the institutional mode of provision of the good has to be determined (Héritier, 2001)."

Callon[155] in his Nick Mullins Lecture in 1993 gave an in-depth analysis of the problem of science as public good. We already ascertained the differences between public good and private good. However, Callon tried to define science as a quasi-public good: indeed, he assimilated the notion of science with information, where this information can be passed through a set of messages, one message or orally. He then proceeded to define science as public good: "a good is appropriable (or exclusive) if it is possible for the person using or consuming it to prevent any other potential user or consumer from doing the same; otherwise, it is non-appropriable […]. In other words, if A sells information to B, is B then assured of enjoying the exclusive use of that

		SUBTRACTABILITY	
		Low	*High*
EXCLUSION	*Difficult*	**Public goods** Useful knowledge Sunsets	**Common-pool resources** Libraries Irrigation systems
	Easy	**Toll or club goods** Journal subscriptions Day-care centers	**Private goods** Personal computers Doughnuts

Figure 2.2: Categorisation of goods. Source: Hess and Ostrom 2007, adapted from Ostrom and Ostrom, 1977.

information?".[156] The answer is yes, in the meaning of A can sell information to B and hide them in cypher or in a code: there are plenty of examples in history of scientific discoveries or information been hidden to others, *de facto* turning a public good non-rival and non-excludible to excludible good. Galileo sent to the Tuscan

[153] Héritier, 2001, 12351.
[154] *The author is conscious of the simplicist analysis: in chapter I, we already introduce a small analysis of WS policy differences across countries. In this context, socialist countries are seen as those countries with free and universal healthcare without any linked with its prevalent political ideology.*
[155] Callon and Bowker 1994
[156] Callon and Bowker 1994, 399.

Ambassador in Prague an anagrammatic phrase for announce his discovery of Jupiter's moons, or in a way, encoding war orders via Enigma Machine can be seen as a shift from information as public good to private good.

In his analysis, Callon continued with the second attribute of a public good, the nonrivalry. Romer in 1993 stated that a good is non rival "because once it has been produced, A and B are not rival for its use. I can listen to the musical recording or take advantage of the software code without any way diminishing its usefulness to you or anyone else". [157] Science, in this scenario, has been defined as a "prototypical non rival good"[158], since once science is 'produced' the need of replicating it does not come up. Moreover, scientific knowledge possesses two other characteristics: it is a durable good – it is not possible to destroy it or alter it – and it is uncertain – it is impossible to predict its production.

In order to summarise various positions, it comes in hand the contribution of Esanu and Uhlir.[159] In their concluding remarks state that science in order to be freely available to all has to meet specific conditions:

> "first, there must be a process for generating knowledge somewhere, and this may not be an inexpensive or simple process. Second, knowledge must be embodied in some sort of socially useful technology, which also requires effort and resources. Third, both knowledge and technology must retain some sort of public goods dimension in terms of being freely available to be of maximum social benefit. Fourth, there must be some ability on the part of recipients or users to adapt the technology to their conditions and needs (Esanu and Uhlir 2003)".

In order to embody these specific conditions, it is fairly compulsory to involve IPRs: indeed, these are the only instruments that can entice private entities to finance basic and applied research. However, as stated by Esanu and Uhlir, "the research process […] where it is publicly financed, the products traditionally have been public goods". In pharmaceutical sector, this statement appears not so quite right, and evidence will be provided in the next sections and chapters.

For what concern the science as public good versus private good debate – as stated in the introduction of this section – there is no answer to the question, at least not economically answers. However, there are solutions for solving the main problem, the non-attractiveness of research for private bodies (except for few industries): two out of three solutions have been already discussed – IPRs and government supports – the third solution, namely a system of prizes, will be discussed in the last chapter of the thesis.[160]

2.7 Pharmaceutical Innovation

Heretofore, we have discussed innovation at glance and tried to explain different perspectives in the categorization of science as good. However, the focus of these chapters should be the pharmaceutical market.

[157] Romer 1993, 354.
[158] Callon and Bowker 1994, 400.
[159] Esanu and Uhlir 2003
[160] Thursby 2018.

Innovation in this industry is the key for developing competitive advantages. We have already defined 'innovation', but we should also point out that there is a lack of definition of 'pharmaceutical innovation'. As stated by Aronson,[161] in different documents and report of regulatory agencies, the word 'innovation' is or briefly defined or totally neglected.

Therefore, innovation in the pharmaceutical industry has different aspects: for instance, a new compound may have a new chemical structure but may not have a new mechanism of administration. However, a compound that is not pharmacologically innovative may be anyway innovative for other aspects: for example, Aronson gives the example of the cimetidine, the first useful 'H_2 histamine receptor antagonist'; the predecessors – burimamide and metiamide – were too toxic for the human bodies and therefore cannot be used. The next similar drug to appear was not so innovative in the mechanism as the cimetidine but it lacked the adverse reactions of the assumption of the cimetidine. There are plenty of examples of different drugs been discovered and categorised as innovative, but at the same time not so innovative as successors or predecessors. The main consequence is the creation of a fine line between innovative drugs and the so called *me-too* drugs.

In order to proceed on the discussion, we should firstly address the meaning of *me-too* drugs. 'Me-too' drug is a term coined in the late Fifties by Louis Goodman (a pharmacologist, pioneer of the first chemotherapy trial): in his Report of the Committee on Preliminary Screening of Drugs, he stated that "the problem of the introduction of 'me too' drugs, that is, drugs without signal advantage of any sort". [162] Therefore, in literature the 'me-too' drugs have been delineated with a variety of definitions: "multiple drugs within the same therapeutic class", "[drugs that are] chemically related to the prototype, or other chemical compounds which have an identical mechanism of action", "drugs which have more or less identical clinical outcomes to pre-existing drugs", "a drugs with a similar chemical structure or the same mechanism of action as a drug that is already marketed". [163] Aronson and Green come to a concise definition:

> "A pharmacologically active compound that is structurally related to a first-in-class compound, regarded as belonging to the same therapeutic class as the original compound, and used for the same therapeutic purposes, but which may differ in some respects, such as specificity of pharmacological action, adverse reactions profile, or drug–drug interactions (Aronson and Green, 2020)"

The authors also provide a set of examples, like the amitriptyline, the paroxetine, enalapril, propranolol, et al. This type of drugs has been hugely developed in the last years. The reason behind this trend in the market can be retrieve in the cost of Research and Development of drugs in general. *Me-too* drugs are usually back-up drugs to others in pipeline which may not be successful: the staff is therefore already trained in either pre-clinical stage or clinical trial phase. There are also other benefits behind the developing of *me-too* drugs: it is less risky for the company (since the chemical compound or method of administration is not innovative and

[161] Aronson 2008.
[162] Goodman in Cole and Gerard 1959.
[163] Aronson and Green 2020, 2.

therefore less unknown), there are knowledge spillover in the scientific community that surely leads to a common developing of drugs across the same branches of the industry, and lastly, it poses as competitive advantage for pharmaceutical companies: indeed, they can offer a variety of similar or biosimilar drugs that can treat a specific disease or condition, through which consumers and doctors can choose in order to individuate the best pharmacological treatment with the least of the adverse reactions.

In order to show the weight of me-too drugs in the market is useful to report a table (see table 2.1[164]), created by Aronson and Green on the matter. It shows from the first-in-class drug the various developing of the same class of drugs which are not a breakthrough discovery, but they correct small details of the first-in-generation drug.

We were saying that there is a fine line between innovation in pharmaceuticals and not innovative products. In order to categorize a new drug or medical device as innovative, the community should address it case by case. However, we can outline brief examples for giving a panorama of the logic mechanism that discriminate between innovation and no innovation. Aronson gives us two examples: the thromboxane synthase inhibitor dazoxiben was categorised as innovative when appeared for the first time in the pharmaceutical community, but it did not prove its efficacy as therapeutical drug; it was pharmaceutically innovative but not in a clinic way. Therefore, a drug can have a novel mechanism of action, but it cannot represent an innovative therapeutic solution. Again, the BAQSIMI®, a nasal spray produced by Eli Lilly and Company for diabetes patients older than 4 years, is considered an innovative drug not for its composition (glucagon) but for its method of deliver of the chemical compound. At the same time, a pharmaceutical product can be innovative in a pharmacokinetic way: Benorylate, a drug delivering paracetamol (acetaminophen) and aspirin with a novel pharmacokinetic mechanism, cannot be considered a novel drug.

Tricyclic antidepressant	**Year of publication**	**Marketing company, brand name**	**Innovative feature(s)**
Imipramine	1958	Geigy, Tofranil	Novel pharmacological target (first in class)
Amitriptyline	1960	Merck Sharp & Dohme, Tryptizol	None
Desipramine [metabolite of imipramine]	1961	Geigy, Pertofran	Less anticholinergic

[164] *For other examples, see Aronson and Green, 2020.*

Tricyclic antidepressant	Year of publication	Marketing company, brand name	Innovative feature(s)
Nortriptyline [metabolite of amitriptyline]	1962	Dista, Allegron	Fewer drug–drug interactions
Trimipramine	1963	May & Baker, Surmontil	None [weak reuptake inhibitor]
Dosulepin (dothiepin)	1963	Crookes, Prothiaden	None
Protriptyline	1964	Merck Sharp & Dohme, Concordin	Not sedative
Iprindole	1965	Wyeth, Prondol	None
Doxepin	1965	Pfizer, Sinequan	None
Dibenzepin	1965	Wander, Noveril	None
Clomipramine	1968	Geigy, Anafranil	Selective serotonin uptake inhibitor
Lofepramine	1975	E Merck, Gamanil	None

Table 2.1: First-in-class and me-too tricyclic antidepressants and their innovative features. Source: Aronson and Green, 2020

Aronson[165] proposed a set of question in order to assess and check the innovation of a new drug: the scope of the analysis has to focus on if the drug significantly produces grater benefit, if it causes less harm and if it is cheaper or more affordable compared to other biosimilar or similar drugs.

We have just seen how difficult is to assess the level of innovation of a certain compound. However, it is possible to summarise the various level of innovation as follows: the spectrum of possibilities for a pharmaceutical product to be defined as innovation begins with structure innovation; it is the principal factor for assessing as innovative a product: indeed, it may bring others to other forms of innovativeness. Another factor is the pharmacological or pharmacodynamic innovativeness of a product: whenever a pharmaceutical product hits a novel target or has fewer adverse reactions than a predecessors with the same therapeutic target it can be considered an innovative drug. Again, pharmaceutical innovativeness can arise when a compound thanks to a medicinal product produces novel pharmaceutical properties. Pharmacokinetic innovativeness arises – instead – when it is primarily possessed by a compound or conferred by a medicinal product by virtue

[165] Aronson 2008.

of novel disposition. And, finally, the border-end of the spectrum is the clinical innovativeness, that is when a medicinal product produces substantially less adverse reactions or more benefits than its predecessors, with the consequences of higher advantages and affordable costs. Lastly, the major innovative characteristic is the price: whenever a medicinal product has fewer costs and minor prices than the predecessors, surely it can be considered innovative *per se*. [166]

With this information, we have a full picture of how the innovation in the industry functions and how complex the categorization is. Romasanta et al.[167] have tried to map the innovation in the pharmaceutical R&D: they found that the majority of papers and articles for the pharmaceutical sectors are focused on Europe and USA. Among them, the majority is about pharmacology and pharmacy, as well as biotechnology & applied microbiology (especially in between 2011-2015). Since the Nineties there have been a surge in the number of articles on innovation in the pharmaceutical industry in practitioners' journals (figure 2.3) and, in the same period of time, there has been a steady increase in NDAs and drug approvals (FDA's data, figure 2.4).

In Chapter I, we discussed about the structure of the industry, and with which path the innovation in the industry is accomplished. It is useful here to underline an important characteristic of the industry: most of the large multinational corporations did not invent the drugs that they sell. According to Jung et al.,[168] most of them appears to have reduced their investments in R&D, especially in discovery of NMEs: for example, in 2017 only two out of 18 Johnson&Johnson's products were discovered in house (11% of the total products), the same for Pfizer which presented a higher percentage but still low (23%). Therefore, the majority was discovered and developed by third parties: some of them came directly from various acquisitions, others instead "originated in universities and academic centers *[sic]*"[169]. For example, Remicade, a monoclonal antibody produced by J&J, was synthesized by NYU in 1989 in collaboration with Centocor; again, Etanercept, Tofaitinib, Darunavir and Daratunumab are all products for "which key discoveries or development steps occurred in academic settings".

In order to conclude this paragraph, we should point out that the innovation market in the pharmaceutical industry is at the same time a key changing factor and a huge problem for the market economic structure. This statement will be clearer in next paragraph.

[166] Aronson 2008.
[167] Romasanta et al. 2020.
[168] Jung et al. 2019.
[169] Jung et al. 2019, pg. 1.

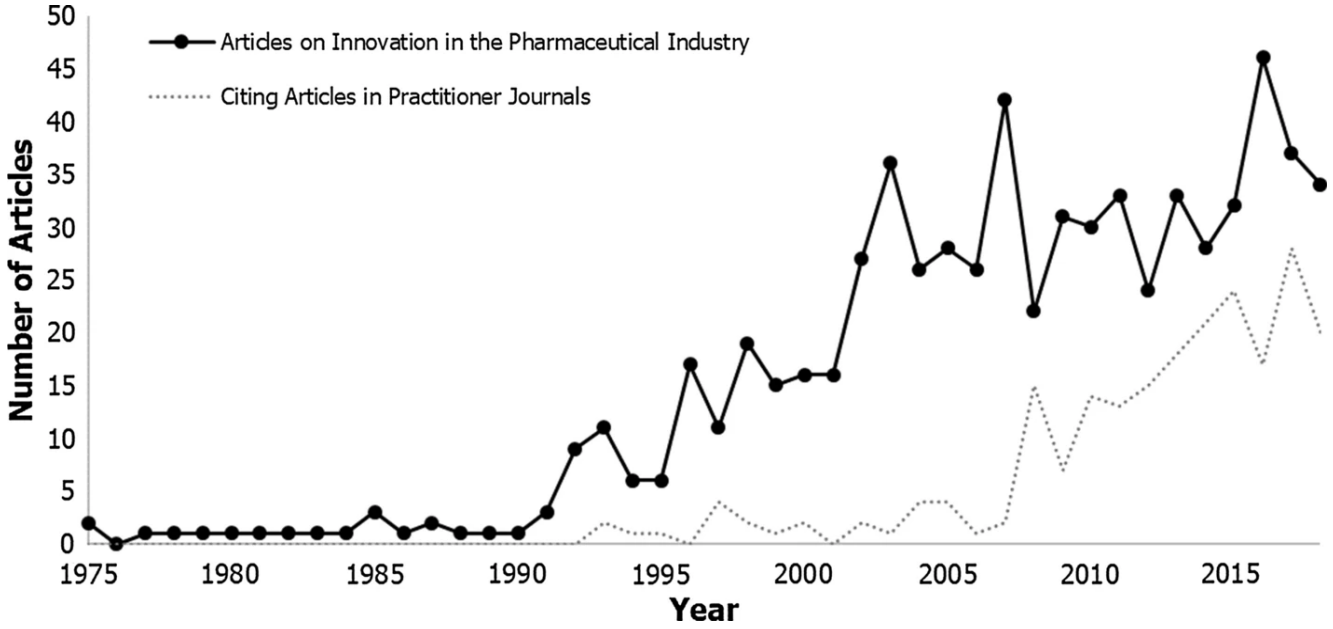


Figure 2.3: Number of articles studying innovation in the pharmaceutical industry. Source: Romasanta et al. 2020.

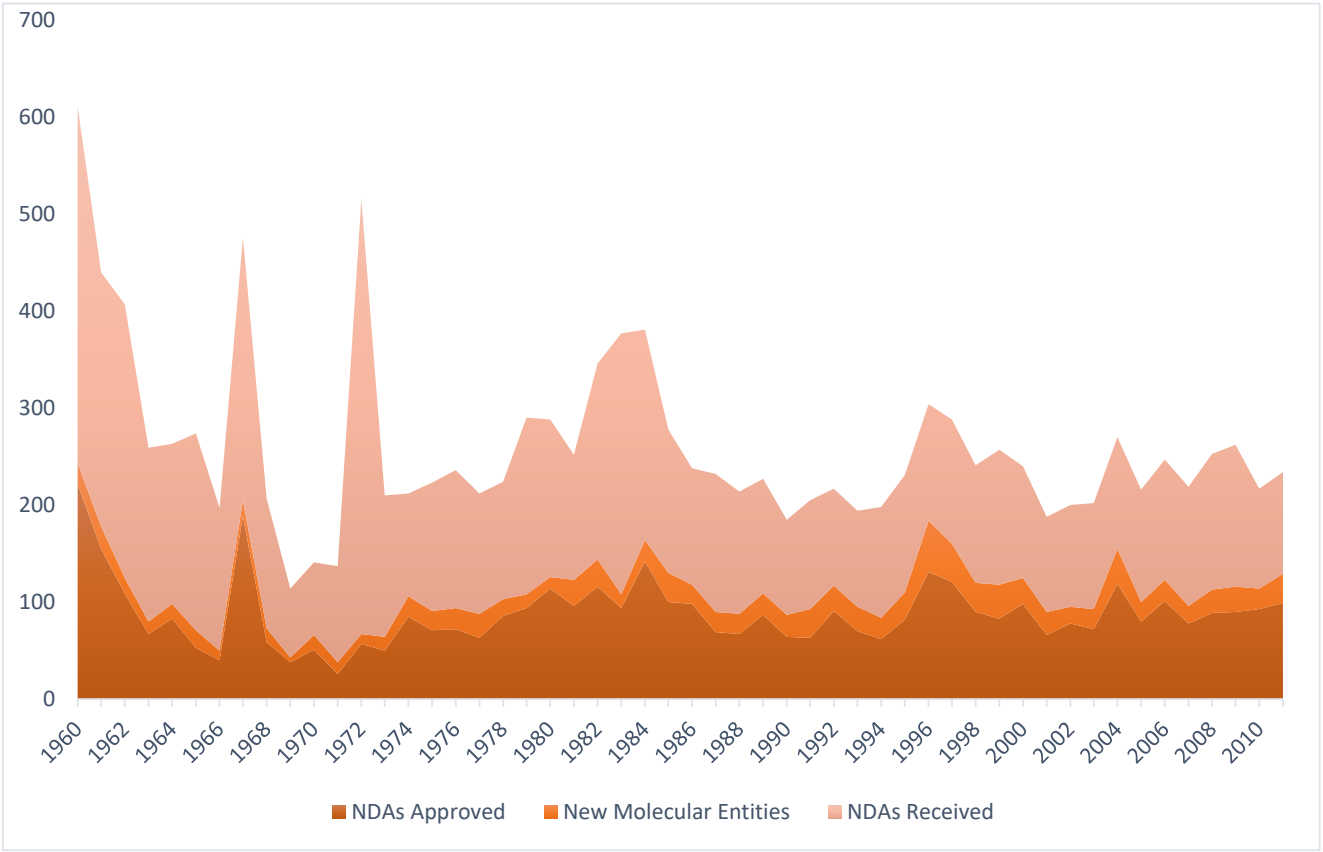


Figure 2.4: Number of Drugs 1960-2011. Source: FDA

2.8 Price regulation and composition of prices

Before covering the pricing regulation in pharmaceutical industry and how these prices should be composed, we should address an obvious statement which sometimes it does not be weighted sufficiently. As we already stated in the past chapter, pharmaceutical industry is one of the few sectors where public interest and private interest are directly linked together and often counterposing each other. These two interests, as already seen, are by some means in contrast with each other: on one side we have the government's aim to ensure the safety and the health of the population, and on the other side we have private firm (often large multinational) that follow the market rules with a for-profit view. Therefore, the equilibrium is precarious.

The topic of this paragraph, as it is possible to deduce from the title, will be price regulation and composition of prices. For simplicity, we will explain two different systems – with some trace with other national systems: one is the USA system of regulation and the other is the Italian system. The reason behind this choice is linked with the values which each system was designed with: the Italian system is part of a universal and free-for-all health system, while Us regulation system is based on insurance paid systems and slightly on governmental funding.

Pricing in the pharmaceutical industry is an important moment: it is the ground where hospitals and NHS plan their expenditures, where negotiations take place between Governments and companies. Nowadays, pricing of pharmaceutical products poses a major challenge for the World: the equilibria between equity, fairness and profit is always more precarious, where innovation – the real driver of the sector – is finding difficult ways to express itself and grasp the needs of the population. The market, indeed, appears to have an inelastic demand, where consumers of patented products cannot defer consumption and, therefore, accept the price as it comes in that particular moment of need. There are different models of pricing with different actors that take part of the negotiations. As above, we discuss of two extreme situations: the Italian scenario where different governmental bodies negotiate with companies the pricing of certain categories of pharmaceutical products following precise analysis and the other part of the spectrum, the Us system, where there is no intervention on the market and economic laws set the prices following the market criteria. [170]

In any case, economic laws are also applied in those countries where governmental actors intervene in the market: pricing discriminations, discounts, value-based pricing, cost-based pricing, competitor based pricing, skimming price, or external reference pricing (hereafter, ERP) are all strategies that are applied in the market.[171] The point to underline here is the impact that those prices have in the healthcare sector, especially for the final consumers.

Setting aside for a moment these pricing strategies, WHO[172] has published in 2015 a guideline in order to overarching the problem and present a path for the countries in order to solve the confusion around the matter,

[170] Morgan et al. 2020.
[171] Delagneau 2018.
[172] World Health Organization, World Health Organization, and Department of Essential Medicines and Health Products 2015.

pointing towards a common direction. The document lists 4 recommendations with relative pros and cons: mark-ups, tax exemption/reductions, cost-plus pricing formulae and ERP. In the following subsection, we will see the various strategies already mentioned and their characteristics.

2.8.1 Pricing Strategies

We can individuate different strategies involving prices; in our analysis, we are going to differentiate them in two categories: the first category – that we will call it 'common strategies' – comprises those strategies that are common with other industries, that is strategies non-pharmaceutical-related; the second category is strictly-pharmaceutical-related and were created or are usually used in a pharmaceutical setting; however, we should take into account that there are different interchangeability among these two categories.

We also should remember that in the formation of prices of any goods there are two factors in play: internal factors, that is those related to marketing objectives, marketing mix strategies, costs and organisational considerations; and external factors that comprise the nature of demand and supply in the market, level of competition and environmental elements (related, but not limited to, negative externalities, composition of the market, population, etc).

Among the common pricing strategies, we will see the cost-plus pricing, value-based pricing, value-pricing, competition based pricing, market skimming pricing and market-penetration pricing. Those strategies are not limited to the pharmaceutical sector, although the cost-plus pricing and the value-based pricing are widely used in different context also in the pharmaceutical industry.

Break-even pricing. This strategy involves the setting of the price in a way that the costs for producing, distributing and selling the good are matched with the price. The objective in setting this strategy is to target the volume of selling and usually it does not involve innovative drugs, since it can negatively affect the 'high-in-market price'.

Competition-based pricing. Setting the price with this strategy involves an analysis of the competitors, since the price is set comparing it with competitors pricing choices. It usually used by marketing oriented companies, considering "not only the perceived value, but also the value being offered by competition, and then arrive at a reasonable price giving them the enough margin in the long run".[173] This strategy is never used for assessing the price of orphan drugs, and in reality, it is never used alone but together with the value-based price. Indeed, a breakthrough product with a significant price only compute with competitor based price may still face down sells since, for the consumers, the discriminant is not the quality or the benefit but the price.

Value pricing and value-based pricing. These two strategies are similar: while the first set the price after an assess of the combination of quality and service that the good offers, the second set the price on the perception of value that the consumers (or buyers) perceive than on the seller's vision. Value-based pricing is widely used by large companies, but in the last decades the decrease of raw material costs and the surge of generics drugs

[173] Khoso, Ahmed, and Ahmed 2014, pg. 3.

have put LMCs to review the strategy to avoid market-share losses. Truthfully, there is another technique in order to set the price with the value-based price: it involves the use of pharmacoeconomic data, "specifically, the potential cost-savings that the product would bring to the current management of the disease".[174] However, the use of this kind of data is fairly hard: for some categories of drugs, such as oncology drugs, it is hard to compute the cost-savings or the value of each extra year of quality life (QALY). Moreover, in some countries, the use of pharmacoeconomic data is used not for compute the price, but for justifying a specific target price already set, while for some regulators is compulsory to provide an assess of pharmacoeconomic data for setting the prices. [175]

Skimming pricing and market penetration pricing. Skimming prices and market penetration prices are strategies involving the first entry of a product. These strategies involve low competition and niche submarkets where volumes are not high as other submarkets. The strategies consist of maximizing margins with the aim to gain and extract the majority of profit from the product. [176]

Cost-based pricing. Cost-based pricing is a strategy adding a mark-up (μ) to the costs that the company have faced and faces in order to develop, produce, distribute and sell the product. Usually, μ is generate by a target set by the company itself or is set by the market in relation with similar products. WHO's recommendations about cost-based pricing (and cost-plus-pricing) are divided in two major preoccupations: the use of cost-based pricing with markup can lead to lower prices in those contexts where there is no prior price control, together with a less involving of resources in computing the μ, and therefore increasing the pharmaceutical products access. However, markups can have negative consequences on availability through the distortion of prices, together with a lack of transparency in the development of mark-up structures. [177]

Together with these strategies, there are other strategies and policies that companies and regulatory bodies can perform in order to assess and fix the prices of a specific pharmaceutical product. These are fixed pricing, cost-effectiveness pricing (similar to the value-based pricing already discussed), profit controls, reference pricing and a policy, widely discussed in literature, called External Reference Pricing (later, ERP), or international reference pricing. It is difficult to explain these strategies before addressing the role of the regulatory bodies for pricing in pharmaceutical sectors. However, with the next paragraphs the picture will be completed by the analysis on US and Italian systems.[178]

Fixed pricing. Different countries in Europe have applied or still apply fixed pricing on patented drugs. During negotiation phase, the regulatory body applies fixed pricing considering manufacturers' costs, therapeutic benefits and innovativeness of the pharmaceutical products, together with R&D costs, international prices, volume sales, etc and then fixing the price of the product to a ceiling. This strategy theoretically allows the

[174] Delagneau 2018.
[175] Delagneau 2018.
[176] Delagneau 2018.
[177] World Health Organization, World Health Organization, and Department of Essential Medicines and Health Products 2015.
[178] Mrazek 2002

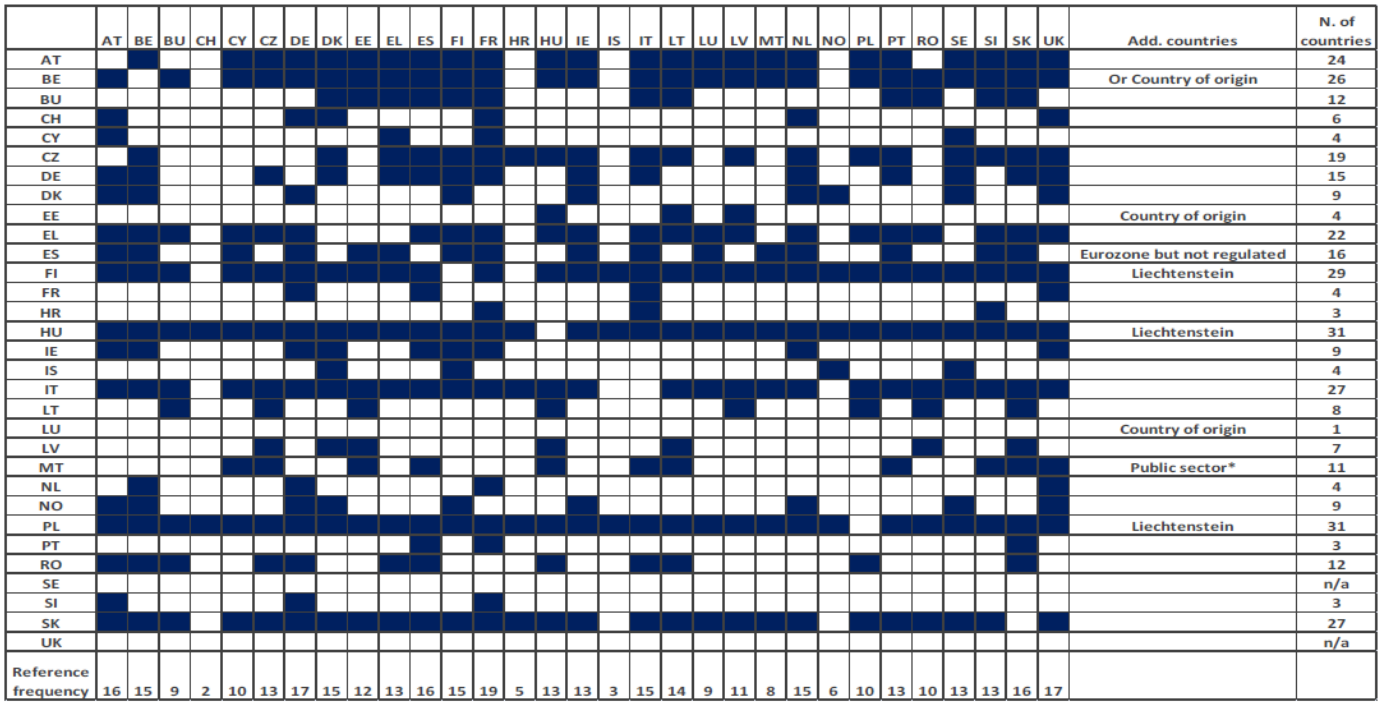
market – and therefore the consumers – to have products that follow the variability of the market itself, giving firms incentives to produce efficiently and a flexibility of price (with a maximum cap). Across the EU, fixed pricing is performed by different countries, except Denmark: Italy for example applies fixed pricing to cost-effectiveness pricing and different policy of reimbursability. Some other countries apply a form of fixed prices that varies with the sold volume (price/volume agreements): the mechanism involves the setting of the price to a specific threshold volume of sails: when the volume pass that threshold, the price will decrease, or the companies can pay a cash rebate. As noted by Mrazek, prices fixing "does not seem to have achieved the pharmaceutical cost-containment goals" which was set as objective of prices fixing "[…] (p)rice fixing seems to achieve only short-term cost containment, while increases in volume also led to expenditure increases".[179]

Cost-effectiveness pricing. As already addressed above, cost-effectiveness pricing is similar to the value-based pricing strategy: using pharmacoeconomic data, some countries can assess the effectiveness of a specific drug for the population. There are no guidelines around this kind of strategy, and countries set their own policy requirements: Italy, for example, considered a cost-benefit ratio in determining the price of the reimbursement, Ireland asks for cost-benefit analysis in the determination of prices. In pharmaceutical and economical literature, the matter is thoroughly debated and despite the implementation of some sort of guidelines, still problems arise.[180] The use of pharmacoeconomic data and economic valuation may lead to overlaps with other strategies: in UK[181], prior to the 2002, the NICE performed a detailed appraisal of the clinical and cost-effectiveness of beta interferon and glatiramer acetate, leading to a negative ruling of the risk-sharing agreement between DoH and pharmaceutical companies on the price of drugs.

Profit Controls. The policy of profit controls is used only in UK, through a scheme called Pharmaceutical Price Regulation Scheme (hereafter, PPRS), which "indirectly regulates the prices of branded pharmaceuticals sold to the National Health Service by setting profit limits."[182] The PPRS aims to balance reasonable price goals with incentives to UK pharmaceutical industry to be strong and profitable, while innovative and competitive. Those companies in this scheme have a profit cap equals to 21%, measured as a return on capital employed or return on sales: if a company exceeds its target, it can retain up to 40% of it permitted return; instead, when the company exceed the allowance cap, it must reduce profits by reducing prices or delaying or restricting previously agreed future price increases. The scheme failed to assure lower prices for pharmaceuticals, while it allows a stable and certain regulatory environment and a level of R&D expenditure higher than the worldwide average. As other scheme centred on rate of returns, it fails to incentive operational efficiency, since whether there is an increase in costs, it allows a surge in prices.[183]

[179] Mrazek 2002, pg. 457.
[180] Hill et al. 1997.
[181] Scott 2002
[182] Mrazek 2002, pg. 458.
[183] Mrazek 2002.

Reference pricing. Reference pricing and ERP can be linked together on the basis that they both take as reference external prices. However, reference pricing is less complex than the ERP. Reference pricing scheme set fixed reimbursement caps for products assigned to the same category: therefore, oncology drug will have a price cap within which the company has to set the price. The main purpose of this scheme is to limit the surge of pharmaceuticals prices: the major consequence of applying this type of policy is the elimination of price discrimination across products of the same therapeutic area, bringing higher transparency to the market.



	AT	BE	BU	CH	CY	CZ	DE	DK	EE	EL	ES	FI	FR	HR	HU	IE	IS	IT	LT	LU	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK	UK	Add. countries	N. of countries
AT		■																															24
BE	■		■		■	■	■	■	■	■	■	■	■		■	■		■	■	■	■	■	■		■	■	■	■	■	■	■	Or Country of origin	26
BU								■	■	■	■	■	■					■	■							■	■		■	■			12
CH	■						■	■					■										■								■		6
CY	■									■																		■					4
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DE	■	■				■				■	■	■	■			■		■					■			■		■		■	■		15
DK	■	■					■					■	■			■							■	■				■		■	■		9
EE															■				■		■											Country of origin	4
EL	■	■	■		■	■	■				■	■	■		■	■		■	■	■	■	■	■		■	■	■		■	■	■		22
ES	■	■					■		■	■					■	■		■		■		■	■						■	■	■	Eurozone but not regulated	16
FI	■	■	■		■	■	■	■	■	■	■		■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	Liechtenstein	29
FR							■				■							■													■		4
HR													■					■												■			3
HU	■	■	■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	Liechtenstein	31
IE	■	■					■	■			■		■										■								■		9
IS								■				■												■				■					4
IT	■	■	■		■	■	■		■	■	■	■	■	■	■	■			■	■	■	■	■		■	■	■		■	■	■		27
LT			■			■			■						■						■				■		■			■			8
LU																																Country of origin	1
LV						■		■	■						■				■								■			■			7
MT					■	■			■		■				■			■	■							■			■	■	■	Public sector*	11
NL		■					■						■																				4
NO	■	■					■	■				■				■							■					■			■		9
PL	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■	Liechtenstein	31
PT											■		■																		■		3
RO	■	■	■			■	■			■	■				■			■	■						■					■			12
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SK	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■		■	■	■	■	■		■		27
UK																																	n/a
Reference frequency	16	15	9	2	10	13	17	15	12	13	16	15	19	5	13	13	3	15	14	9	11	8	15	6	10	13	10	13	13	16	17		

*For private sector in Malta, data from 12 European reference countries, classified in a three-tier system, is used for ERP: Low- priced tier: ES; UK; PT; FR/Medium-priced tier: BE; IS; CY; IT/High-priced tier: DK; DE; IE; NO. AT, Austria; BE, Belgium; BG, Bulgaria; CH, Switzerland; CY, Cyprus; CZ, Czech Republic; DE, Germany; DK, Denmark; EE, Estonia; EL, Greece; ES, Spain; FI, Finland; FR, France; HR, Croatia; HU, Hungary; IE, Ireland; IS, Iceland; IT, Italy; LT, Lithuania; LU, Luxembourg; LV, Latvia; MT, Malta; NL, the Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; SE, Sweden; SI, Slovenia; SK, Slovakia; UK, United Kingdom

Figure 2.5: Table of Reference Countries for Country. Source: Toumi et al. 2014.

The reference pricing scheme differs across countries: for example, in Denmark, Germany, Spain and Sweden the reference pricing scheme up to 2002 were only applied to multi-source drugs.[184] Without going case by case, generally speaking the reference pricing scheme is applied on interchangeable drugs of the same therapeutic area: however, the classifications are fairly controversial, and, at the same time, there are different strategies aiming to calculate the prices. In using the reference pricing,

> "patients must pay the difference between the price of the prescribed drug and the reference price if the former is higher. A common reimbursement price for products that are close equivalents creates an incentive for physicians to consider cost when making choices. In this way, reference pricing was

[184] *A multi-sourced brand drug is a brand name drug that is marketed or sold by two or more manufacturers or labellers, is no longer protected under patent exclusivity, and has a therapeutically equivalent generic available [source: Cigna, 2021. Insurance pamphlet].*

expected to bring the prices of all products in the same reference price category down to the same level (Mrazek 2002)"[185]

ERP. Instead, ERP or international price comparison is a common instrument for curbing pharmaceutical expenditure. The Regulatory body applying this policy requires the pharmaceutical company to apply a price that has to be no more than a maximum value set by a basket of countries, called reference basket. The mechanism is not new in the policy making world: for example, the funding that the Italian Government gives to the Regions in order to operatively function the Regional Health System is calculated on the basis of a reference basket of virtuous Regions.[186] Aside this note, ERP was first created in Germany in 1989 and since then has been adopted by different countries in EU. According to Rémuzat et al.,[187] 28 European countries has applied the ERP (except UK and Sweden) and 23 of these countries make ERP the main policy in calculating prices. External reference pricing is either applied to all marketed drugs – like in Luxembourg – or to specific therapeutic area drugs, or to specific categories of drugs (OTC, prescription drugs, innovative medicines, etc). The main aspect of this policy is the external reference that is taken: the reference basket is not equal in all countries applying ERP. Country basket has been defined using economic and demographic data, but throughout the years, the basket of different countries has been changed towards a complex and quasi-non-rational basket. Indeed, the number of reference countries for each basket varies in each country: in Luxembourg there is one reference country, in Croatia, Estonia, Portugal and Slovenia 3 countries, to 31 countries for Hungary and Poland. According to a report of European Union[188], the most referenced country is France, followed by UK (before Brexit), German, Austria, Spain, Slovakia, Italy, Netherlands. In order to have a clear picture of the situation, see figure 2.5.

The calculations behind ERP are based on two criteria: lowest price and average price. Whenever the price has not been set yet, the country usually takes the lowest price of a single state if available, or, if exists a comparable drug, the price is set on the same price of that drug. In most cases, the reference price is set from the ex-factory price or from the pharmacy purchasing price (PPP): the pharmacy retail price is only used in two countries (Luxembourg and Malta). According with Rémuzat et al., Italy used ex-factory prices, PPP and PRP depending on which information has been provided by the pharmaceutical company.

The main problem associated to the ERP is the "path dependence": indeed, the price is influenced by the rules that the reference system has imposed itself which in turn is influenced by the same reference system – a process that feeds on itself. Moreover, the available prices in the reference countries are usually heterogenous, making the comparison of prices difficult and do not consider the managed entry agreements between governments and companies. Another problem of the ERP is the possible spill-over effects on other countries and the price convergence: indeed, "wide application of ERP, a low price for a new product in a given market

[185] Mrazek 2002, pg. 459.
[186] Distaso 2019
[187] Rémuzat et al. 2015
[188] Toumi et al. 2014.

[let's say France] might affect manufacturer's pricing strategies elsewhere and could lead to parallel trade".[189] On the contrary, literature[190] demonstrates that ERP has become an incentive for pharmaceutical companies to adopt international pricing strategies, launching in sequence their products to delay or avoid launching new drugs in those countries where lowest prices is applied. For example, pharmaceutical companies usually delay filing in Belgium due to Belgian price policy, causing a problem of accessibility of new drugs. [191]

These are the main pricing strategies that the market and regulatory bodies apply for setting the price in their specific markets. In the next subsections, we will see two specific case and their respective policy in setting prices: Italy and USA.

2.8.2 Italian Pricing Setting

As we already saw in Chapter I, Italian pharmaceutical regulatory body is AIFA which regulates the market together with negotiating the prices of pharmaceutical and medicinal products. It acts as wall for the IT-NHS, regulating the reimbursement for specific categories of drugs. In the Italian market, there are four types of drug classes that differ each other: class A/H, Class C with prescription, Class C/SOP/OTC and class C/NN.

Drugs distributed through hospital pharmacies or for certain patient categories or administered in hospitals are grouped in the Class A/H: these drugs are essential drugs and chronic diseases drugs that have a certified efficacy in increasing life expectancies, reducing disabling complications due to the disease; moreover, in this class, AIFA adds also those drugs that have been proved to have less adverse effects than other identical or semi-identical drugs and that are cheaper than similars and biosimilars. Price of drugs in this class are negotiated between AIFA and pharmaceutical company and reimburse by the State. Class C with prescription are those drugs that are not included in the Class A/H Drugs, but the sell is still restricted to the public: these are not reimburse by the State and the price is not negotiated by AIFA, but prices are still monitored. Class C/SOP/OTC Drugs are pharmaceutical products that include over-the-counter drugs, drugs with no prescription obligation but not OTC and generics: they are not reimbursed, and the price is not negotiated. Finally, Class C/NN are drugs in a limbo: the class was created with the Law n. 189 of 8th November 2012 aiming to solve the long-standing problem of pharmaceutical products with MAA but with no price negotiation. Therefore, the Legislator prescribed that those drugs with MAA do not have to wait the negotiation, they can start distributing the products and, whenever found appropriate, they can apply for negotiation (if prescribed).

Let's now focus on the negotiations of Class A/H drugs and the price determination of medicinal products. Throughout the AIFA history, the methods of determination of prices for pharmaceutical and medicinal products have changed. From 1978 to 1993, the pricing method was based on cost-based pricing (see, previous subsection); from 1994 to 2001, the method was based on the European Middle Price, and from 2001 to 2019

[189] Rémuzat et al. 2015, pg. 9.
[190] Espin et al. 2011; Vogler et al. 2011; Cueni 2012. Iravani, Mamani, and Nategh 2020
[191] Rémuzat et al. 2015.

the CIPE[192] Resolution of February 1st (2001) introduced a different method. The CIPE indeed set the price determination based on cost-efficacy ratio, considering the usefulness of the pharmaceutical drug on different areas (art. 3 comma 1): efficacy in prevention or treatment of diseases for which there is no another therapy more efficient yet (n.1), or efficacy in prevention or treatment of diseases for which there are other means but are still not efficient as the drug in negotiation (n.2) or the pharmaceutical product in negotiation has a risk-benefit ratio more favourable than pharmaceutical products already distributed in the IT-NHS. Whenever the pharmaceutical product in negotiation has higher benefits than other pharmaceutical products in the same therapeutic area, AIFA has to consider (with consuming internal data) the budget allocated by the NHS Fund (Fondo Sanitario Nazionale) and comparing it with the provisional price and its effective impact on the budget itself. The CIPE, actually, did not cancelled the European Middle Price method, but it provided that the average price in HTA-EU can be considered as helping instrument in setting the price.[193]

Finally, with the Decree of the 2nd of August 2019 (published in GU Serie Generale n.185 of 24/07/2020) the Italian Department of Health, together with the Italian Department of Economics and Finance changed the price determination of pharmaceutical and medicinal products for those products that are included in Class A/H Drugs and for which the Italian State provides a reimbursability (total or partial). With the 2019 Decree, the method changed towards a focus on the added therapeutic value that a new pharmaceutical product can bring to the IT-NHS: it means that "the company will have to submit […] documentation showing added therapeutic value. If *[it]* is proven, the company will be required to submit further data deemed of interest in terms of economic benefit for the NHS."[194]

The innovativeness of a drug is calculated on three main parameters: the therapeutic need, the added therapeutic value and the quality of evidence. Regarding the first, it is divided in two urgent categories, important or conditional: the first implies economics benefits and an immediate listing in the Regional Pharmaceutical Formularies with a validity up to 36 months, the latter instead implies a listing in the Regional Pharmaceutical Formularies and a revaluation up to 18 months. The therapeutic need is then divided into 5 categorizations: maximum (there are no other similar or biosimilar drug with the same need), important (there are alternatives but no clinical validated outcomes), moderate (there are alternatives with limited impacts), poor (there is one or more alternatives with higher benefits) and absent. Regarding the added therapeutic value, we can individuate the same grade of the therapeutic value but with different limitations: the maximum added therapeutic value refers to a greater efficacy than alternatives, the important level demonstrates a greater efficacy or an ability to reduce the risks of disabling or potentially fatal complications or better risk/benefit ratios, moderate level, poor level and absent level. Lastly, for the quality of evidence the level may result high,

[192] Comitato Interministeriale per la Programmazione Economica – *in english, Interministerial Committee for the Economical Programmation*.
[193] CIPE 2001
[194] Altamura 2021.

moderate, low or very low: in order to assess the quality of evidence, it is used the GRADE method, that is the Grading of Recommendations Assessment, Development and Evaluation.[195]

However, the new price determination method cannot be categorised as done in the last subsection: indeed, the determination is a mix of different strategies and assessment methods that include an economical and financial assessment of the future drug uses, an assess of the forecasted market share that the drug is forecasted to acquire, the forecasts and budget variation that the IT-NHS has to undergo in case the proposed firm is accepted by AIFA (art. 2, comma 2, let. a-j). Moreover, the Decree requires that the pharmaceutical company and AIFA have to take into consideration the selling volumes, the availability of the drug to the IT-NHS, to every entity of the IT-NHS and the public funding (if any) that the Italian State had distributed in the early phase of the R&D phase (art. 4, comma 1, let. d). [196]

The Decree also describes the mandatory process of negotiation between AIFA and the pharmaceutical company. The negotiation itself can be activated both by AIFA (in case the reimbursability would have a considerable impact to the NHS's budget) and the pharmaceutical company. The negotiation lasts for 180 days during which it can be halt once by AIFA, only in the case that it requires more solid and thorough document for the assessment; the pharmaceutical company can also halt the process once in order to provide other documents useful to the assessment. AIFA, through the CTS (Comitato Tecnico Scientifico – Technical Scientific Committee) files a response to the application in which list its observations on the added therapeutic values. With the filing, the CTS passes the response to the CPR (Comitato Prezzi e Rimborsi – Pricing and Reimbursment Committee) which start the path for the negotiation with the involved party. When the parties agree on the price negotiation, the process is ended, and the price outcome refers to the maximum price that the IT-NHS can buy the drug from the producer. In case the outcome of negotiation is negative, the product is classified in the Class C/NN as per the comma 10, art. 8 of Law n. 537 of the 24th of December 1993. Once the negotiation fails, the pharmaceutical company can re-apply or AIFA can reinstate the process. The contract between AIFA, IT-DoH and IT-NHS lasts for 24 months and can be rediscussed prior the deadline in order to renegotiate the price in case there are variations in therapeutic indications or posology.[197]

In the following paragraph, we will explain the reimbursability of pharmaceutical products: the analysis will not go deep as above (it is not the scope of the thesis) but it will serve for better contextualise the Managed Entry Agreements (MEAs). AIFA, and in general the IT-NHS, faces three main challenges regarding pricing and reimbursability: indeed, they have to guarantee the access of new means of treatment to Italian population, they also have to cope with the uncertainty in deciding the price of a certain pharmaceutical product and, finally, have to the sustainability of the National Health Service Budget. Therefore, they face a complex trade-

[195] Altamura 2021.
[196] Italian Minister of Health and Italian Minister of Finance 2019
[197] Italian Minister of Health and Italian Minister of Finance 2019; Altamura 2021.

off between promoting and protecting the general health and control the pharmaceutical expenditure: it comes to aid the HTA, "a useful approach that helps policy makers in taking *this kind of* decisions."[198]

The scenario applies to all pharmaceutical products that prove to be innovative or are in the 'early access' (new to the market). Whenever the innovative drug has received a MAA from EMA or AIFA, the pharmaceutical company can apply con a condition reimbursability, signing a Managed Entry Agreement (MEA) with AIFA. The scope of this agreement is to manage the uncertainty associated to an innovative drug and related to clinical benefit and cost-effectiveness, not completely proved by the market (since the 'early access'), and also it helps government agencies to control and manage the budget impact of such drug. Therefore, in this situation, MEA can prescribe different solutions in the reimbursement area, both in the means of expenditure cap and performance based terms, respectively:

1. Capping: AIFA imposes an expenditure cap to the pharmaceutical company aiming to ensure prescription appropriateness and managing the impact in the budget; the cap is set with a dose method, that is, for example, the treatment cost is set on the lowest therapeutic scheme cost; at the end of the contract, AIFA verifies if the cap has been respected by the pharmaceutical company, if no, the firm must pay back the administration the excess [in order to give a picture, in 2019 the payback amount was 130 million of Euro];
2. Cost Sharing: the strategies is performed through the MEA with a fixed discount at the start of the therapy; patients who responded to the therapy, continue with the therapy, those did not respond, halt the therapy.
3. Risk Sharing: the risk of the therapy is shared between NHS and pharmaceutical company; the pharmaceutical company receives a reimburse by the NHS if the patient responds to the therapy, if the patient does not respond to the drug, the pharmaceutical company refund part of the therapy.
4. Payment by Result: the method is similar to the previous one, with the difference that if the therapy fails, the treatment is reimbursed in total by the pharmaceutical company.
5. Payment at Result: similar to risk sharing method, with the difference that if the treatment is successful the paid by the NHS to the pharmaceutical company, if not is not paid by the NHS.

Until 2019, overall, 56 MEAs were active, among them the 53.6% were with payment by result mechanism, 7.1% with capping mechanism, 32.1 with cost sharing, and the other with mix mechanisms.

Summarising, it appears evident that Italian Government through its agencies intervenes in the market in order to protect the population and to guarantee the safety (both in a health sense and in an economical sense) of the patients. The behaviour does not appear unexpected: historically and socially, Italian WS has been always centred on the interventions of the State in the economy with a profound regard to the universality of the

[198] Altamura 2021, pg. 21.

Health Care system in place. Instead, Us Health Care system is the complete opposite of the Italian model, as per the following subsection.

2.8.3 US Pricing Setting

Contrary to the Italian setting, the US health care system, and in particular the pharmaceutical sector, does not have solid and massive interventions from the Us State. As stated in Chapter I, the US WS does not fall in the Esping-Andersen categorisation, but it is still assimilable to those situations where the market laws are predominant over the equality, free-for all and universal value which are present in various European WS. Surely, the US setting does not imply a regulation in the pharmaceutical products pricing: indeed, the entire system is based on the exacerbation of capitalistic views, seeing any kind of regulation, interventions in the market or even a public and free-for-all healthcare system as socialistic and communistic as possible. It is not the *locus* where to debate the rightfulness of this view or the causes that have brought USA to this situation (surely, Cold War and the US propaganda have helped shaping this kind of behaviour), but the reader should take into consideration that the European WS setting is far from similar to the US one.

We thoroughly treated the US Pharmaceutical Industry in the previous paragraphs and chapters, but in order to give a complete picture we should address the last detail: USA has no regulation nor reimbursements of pharmaceutical products. The problem around the pharmaceutical pricing in the USA is well known and the cost for the final consumer is year after-year-getting higher. The causes of these surges in pricing and costs for the general population can be retrieve in the sense on which USA has built the healthcare system.

Indeed, USA face a trade-off in the pharmaceutical industry, but – contrary to Italy – they approach the problem from another angle: they take out the 'variable population' (and, therefore, protecting and ensure the health of the population), outsourcing it to the individual, and focus only on innovation/competition/success: citing Wertheimer and Huang "*(p)*harmaceutical pricing combines science and a bit of art." [199]

Therefore, the market is free to 'adjust' following its own practices, imposing prices higher enough to turn pharmaceutical products useless or inaccessible to the general public. Going deep into the analysis, there are no regulation strategies nor pricing methods imposed from the State nor negotiations (with some exceptions) around pharmaceutical products: the pricing strategies are decided by the pharmaceutical company and imposed in the market: a market with the same mechanism of other industries.

The Us pharmaceutical and healthcare chain is composed by producers, insurances and wholesalers, retailers and hospitals: producers sell to wholesaler and insurances, that resell the products to pharmacies and hospitals. In this context, pricing is decided through market laws, usually applying discount pricing to the first level of this chain and then using cost-based pricing. Moreover, since the surge in pharmaceutical products prices, different intermediate and end consumers start to pool resources and voices in order to have applied discounted prices: therefore, different consortia between hospitals start to rise in order to raise the purchase power and

[199] Wertheimer and Huang 2015, pg. 313.

lower the prices. In any case, the end consumer (the patient) faces anyways the surge of prices in the day-to-day life: different patented-drugs, OTC and generics (epi-pens, insulins etc) have even higher prices of the Us neighbour, Canada. [200]

The pharmaceutical pricing problem in USA has been treated a lot in scientific literature and on the media. Although there are some resistances on the admission of the problem itself,[201] the consensus on the existence of the problem is fairly unanimous, even more since the 2008 crisis and the recent SARS-CoV-2 pandemic. For example, Delagneau – former Vice President of Gilead (producer of Sovaldi) and former CEO and founder of Idekos – has tried to demonstrate that the pricing of pharmaceutical products in US is similar to the pricing in EU and other developed country: the logic behind the demonstration is to compare the price of products (Sovaldi, Olysio, Yervoy, and Zytiga) across countries, applying as comparison term the average selling price (ASP) and not the average wholesale price (AWP), motivating the choice since ASP is discounted from the AWP. The logic does not seem fallacy, but he forgets to mention the higher welfarism present in Europe that helps to mitigate the listed price. Surely the Delagneau's opinion is not scientifically proven via a peer-to-peer review, but he still brings to the table the criticism towards a regulatory intervention. Different other media and observers recognize the worryingly absence of regulation on the lives of millions of people.[202] For example, Kliff (2018) reports that Harvoni (a hepatitis C drug) costs in US only more than 30.000 Us-$ while in UK costs around 20.000 Us-$ (with a universal and free-for-all health care system); again, Entis reports that Humira (AbbVie's rheumatoid-arthritis drug) has climbed from 19.000 $ per year-treatment in 2012 to 60.000 $ per year-treatment in 2019. In 2016, after the same move of Sanofi and to Eli Lilly, Novo Nordisk A/S decided to cut the AWP of its insulin based drug for type 1 diabetes with a discount equal to 50% of the original price (144.68$ with the discount): for contextualise the price, the price of the same drug in Italy has been negotiated with a price equal to 49.74 €[203] (58.24$).

Moreover, the absence of pricing regulation nor price negotiations eliminate any kind of barriers of entry of specific drugs that, although they have been given authorization for the marketisation by FDA, do not bring to the consumer valuable and innovative therapeutic benefits. For example, in 2012 a drug called Zaltrap (treating colorectal cancer) have been sell by the manufacturer at 11.000 $ per therapeutic month: the price was twice compared with biosimilar and alternatives and offered no additional benefits to other drugs in the same therapeutic area.

Different observers have asked what happens if some sort of intervention from the State would be taken in place. The first move should be the institution of some sort of HTA agency or the centralization of HTA processes, but "due to the complexity of health care system, or non-system, there is neither a single HTA

[200] Wertheimer and Huang 2015.
[201] Delagneau 2018.
[202] Chung, Kaufman, and Rauenzahn 2020; Entis 2019; Wertheimer and Huang 2015; Kliff 2018.
[203] Class A Drugs per trade name, AIFA.

agency nor centralization of HTA"[204] in the USA. Surely, the second move would be the creation of reimbursement scheme or the imposition of prices to insurance agencies from the Administration. However, considering the values in place in USA, this kind of scenario is highly utopic.

To summarise, Italian and US price setting system is completely different: the latter is based on interventions in the market by the State, with thorough negotiations, HTA processes, and reimbursement schemes; while the former appears to be devoid of incentives to lower prices and interventions on the market for protecting its own population.[205]

2.9 Paying-twice

In the chapters, we have treated different side of the pharmaceutical world, addressing various problematic: the healthcare systems differences, the pharmaceutical patent situation both in common law and civil law, the pricing system that are present in EU (Italy) and USA, and now one of the major problems in the public-private pharmaceutical relationship, the paying twice.

This critique is the follow:

> "where subsidies are present, prices are alleged to be too high because product research and development has been co-finance by taxpayers *[and this]* is often framed in terms of 'paying-twice' – first for the research and, second, through the above-market pricing of resulting privatized products (Wolitz 2019)."[206]

In other words, paying-twice in the pharmaceutical industry occurs in the situation where a State (via public agencies or direct funding) invests in pharmaceutical research and then, also pays the drug once is authorised to enter the market. The problem is cross-countries and cross-healthcare-systems: it occurs in Italy, as well as in the USA. However, the scientific literature around this topic covers only the US scenario and does not treat any kind of situation in Europe. Therefore, in this paragraph we will address both the issue with some limitations: Italian regulation embodies in its pricing strategies the situation in which specific drugs have been funded via public investment and funding and discount them to the negotiation price. However, this behaviour is not specifically and thoroughly address from the Decree of the 2nd of August 2019 (see, paragraph on Italian pricing settings). Also in the European Union, the matter is not addressed completely, but still persist situations where EU funds research and MSs pay twice.

Contrary to general believes, the 'paying-twice' critique does not start with the approval of BDA in 1980, but has historical roots: indeed, the concern on "taxpayer subsidization of private sector windfalls as an important issue at the of the Bayh-Dole Act's passage and even precedes it."[207] The debate around patenting and licensing

[204] Wertheimer and Huang 2015, pg. 315.
[205] *Due to the scope of this thesis, we decided to not go further into the debate on the healthcare systems and their differences across countries. However, we should also notice that there are US insurance schemes that allows low-class population to have covered the basic health expenditure (Medicare, Medicaid, etc), but the schemes are not enough to ensure the health of all population.*
[206] Wolitz 2019, pg. 178.
[207] Wolitz 2019, pg. 180; Eisenberg 1996.

policies began with the World War II.[208] With the season of the BDA, the Federal Administration relinquished the rights of those research that it funded, establishing a regime in which grantees have kept the rights of the research funded with public money. However, the regime modification did not erupt with the BDA, but was a slowly movement started with the Stevenson-Wydler Technology Innovation Act (STWI Act) of 1980 that transferred the owned or originated technology rights of the Federal Administration to State, local governments and private sector. The other bill passed on the topic was the Federal Technology Transfer Act of 1986 (FTTA) that created an advanced mechanism for furthering the SWTI Act: the CRADA (Cooperative Research and Development Agreement). CRADA enables the exchange of knowledge, personnel, facilities and other resources between State and public laboratories, and private sector.

Coming back to the BDA, the 'paying-twice' critique was firstly address during the debate on the Bayh-Dole Bill: indeed, Senator Long – Us democratic senator, member of the Us Senate Finance Committee from 1966 to 1987 together with Bob Dole – observed:

> "The disposition of rights resulting from Government research and development can increase monopoly and the concentration of economic power or, alternatively, can spread the resulting benefits throughout society with consequent benefit to the maintenance of a competitive free enterprise system and more rapid economic growth. […] It is dismaying, therefore, to find that S. 414 provides for contractors, in this case small business firms, universities and nonprofit organizations, to receive gifts of ownership of taxpayer-financed research, and according to S. 414's chief sponsor, this is to be only a first step. […] There is […] absolutely no reason why the taxpayer should be forced to subsidize a private monopoly and have to pay twice: first for the research and development and then through monopoly prices. […] It would hamper the rapid dissemination of scientific and technological information and hence will retard economic growth and increased productivity. This proposed legislation is one of the most radical, far-reaching giveaways that I have seen in many years (Mr Long, Us Senate 1980)."[209]

Wolitz (2019) has undergone a thorough investigation of the meaning and principal aspects of the 'paying-twice' critique: we should also notice that the point of view of the paper cited is far from being objective. There are four features and question on the 'paying-twice': the first question that Wolitz addresses is the meaning of the 'paying-twice'. Unquestionably, the meaning is not literal (contrary to the provocation that Wolitz wrote in the paper): the final consumer does not pay double the amount of the products – in this context, pharmaceutical product. However, s/he pays twice: the first time by the State via taxes that the final consumer has paid to the Administration and the second time when s/he purchases the product. Surely, the process is not literal, but in reality, s/he ends to buy a product which has been funded through *their* taxations and practically 'paying it twice'.

[208] Eisenberg 1996, pg. 1671.
[209] Us Senate 1980

Again, the 'paying-twice' critique depend on ideas about the normative relationship that ought to achieve amongst government funding and the pricing of products. This relationship can be structured on three possibilities: the gift view, the transaction view and the access view. The former relies on the assumption that the State should not intervene on the pricing of any resulting products: the relative funding, therefore, would be a plain gift to the private sector. A second structuring of this relationship can be viewed as "a complaint about transactional unfairness. It expresses the view that the terms of an arrangement between taxpayers and a private party with license or patent rights covering a medication are unfair."[210] In this context, an agreement set between two parties by an intermediary (the State) treats one of the parties (the taxpayers) in a weak position compared to the other party which receives funding and then money through the selling of the funded product.[211] This second perception does not strictly hit the pricing critique, but focuses on the unfairness of the game as "if US taxpayers are already funding university research to the optimal level, then adding patent rights to the incentive package gives an excessive reward."[212]

Finally, the third view is focused on the fact of government funding: in other words, the critique is not on the unfairness of the transactions but is a "complaint based on inaccessibility and unaffordability in spite of government funding. Some articulations appear to rely on an implicit assumption that the presence of government funding in itself entails obligations regarding product pricing."[213] Wolitz continues using terms with negative acceptations, citing the founder of Patients For Affordable Drugs:

> "[D]rugs don't work if people can't afford them, and no American should pay $373,000 for a drug that taxpayers helped invent… American taxpayers paid for the basic science behind this drug, and now we're asked to pay outrageous sums to get the treatment. Patients will suffer. It's time we focus on maximizing access and affordability for patients instead of maximizing profits for drug corporations. [214]
>
> […]
>
> This points to a very different understanding of the essential moral grievance. It is not about transactional fairness, but rather some kind of governmental obligation. Indeed, an extreme version of this view would be that regardless of any of the details—no matter how small or how attenuated—the fact of government funding implies conditions ought to be placed on the pricing of subsequently privatized products. (Wolitz, 2019)."

We decided to cite this passage from Wolitz to better explain the statement above: the 'paying-twice' critique is treated by different observers like a 'child caprice' of a part of the Us society, failing to understand the principals behind the general tax collection. General public pay taxes in order to have a service from the Government, or to invest those amounts in public investment that may give benefits to the population. The

[210] Wolitz 2019, pg. 184.
[211] Sage 1996; Wolitz 2019.
[212] Hemel and Ouellette 2017, pg. 7.
[213] Wolitz 2019, pg. 187.
[214] Wolitz 2019, pg. 187, citing New CAR-T Drug, David Mitchell 2017.

critique is not so difficult to understand and still is treating as by different sides as a “complaint”. Truthfully, Wolitz tries to give a solution to the 'paying-twice' critique through pricing schemes: in the last chapter we will address it.

2.9.1 European Union and Italy: 'paying-twice' critique?

We have addressed the critique in the USA, but we should also ask ourselves if the same critique is present in the European Union setting and, specifically, in Italy. In scientific literature, there is no trace of any interventions nor inquiries on this topic. We can see two main causes for this: the first is the presence of a pricing regulation for pharmaceutical products and the second is the difference on IP regimes with the USA. Therefore, the problem is not so urgent as could be in the USA, but still relies on the unfairness of the agreements and the absolutely no compensation of them.

If we look at the pricing policies in place in the European Union and EEA, we will see that there is not a common strategy for every MSs, and – we already discussed about it in the early paragraph of this Part – every Member State applies different pricing strategies: whenever the pricing strategy is common to other countries – for example, applying ERP policy – the reference basket is often different.

Instead, if we look at the Italian regulation on the pricing of pharmaceutical products, we will see that the Pricing and Regulation Law of the 2nd of August 2019[215] states that

> “*The negotiation procedure is perfected with the agreement between AIFA and pharmaceutical company, through the fixation of the reimbursability conditions and pricing conditions, coherently with the disposition of this Decree, together with the following provisions:*
>
> *a) selling volumes;*
> *b) availability of the product to the NHS.*
> *c) discounts to the entities of the NHS.*
> *d) public contributes to the research and development programmes (art. 4, comma 1)”*

Letter *d* of the article 4 underlines and tries to solve the problem of public research/funding and private sector. However, it does not provide a solution to the matter in particular: instead – and does not seem surprising, considering the quality of policy making in Italy – shelves the problem to a letter of a comma of a decree. The critique, here, is not towards the Legislator’s actions and relative pronouncing on the matter: instead, it is more focused on the absolutely no specific direction that this *letter d* imposes on AIFA and its Pricing and Reimbursability Committee.

[215] Italian Minister of Health and Italian Minister of Finance 2019

Throughout this Chapter, we have seen different side of the same topic. Part I focuses on the legal side of the matter, while Part II on the admixture of innovation economics, legislative and pricing sides. In the following two chapters, we will try to provide two real examples of the matter in discussion here: Sovaldi Scandal and the SARS-CoV-2 vaccines. The aim is to better explain the reality of the 'paying-twice' critique and try to solve it, through a mixture of different pricing strategies.

Chapter III

Gilead's Sofosbuvir and SARS-CoV-2 Vaccines Cases

In the early part of this thesis, we have discussed about different characteristics of the pharmaceutical industry, citing different cases of extraordinary anomalies and stretches of the market itself, especially in the US market. We will now focus on two cases: Sovaldi and SARS-CoV-2 vaccines pricing settings. Sovaldi is a breakthrough pharmaceutical product for the treatment of hepatitis C, while the SARS-CoV-2 vaccines are vaccines aimed to prevent the spread of the pandemic of Covid-19. Both these pharmaceutical products have been funded by states financing and have an impact on the life of various patients as well as on the financing of the world countries. The chapter will be divided in two paragraphs: the first will focus on Sovaldi, while the second on the two vaccines produced by Pfizer and AstraZeneca. While in the first case, we have different contents in literature, the information around the second one is few and, in some cases, comes from media leaks of official documents.

3.1 Sovaldi Case: Pharmasset, Gilead and US Senate

Sovaldi is a hepatitis C pharmaceutical product developed in the early part of the 2000s. Hepatitis C

> "is an acute or chronic hepatitis that is caused by a flavivirus (species Hepatitis C virus of the genus *Hepacivirus*), is often asymptomatic in its early stages but may be marked by fatigue, fever, nausea, loss of appetite, abdominal tenderness, and muscle and joint pain, and is usually transmitted by infected blood (such as by injection of an illicit drug, blood transfusion, or exposure to blood or blood products)."[216]

The fight against *Hepacivirus* has been in place since its discovery in 1989: in the reality, the virus was known before the 1989 as a non-A nor non-B hepatitis virus. With its discovery, the scientists have been able to find seven genotypes of the virus and 86 subtypes: for example, GBV-B virus was discovered in 1995 and is capable to infect different species of monkeys.[217] In the genus of the *Hepacivirus,* there are 14 species: among them, the Hepacivirus C (Hepatitis C virus; later on, HCV), Hepacivirus B (GBV-B), Hepacivirus A, Hepacivirus N (bovine hepatitis). Sovaldi has therefore been created with the goal to fight the HCV.

However, Sovaldi is the trade name, while the pharmaceutical product is called *sofosbuvir* and it is marketized in two solutions: Sovaldi 400mg film-coated tablets and Sovaldi 200mg film-coated tablets. The former is yellow, capsule-shaped, film coated tablet of dimensions of approximately 20 mm x 9 mm, debossed on one side with GSI (that stands for Gilead) and on the other side 7977. The latter is a yellow, oval-shaped, film-

[216] Merriam-Webster 2021
[217] Stapleton et al. 2011

coated tablet of similar dimension, debossed – however – with a different acronymic: GSI on one side and 200 on the other.

Contrary to general believes, Sovaldi (sofosbuvir) is not a single pharmaceutical product that cure HCV: instead, it is a drug that has to be used combined with another drug (the medical doctrine suggests ribavirin) and, for specific genotype, with an additional one, that is the peginterferon-alfa. We will come back to posology and administration of Sovaldi later on the chapter: for now, it is useful to understand the picture where sofosbuvir fills in in the medicinal panorama.

Therefore, in this situation we have two private company and various public and regulatory agency. Pharmasset, Inc is a pharmaceutical company founded by Raymond Schinazi and Dennis Liotta, both professors and scientists from the Emory University (a private research university based in Atlanta, Georgia [USA] founded by the Methodist Episcopal Church). Pharmasset was founded in 1998 in Tucker, Georgia and its focus was mainly on antiviral research (HCV, HIV, HBV). The other private company – in this case an LCM – is Gilead Science, Inc (later only Gilead) founded in 1987 in Foster City, California (USA): its scope has developed during the years, and it now involves different branches of the biopharmaceutics, but still in the same therapeutic area of Pharmasset (HIV, HBV, HCV and influenza); it is the manufacturer of Sovaldi (the case in scope) and Harvoni (another pharmaceutical product that has been fairly criticised by the general public). Two agencies and public bodies enters this picture now: one is the US Senate, the 114th US Congress, presided by Joe Biden and with Republican majority, in particular the United States Senate Committee on Finance chaired by a republican Senator – the US Senator Orrin Hatch – with Ron Wyden as ranking member. According to different sources, however, the investigation around Gilead and Sovaldi was commenced by Us Senator Grassley and the ranking member already cited. The last agency, that actually has little movement capacity regarding this topic, is the FDA (§Chapter I).

In the next lines we are going to describe the history behind this case and the main events that led to the Investigation by the US Senate Committee on Finance.[218] As we already stated, Pharmasset was found in 1998 in Georgia by to scientists while Gilead was founded in California in 1987: the former became a public traded company in 2006, while the latter in 1992 (with an IPO equals to 86.25 million US Dollars). According to SEC[219], Pharmasset was founded in Barbados as Pharmasset Ltd, filing its first patent in 1995, [220] as "a clinical-stage pharmaceutical company committed to discovering, developing and commercializing novel drugs to treat viral infections." [221]

From 2000 to 2006, NIH granted Pharmasset with a total amount of 2.28 million of US Dollars in order to fund research on antiviral drugs (2.284.911 Us $).[222] The funds were granted to different scientists of

[218] The timeline is taken and rearrange by US Senate Committee on Finance and 114th US Senate 2015
[219] SEC 2006
[220] Pankiewicz, Lesiak, and Watanabe 2001
[221] SEC 2006, pg. 3.
[222] NIH Grants Database.

Pharmasset, for basic research: with them, Michael Sofia invented the Sofosbuvir, a molecule composed by $C_{22}H_{29}FN_3O_9P$ appearing as white/off-white powder. According to the US Senate, in 2008 Pharmasset spent 770.000 US Dollars for researching a new molecule called PSI-7977 for treating HCV: however, according to WHO,[223] Pharmasset filed the first patent for Sofosbuvir in 2003.[224] In 2009 Pharmasset spent other 6.9 million of US Dollars in developing PSI-7977, completing the phase 1 of the clinical trial required for the NDA. In 2010, Pharmasset announced the initiation of Phase 2a and 2b of the clinical trials on PSI-7977, making the announcement the first acknowledge of choices between different molecules candidate to be an HCV drug: only in 2010, the spending in R&D reached 16.4 million of US Dollars.

Alongside Pharmasset, two other companies began research new means for treating HCV: Merck & Company and Vertex Pharmaceutical. In 2011, both the drugs developed by these companies have been approved by FDA respectively (in order of ownership): Victrelis (boceprevir) and Incivek (telaprevir). The former has been created for the treatment of chronic HC genotype 1, in combination with pegylated interferon-alfa and ribavirin; the latter has been developed for treatments of chronic HC (CHC) genotype 1 in combination with pegylated interferon alfa and ribavirin. In the same year, Gilead Science begins the negotiations to acquire Pharmasset, which had already begun the Phase 3 of clinical trial for PSI-7977; in the end of 2011, Pharmasset released a press release stating that PSI-7977 has been proven efficacy to treat HCV: after the release, Gilead increase its price offer from 100 $ per share to 137 $ per share, since different pharmaceutical companies began negotiated with Pharmasset. The problem around HCV is the nonexistence of a single drug that cure Hepatitis: indeed, all the treatment solutions involve a combination of drugs that use them together provide therapies for HCV. Lastly, in the same year, Pharmasset halted clinical trials for PSI-938, another drug for HCV treatments. With the new year, Gilead announced the acquisition of Pharmasset for 11.2 billion of US Dollars. According to Reuters,[225] different investors of Gilead had expressed doubts on the value of the acquisition: Schinazi, who founded Pharmasset, told the journal that the company might have had a deal of 98% off the real acquisition, buying the company for 300 million US Dollars; the calculated premium to share of the acquisition contract has been set for 89% of the share itself. At the same time, Gilead Science Inc the day of acquisition announcement, have fell off of different share points: different investors feared that the acquisition with that premium was too risky for the firm.

Anyways, in 2013, Gilead begins the evaluation of Pharmasset PSI-7977, which changed name in GS-7977 and was afterwards marketed with the trade name of Sovaldi. At the same time, Gilead filed the NDA for Sovaldi to FDA which authorized the marketisation recommending the use with the ribavirin for patient with GT3 HCV plus the interferon and ribavirin for those with GT1 and GT4 HCV. [226] On the 10th of October, FDA decided to grants Sovaldi the designation of "Breakthrough Therapy" allowing Gilead to include two

[223] WHO 2016.
[224] It seems hard to precisely collocate the exact time of the invention of Sofosbuvir. According to diverse sources, it happens before 2003 and 2007.
[225] Reuters 2011.
[226] FDA 2013.

additional Phase 3 clinical trials with two other drugs (VALENCE and PHOTON-1) which provided data supporting treatment of GNT-3-HCV and GNT-1-HCV patients with HIV. In the same time window, FDA approved another drug – Olysio (simeprevir) – for the treatment of GNT-1-CHC as a component of a cocktail of drugs for HCV. At the end of 2013, Gilead set the price of Sovaldi at 84000 US Dollars [see next paragraph for the discussion on the price].

With the price fixing and relative announcement, for Sovaldi and Gilead began a set of different problems, involving its price and its feasibility on the market. The American Association for the Study of Liver Disease (AASLD) and the Infectious Disease Society of America (IDSA) released a recommendation to healthcare providers prescribing that Sovaldi and Olysio should be prescribed in combination for GNT-1 patients who were not eligible for treatment with interferon. In mid-July 2014, Us Senator Wyden and Grassley sent a letter to Gilead CEO John Martin trying to understand the process and the output reason for the price of Sovaldi, *de facto* beginning the Senate investigation on Gilead's practices. In the same period, Vertex discontinued the sales of Invicek, and FDA approved the marketization of Gilead's Harvoni (ledipasvir and sofosbuvir) for the treatment of GNT-1-CHC. In the last months of 2014, the US National Association of Medicaid Directors sent a letter to Congress raising different concerns on the feasibility for the system of the utilization of Sovaldi with that fixed price. With the ending of 2014, FDA approved two other drugs: the J&J's Olysio-Sovaldi combination for treatment of patients with GNT-1-CHC and the AbbVie's Viekira Pack (ombitasvir, paritaprevir, ritonavir and dasabuvir) with or without ribavirin to treat the same patients. The situation at the end of 2014 saw different means of treatment CHC besides Sovaldi, ranging from around 30.000 US Dollars (Olysio) for treatment cycle to 95.000 US Dollars (Harvoni).[227] On December 22nd 2014, Express Scripts Holding Co, one of the largest pharmaceutical benefit manger in the USA released a statement announcing the reach of an agreement with Viekira Pak manufacturer for the supplying of the drug for a significant discount on the original price (undisclosed discount), sparkling the competition between AbbVie and Gilead.

The first results of selling HCV drugs came with the initial month of 2015: according to US Senate, J&J sold 2.3 billion of Us Dollar of Olysio in combination with Sovaldi (together with a drop in market share, attributed to the competition of Harvoni). At the same time Merck announced the discontinuation of sales of Victrelis. Gilead announced the results for 2014: 10.3 billion of US Dollars from sales of Sovaldi, 2.1 billion from Harvoni (which competed with Olysio); the company "announce[d] that it expects the ''gross-to-net'' discount for HCV drugs to average 46% in 2015, compared to 22% in 2014."[228] In the same year, FDA pharmacovigilance issued a safety warning involving Olysio, Harvoni and Sovaldi: Sovaldi and Harvoni when used together with Olysio and other HCV drugs might cause serious bradycardia when used with amiodarone. In mid-July FDA approved Bristol-Meyer Squibb's Daklinza (daclatasvir) for GNT-3-CHC together with Sovaldi and Technivie (AbbVie) for GNT-4-CHC patients without cirrhosis. Moreover, FDA issued a safety warning for Viekira Pak and Technivie regarding the possible harm of patients with advanced liver diseases.

[227] Brandy 2018.
[228] US Senate Committee on Finance and 114th US Senate 2015, 5-123.

With the end of the third quarter, Gilead announced increasing financial result from the marketisation of Sovaldi and Harvoni: respectively, 3.7 billion of Us Dollar in net product sales of Sovaldi and 10.5 of US Dollars of Harvoni; also, AbbVie announced its first result from Viekira Pak, assessing the net revenue to 1.1 billion of US Dollars only in the first 9 months of 2015.

Therefore, the situation of US pharmaceutical market HCV drugs has seen Harvoni and Sovaldi as main drugs, with other different molecules developed by other pharmaceutical companies. We can safely affirm that Pharmasset with its research on antiviral drug had incentivised the market to focus their scopes on the means to treat HCV with new settings. If we apply the framework developed by Aronson[229] regarding the drug innovativeness, we can safely state that Sovaldi is an innovative drug, adding that it created a new momentum for the market, exploiting Harvoni and Sovaldi and leveraging them. However, there is one downsize in this picture: the price of Sovaldi. Different scholars have focused their research on this topic,[230] reaching a strong consensus on the not-affordability for the Us healthcare system of the use of Sovaldi and Harvoni, combined with other molecules from J&J, AbbVie: the matter is fairly amenable to the characteristics of the Us system itself. Indeed, the absence of pricing regulation – as already state in Chapter II – leaves the market at its own mercy, pushing it to thoroughly apply the capitalistic views and rules. It is on this view that the Us Senate start the investigation on Sovaldi: the results for Gilead from the marketisation of Sovaldi and Harvoni have had two consequences: the enrichment of the company and the failing of the NIH role in the market. However, we prefer to leave the final assessment of this case for the ending paragraphs.

3.1.1 Pricing setting of Sovaldi

Before deeply examine the pricing process of Sovaldi, we should remind that Us Drug Patents are covered by an exclusivity period of 20 years: basically, with the filing of a patent the company has the right to marketize it in a quasi-monopolistic setting for 20 years without interferences from other competitors.

With the marketization of Sovaldi and Harvoni and their pricing fixing, the US Senate began to investigate Gilead's practices. After 18 months of investigation, in 2015, Us Senate Committee on Finance released a report containing the information and practices that Gilead applied in order to set the prices. The report containing confidential information, reports, market access assessments, and correspondence between top-managers (more than 20000 pages of information) has been totally published by the Us Senate: however, no actions have been taken by the Federal Administration (§3.1.3).

Shortly after the acquisition of Pharmasset, Gilead began the market access assessment in order to set a 'congruous' price for Sovaldi. We have seen various forms of pricing settings in Chapter II, it will be fairly evident that none of the pricing strategies has been taken into consideration in order to retrieve and set a price

[229] Aronson 2008
[230] Silver and Hyman 2020; Henry 2018.

for Sovaldi, or at least, the only pricing strategy considered was the μ-strategy. We also have to point out – as Us Senate underlines it fairly often – that Gilead did not produce all documents and information required by the Committee: however, we do not understand for which political reason (if any) Gilead and its top-managers have not been served by subpoenas, and whenever refused to properly respond, they would not have been charged with Contempt of Congress (as per 2 USCA §192). We should, however, point out towards a logical reason: the non-willingness of creating a precedent for the Us pharmaceutical industry; there are a few of cases where contempt of congress has been charged to companies and individuals and, surely, there was no need to un-stabilize precarious equilibria (also since the announcement have been issued at the end of the 113th Us Congress window and in the last two years of Democratic presidency).

As we were treating, Gilead began the pricing process just after the acquisition of Pharmasset Inc: the price chosen at the end of the process was in a interval between 80.000 $ and 85.000 $, in order to "allow Gilead to capture value for product without going to a price where the combination of external factors and payer dynamics could hinder patient access to uncomfortable levels."[231] At the end of 2012, the company was underway the Phase 3 of trial of Sovaldi and setting its strategies of marketize the product: one of the document given to US Senate[232] by Gilead analysed the HCV sub-market and its target customers, underlying Gilead's strategy to gain market share through expanding the patient pool. The first method to set the price – in this stage – was to benchmark Sovaldi with others HCV SOCs, giving qualities to Sovaldi and pricing it according to drug values and hypothetic customers perceptions. Together with this assessment, Gilead explored the likelihood of happening of so-called 'soft events' (external events not controlled directly by the company): the distribution of probabilities and relative outcome were set on the US market only, non-considering the Eu market and RoW market.

As part of pricing considerations, Gilead aimed to benchmark how similar drugs were priced in the market: it then focused on GNT-1-CHCV patients in the USA. Indeed, there were two other competitor drugs in the market: Merck's Victrelis and Vertex's Incivek, but Gilead's top-management was sure that "Sovaldi […] ha*[s]* an edge because clinical studies showed it would provide faster, more effective treatment and reduced time on, or outright elimination of, interferon injections."[233]

[231] US Senate Committee on Finance and 114th US Senate 2015, Appendix E, Ex. 28, 0014044.
[232] US Senate Committee on Finance and 114th US Senate 2015, Appendix E, Ex. 29, 0013489.
[233] US Senate Committee on Finance and 114th US Senate 2015, §1, pg. 33.

GSI Confidential

Aside from payer access and physician demand, there are a number of softer issues that could affect Gilead's final pricing decision

GILEAD

Stakeholders	Wave 1 Regimen	$60,000	$70,000	$90,000	$105,000	$125,000
	Wave 1 SOF product (12 wks)	$50,000	$60,000	$80,000	$95,000	$115,000
	Wave 2 FDC (8 wks or 12 wks?)	$70,000	$80,000	$100,000	$115,000	$135,000
Payers	Likelihood of applying directly observed therapy due to high price	Unlikely	Possible	Possible	Likely	Likely
Physicians	Likelihood of delay treatment of GT-1 TN patients due to pricing	Unlikely	Possible	Possible	Likely	Likely
	Likelihood of losing some KOL endorsement/support as price too high	Very Unlikely	Unlikely	Possible	Likely	Likely
	Likelihood of getting rejection on TE patients and delay treatment for all due to misconception of restriction for SOF	Possible	Possible	Possible	Possible	Possible
Patients and Advocacy groups	Likelihood of AHF, FPC and other advocacy groups reacting negatively to price, and affecting public opinion	Likely	Likely	Very Likely	Very Likely	Very Likely
	Higher out-of-pocket costs (not offset by patient support) could drive patient choice away from SOF, especially AbbVie has great patient support programs	Very Unlikely	Very Unlikely	Unlikely	Unlikely	Possible
	Likelihood of AHF, FPC and other advocacy groups promote AbbVie products due to the relationship and lower price	Unlikely	Unlikely	Possible	Possible	Likely
Treatment Guidelines	Likelihood of AASLD develop treatment pathway to prioritize (staging) patients (per KOLs or/and professional community request)	Possible	Possible	Possible	Possible	Possible
	Likelihood of a "price mention or asterisk" in AASLD (per KOLs or/and professional community request)	Unlikely	Unlikely	Possible	Possible	Likely
Others	Likelihood of public outcry if SOF revenue exceed $2B as government trying to control healthcare cost	Possible	Possible	Possible	Likely	Very Likely
	Likelihood of a letter from congress on SOF price	Possible	Likely	Likely	Likely	Likely
	Likelihood of a congressional hearing if SOF revenue exceed $2B	Unlikely	Unlikely	Unlikely	Unlikely	Possible

Figure 3.1 Likelihood of happening of 'soft events'. Source: US Senate 2015.

Therefore, Gilead set the base price on Incivek and Victrelis prices and then add the value perceived by the market, value that was originated by the characteristics of efficacy and tolerability that Sovaldi might give to patients. Using this model, the company came to the result that a price in an interval between 82.000 and 121.000 US Dollars was a justification for the innovativeness of the drugs itself. We should point out that at the time assessing this position, Gilead was the first producer launching in the market this 'breakthrough therapy', but it would have been followed by AbbVie (Viekira Pak) and J&J (Olysio) with similar properties. Indeed, the main concern was the launch timing, since Gilead was developing Harvoni, and AbbVie's drug was in the final steps of NDA. Whenever Harvoni would have failed the FDA review, Gilead will face the market with one strong drug and fairly better than competitors' ones.

In all this reasoning, Gilead failed to understand – and somehow forecast – that Sovaldi was not only for GNT-1 but also GNT-3-HCV: however, medical data showed that Sovaldi was not efficient for GNT-3 patients as for GNT-1 patients, especially for those patients with history of treatment for HCV or with chronic liver diseases. Moreover, US Senate stated that:

> "Gilead also would have been aware that its drug faced shortfalls in other patient populations. People with subtype genotype1b and cirrhosis had lower SVR rates (82% and 80%, respectively) than those with subtype gentoype1a and non-cirrhotic (both at 92%). For patients facing a liver transplant, the FDA label recommended using Sovaldi with ribavirin for 48 weeks. However, clinical trials showed SVR of just 64% following a transplant.164 The cost of Sovaldi for those patients alone would be $336,000 at wholesale prices (US Senate and US Senate Committee on Finance, 2015)."[234]

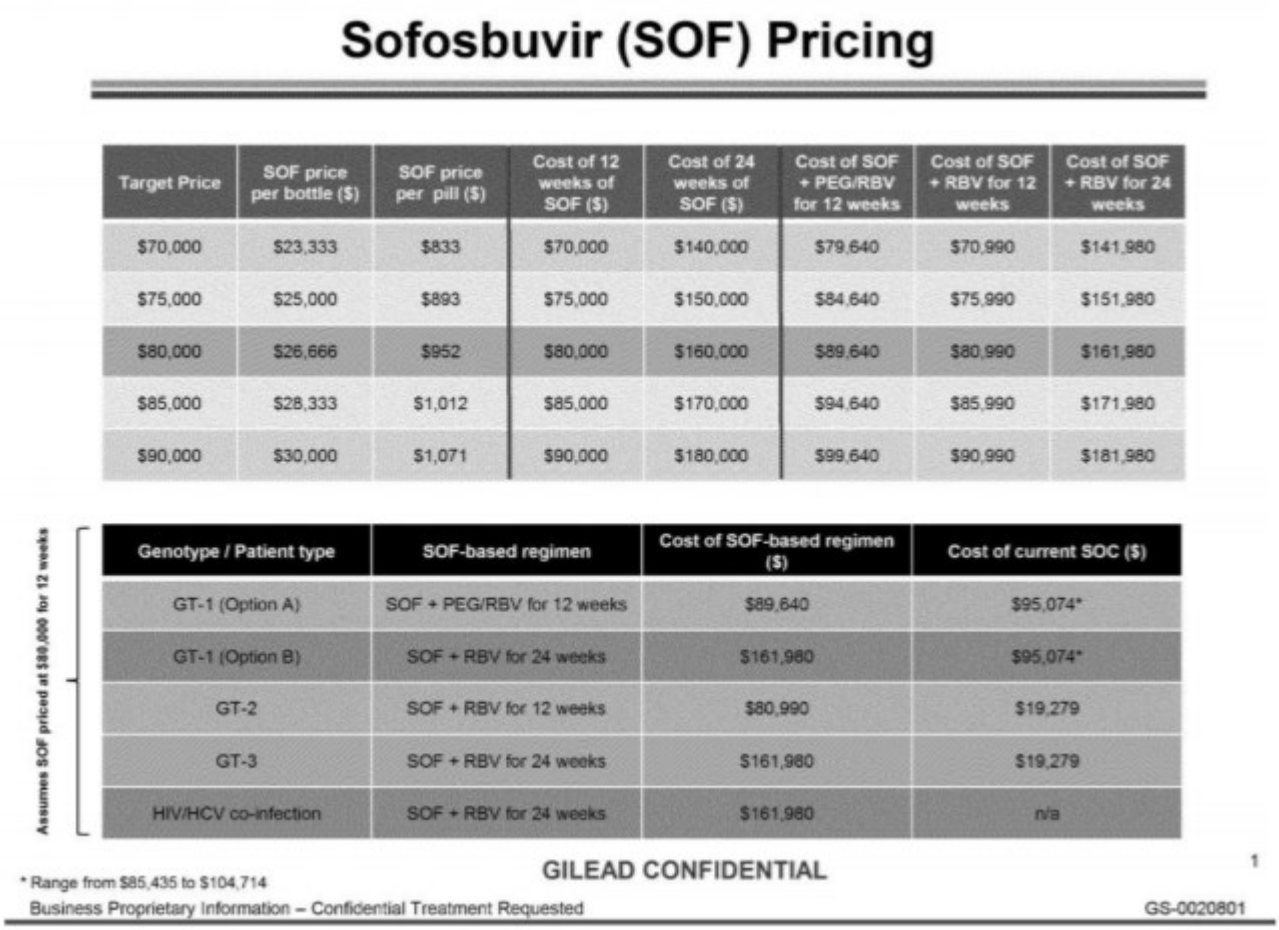
Among top-management, the problem was well known: indeed, according to a US Senate Hearing on the matter, Gilead's Senior Executives were conscious of differences in the efficacy of Sovaldi for population target, but they ended anyway to set a single price non-considering the differences for subgroups.

At the end of 2013, Gilead began the second round of pricing settings: until then, the price was an interval between 82.000 and 121.000 $. The company hired IMS Quintiles (now IQVIA) in order to "determine the access-optimizing price point for its novel HCV therapy sofosbuvir in support of the brand's US launch."[235] IMS reinforced to Gilead's top-management the idea of using premium prices (μ or markups) in order to set the price of Sovaldi and Harvoni, reasoning the advice with the fact that Gilead's drug has a strong perception in GNT-2 patient pool and in GNT-1 one. It also presented the evidence that setting a premium price was a regimen pricing argument: in other words, for GNT-1-HCV patients using Incivek the FDA certified the duration of the treatment up to 48 weeks of pegylated interferon/ribavirin, but the new Sovaldi treatment, besides allowing the patient to take only one pill, required only 12 weeks with a potential savings equal to 27.000 Us Dollar; however, IMS suggested to capture this amount – instead of lowering the price – adding it onto the sofosbuvir's top-line revenue. IMS calculated that "the Incivek regimen would cost 95.766 $ of which roughly 35.000 $ could be attributed to interferon and ribavirin" leaving 25.000 $ of "potential savings capture."[236] The pricing strategy applied by IMS was built mainly on the experience of launching new HCV drugs in the Nineties: indeed, they notice that Schering in 1998 launched a new treatment for HCV and in over 3-4 years they were able to double the costs of the drug reaching 17.300 $ for a yearlong therapy. [237]

In the end, after the IMS consulting, Gilead directors gave to top-management their suggestions around the pricing of Sovaldi: the evidence can be retrieved on the documentation presented to US Committee on Finance (see figure 3.2). The price chosen for Sovaldi was 28.000 $ per bottle, roughly 84.000 $ per cycle (cost of 12 weeks of SOF).

The ironic point of view on the pricing of Sovaldi can be seen onto non-US pricing strategy. According to correspondence between US Senators and Gilead, the pricing strategies for non-US markets contemplated

[234] US Senate Committee on Finance and 114th US Senate 2015, §1, pg. 35.
[235] US Senate Committee on Finance and 114th US Senate 2015, Appendix E, Ex. 34, 0013972.
[236] US Senate Committee on Finance and 114th US Senate 2015, §1, pg. 41.
[237] Grady 1999.



Sofosbuvir (SOF) Pricing

Target Price	SOF price per bottle ($)	SOF price per pill ($)	Cost of 12 weeks of SOF ($)	Cost of 24 weeks of SOF ($)	Cost of SOF + PEG/RBV for 12 weeks	Cost of SOF + RBV for 12 weeks	Cost of SOF + RBV for 24 weeks
$70,000	$23,333	$833	$70,000	$140,000	$79,640	$70,990	$141,980
$75,000	$25,000	$893	$75,000	$150,000	$84,640	$75,990	$151,980
$80,000	$26,666	$952	$80,000	$160,000	$89,640	$80,990	$161,980
$85,000	$28,333	$1,012	$85,000	$170,000	$94,640	$85,990	$171,980
$90,000	$30,000	$1,071	$90,000	$180,000	$99,640	$90,990	$181,980

Assumes SOF priced at $80,000 for 12 weeks

Genotype / Patient type	SOF-based regimen	Cost of SOF-based regimen ($)	Cost of current SOC ($)
GT-1 (Option A)	SOF + PEG/RBV for 12 weeks	$89,640	$95,074*
GT-1 (Option B)	SOF + RBV for 24 weeks	$161,980	$95,074*
GT-2	SOF + RBV for 12 weeks	$80,990	$19,279
GT-3	SOF + RBV for 24 weeks	$161,980	$19,279
HIV/HCV co-infection	SOF + RBV for 24 weeks	$161,980	n/a

* Range from $85,435 to $104,714

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1

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GS-0020801

Figure 3.2 Confidential Slide sent to Top-Management around pricing alternatives. Source: US Senate Committee on Finance and 114th US Senate 2015

significant lower prices: for example, in Egypt Sovaldi has been sold at 900 US Dollars per course of treatment; in EU, the price paid by healthcare providers are 40% less than the US prices. For example, in Canada the treatment costs around 50.000 US Dollars, in UK 57.000 $ and in Germany 63.000 $ (all countries with pricing regulation and negotiations).

Country	Price
Austria	$63,189.70
Canada	$50,525.00
Denmark	$56,449.40
Finland	$54,381.20
France	$72,508.00
Germany	$63,198.70
Luxembourg	$62,149.90
Norway	$53,043.90
Sweden	$51,453.60
Switzerland	$59,594.80
United Kingdom	$57,100.20

Source: *Gilead Sciences, Inc.*, Response to Chairman Wyden/Senator Grassley letter dated July 11, 2014, narrative answer to question 21, September 9, 2014 (Appendix F)

Figure 3.2. Pricing comparison in non-US markets for Sovaldi (treatment course). Source: US Senate Committee on Finance and 114th US Senate 2015.

In formulating its strategy for pricing in European countries, Gilead declared to try achieving "the highest price we can get accepted in early launch markets (UK, Germany, France)."[238] The commercial pricing team expected the UK to set the European price floor for the drug and Germany to set the ceiling, but Gilead, in the end, Gilead negotiated a price with the French authority to set the price via an ATU (Autorisation Temporaire d'Utilisation) at 74.000 $ in 2013. This program

> "allows access to drugs for serious illness prior to final marketing authorization approval and was seen as an important benchmark for European negotiations. Under this program, companies are granted a price premium, averaging 12% (US Senate Committee on Finance and 114th US Senate 2015)."[239]

We also have to point out a fact that change completely the assessment on the behaviour of Gilead. Pharmasset expected pricing strategy for Sofosbuvir (the future Sovaldi) was considerably less capitalistic (although it incorporates a higher price) than Gilead future strategy. Indeed, in a document filed to SEC after the acquisition of Pharmasset, the acquired company had set its price of sofosbuvir to a ceiling equal to 36.000 Us Dollar, around 40% less than the price marketed in USA. In the investigation led by US Senators, Pharmasset has been tried as completely ignorant on the future price set by Gilead: although the hypothetical price of 72.000$ have been considered both by Morgan Stanley's presentation to Pharmasset and Gilead's presentation, it has not been taken as credible and feasible by the Board of Pharmasset.

Therefore, Pharmasset top-management had set a considerably minor price for Sofosbuvir while, in its assessment and also thanks to IMS, Gilead opted for a higher price trying to capture all the value that Sofosbuvir had in the market.

3.1.2 Price and 'paying-twice' critique

Gilead's Sovaldi is one of the numerous drugs in the US market that had attired fairly high critiques for its price. We explained in the Part II of the Chapter II how the pharmaceutical pricing regulation is 'not'-led in the US and how the negotiation on prices involved pharmaceutical companies and distributors or hospitals. The discussion should be centred on the 'paying-twice' aspect of Sovaldi but would be unethical to not address firstly – at least summarising – the pricing problem of Sovaldi.

The investigation commenced by the US Committee on Finance was started "because we *[Senator Grassley and Wyden]* saw the impact the price of drug Sovaldi was having on the market-place both public and private."[240] We believe, however, that the reason of the investigation had been the weight that this drug was having in the budget of Medicare and Medicaid. Indeed, according to the investigation documents and to the Federal Administration (although not all the States have lend over the data), Sovaldi with Harvoni only were

[238] US Senate Committee on Finance and 114th US Senate 2015, Appendix E, Ex. 41, 0019913.
[239] US Senate Committee on Finance and 114th US Senate 2015, 1-59
[240] Ron Wyden 2015, 00:11:00 minutes.

costing respectively 3.7 billion of Us Dollar and 4.4 billion of US Dollars, while non-Gilead HCV drugs only 1.1 billion (inside this calculation, there are J&J, Merck, and AbbVie's drugs).[241] Surely, as confirmed by different sources and by the FDA breakthrough drug designation, Sovaldi together with Harvoni are a more efficient and faster drug compared to competitors ones, but they still do not justified a price so elevated.

As we have already mentioned, Sovaldi price was set at 84.000 Us Dollar for a therapy cycle and it was targeted to chronic HCV patients with all GNTs: although GNT-3 is not so frequent in the population, Sovaldi course of therapy prescribed two cycles, increasing the costs for healthcare providers and Us general public. A study published in PLOS Medicine by Iyengar et al.[242] have focused its scope on the economic analyses and affordability of new pharmaceutical products for HCV, taking a sample of 30 countries (developed and developing). What clashes of these two documents (US Investigation and the paper) is the complete absence of the former of a cross-countries analysis of the pricing situation: Us Senators apparently refused to completely address the problematic, failing also to attribute a responsibility to US Federal Administration.

Taking for a moment aside the pricing problematic and the 'paying-twice' critique, the Us Committee on Finance with its findings on Sovaldi did not begin any of the possible action that the US Congress has the power on: Us Senate for example should have approved a bill with a blinding clause of *facere* through which Gilead was obliged to decrease the price to a certain level (examples of such actions are retrievable in the National Industrial Recovery Act [1906], in a decision of the Federal Energy Regulatory Commission and in the Gas Cap Law of the Hawaii state). In the aftermaths of the investigation, Gilead did not change the price of Sovaldi, while in the academic literature and in the press critiques and different findings underlined the non-feasibility of the situation kept increasing.

Regarding the responsibilities of the US Administration, we should point out that the 'narrative' presented in the press conference at the end of the investigation was centred on the slogan of 'pharmaceutical companies are exploiting the market harming the Us public' instead of addressing the completely negligence – or at least the non-political willingness – in pooling the interests of the customers and of the Administration and regulated the price, as European countries do since the creation of the first regulatory agencies.

If we look at the figure 3.4, the above statement is clearer: US market exchange Sovaldi (a) and Harvoni (b) at the highest price possible (with one exception, Poland, that has a PPP price higher than USA for its currency weakness), while the prices – with or without rebates – are settled around 50.000 Us Dollar (using Forex) or 60.000 (using PPP process of conversion). The figure underlines two different aspects: the first is that in a regulated market with pricing negotiations, the prices are contained instead of left free of variations; the second

[241] US Senate Committee on Finance and 114th US Senate 2015, Appendix C, 2.
[242] Iyengar et al. 2016.

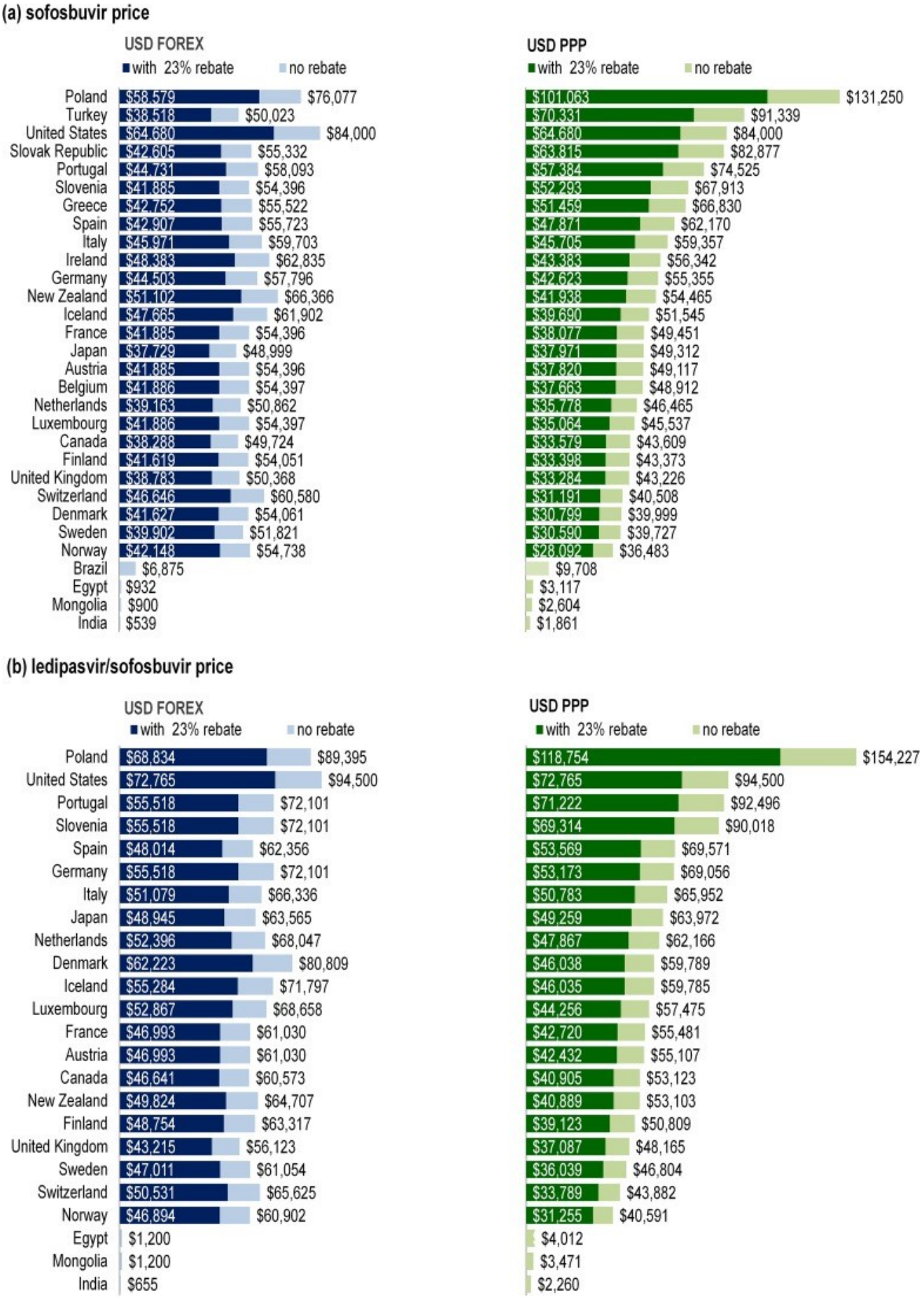

Figure 3.3: Differences on prices in the World of Sovaldi (a) and Harvoni (b). Source: Iyengar et al. 2016.

aspect opens the discussion on the 'paying-twice' critique, that is why USA has the highest market price (let us not consider Poland for now) while the Federal Administration has funded the basic research behind the development of Sofosbuvir?

The question is the centre of the critique itself and goes along with the price problematic. In order to fully capture it, let us consider lastly the financial impact of the treatment of HCV with Sovaldi and Harvoni (figure 3.5). It shows the financial impact of pharmaceutical budgets in covering the entire estimated HCV population.

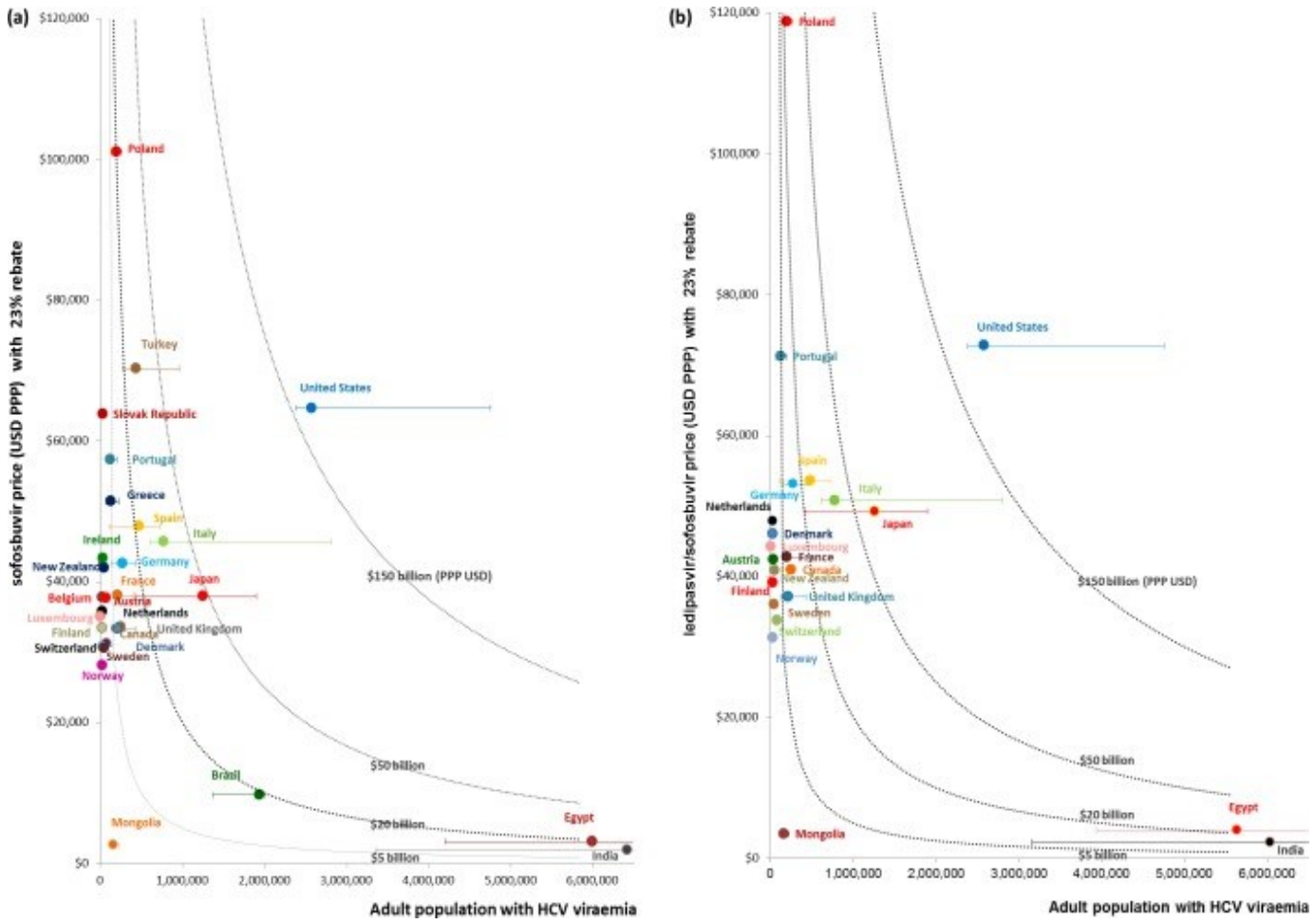

Figure 3.4: Financial impact of treatment coverage for the entire estimated population of people with HCV. Source: Iyengar et al. 2016.

The error bars indicate the lower and upper limit estimation of population. Without considering Poland (that seems to be an outlier, and frankly, we should not have considered it as target country for its social-healthcare and monetary particularities), United States appears to be the most exposed country to the financial burden that Sovaldi and Harvoni bring on the plate, and thus the Us investigation.

'Paying-twice' critique has breeding ground with Sovaldi case. Pharmasset is a spin-off of 4 Emory University researchers' research (Georgia, USA) and has been funded by the NIH in the initial phase (basic research and applied research). The basic research was and still is – in a sense – a breakthrough innovation (as afterwards was designated by FDA), and in a logical reasoning should have never been exposed if the Federal

Administration would not grant funds to the researchers. We have already seen in the early part of the Chapter II that the research in USA and in RoW rely a lot on public funding of basic research (while private companies tend to fund applied research since they see it as investment for future products). Therefore, it is safe to affirm that without NIH, Sovaldi would have not seen the light of Emory University yard nor of Pharmasset's labs. Citing a paper published in 2001, public funded

> "basic research is crucial for the strategic position of industrialised nations in the world economy, and for remaining at the leading edge of technology. This has been true in the past (especially in chemicals and pharmaceuticals) and will remain true in the future as new technologies draw increasingly on the outputs of basic research, on leading-edge scientific problem-solvers, and on the emerging fields based on a combination of scientific and technological know-how (Salter and Martin, 2001)."[243]

The matter is academically unquestionable, but still there are scholars that do not appreciate nor consider the existence of a 'paying-twice' problem in the substratum of the pharmaceutical industry. In a passage of Sylver and Hyman's (2020) paper, the authors addressed the problem of pricing in relation of drugs linked or directly sponsored with public fundings as of implausible solution: in other word, they recognize the existence of a problem, but they 'dissolve' it as 'the government has no power in reasoning on pricing with pharmaceutical companies. The underlying assumption is the impossibility of putting in place a regulated pricing system that financially and socially capture the value of the fundings with a future scope. Truthfully, between the 1989 and the 1995, the NIH attempted to insist on a reasonable pricing term with the Federal Administration and the pharmaceutical companies, but it hit the wall of "detracti*[on]* from the goals set by BDA".[244]

Is Sovaldi and Harvoni considered in the middle of the 'paying-twice' critique, and should they be priced accordingly? We saw in the previous paragraph how Gilead chose the price applying a premium rate on a valuation based on perceptions and medical value, with no mention to public fundings. However, we also have to point out – and frankly we are metaphorically obliged to – that companies follow what the capitalistic market imposes to follow. Therefore, pharmaceutical companies find themselves between the anvil and the hammer, trying to weight different parameters and characteristics of the market in order to make an oculata decision.

In this picture, US HCV patients happen to be in a 'paying-twice' situation: where through general taxation the Federal Administration has sponsored the basic research behind the Sofosbuvir, *de facto* investing in a future product. Now, the question that we should pose is whether the Federal Administration granted the sponsorship aiming to invest in order to spoil after the outcome or trying to fill a failure of the market. The answer to this question is the key for the policy making. In both cases, the 'paying-twice' critique has to be addressed; however, the difference of each case hits the political perception of such intervention.

[243] Salter and Martin 2001, pg. 31.
[244] Silver and Hyman, 2020, pg. 26.

There is no unanimous and simple method to resolve the critique, especially for the US market. The point is fairly clear (we treated it in Chapter II), however the result for the Sovaldi (and Harvoni) case is the situation where Us general public have – in a way – funded the basic research and then they have purchased the drug at a price where the premium is all on the hands of the selling company. We have not and will not treat the social actions that Gilead could have taken in order to appease the HCV problematic in USA, but we should keep in mind that corporations must – at least in our opinion – weight their actions on the communities where operate and act accordingly with the business ethics. Have Gilead acted upon this? The answer is evidently negative, also considering the documents and correspondence that the US Committee on Finance have presented with the Report on Sovaldi.

However, we also have to point out the enormous resources that Gilead have put in place to finalize Sovaldi and exit it from the Phase 3 of clinical trials. According with US Committee on Finance,[245] Gilead responses after the hearing presented the prompts of Sovaldi R&D spending (before and after the acquisition of Pharmasset). If we consider only the clinical expenditure, Pharmasset have spent around 62 million of US Dollars only in the years from 2008 and 2011, while Gilead from 2012 to 2014 (estimation of expenditures) have spent around 273 million of US Dollars (in table 3.1). These expenditures involve only Sofosbuvir R&D and – as pointed out by Gilead – all the financial commitments that both the companies have faced during the years. The note on the text filed by Gilead is somewhat embarrassing, in our opinion: indeed, it seems that Gilead justifies its pricing strategy on the assumptions that they faced different expenditures and risks in the developing of GS-7977 and other molecules, and therefore they have been forced to charged higher prices in order to gain from the investments. Gilead took the risk to price Sovaldi, in a market where innovation is continuous, and drugs values are quickly decaying: but at the same time, in order to developed a new breakthrough drug, decades have to flow.

Sovaldi and Harvoni are not the only drugs produced by Gilead that have been in the centre of the pricing hurricane, also Truvada – a HIV treatment drug – that combines two different drugs emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) into one single pill. The FTC have been discovered by Pharmasset scientist and Gilead then acquired the patent with the acquisition of the company. The price of this drug in 2019 in the US market was around 2.000 US Dollars per month. The drug is a PrEP drug, that is a pre-exposure prophylaxis drug that has been estimated to work at the 99% of the cases. The matter around the case began legal in 2019, for patent infringement by the DoJ which states that the drug has been patented by CDC and Gilead has no right to exploit the discovery without paying royalties or lowering the price (as substitution of royalties) to the CDC. Surely, Gilead denied the allegations in the DoJ complaint and legal proceedings. According to Silver and Hyman (2020), CDC was not the first entity to recognize the use of antiretroviral as prevent drug for HIV: however, there is the case of Mylan, a pharmaceutical company which sell generic version of Truvada in Europe and Australia, which lost the challenge to CDC's patent ownership to European

[245] US Senate Committee on Finance and 114th US Senate 2015, Appendix F.

Patent Office that obliged it to pay royalties to CDC. The example fits – in some way – with the Sovaldi Case for the fact that the FTC has been discovered by the same funds that NIH has granted to Pharmasset.

In thousands of US $	2008	2009	2010	2011	2012	2013	2014	TOTAL
Pre-Clinical Studies	665	1,251	34	-				
Drug Compound/Standard of Care	95	1,165	6,471	14,039				
Clinical Operations/CRO costs	9	4,474	9,925	24,292	136,942	238,986	242,830	
Overhead Allocations/Facilities Costs/Materials and Supplies	865	755	266	336	27,859	29,339	31,367	
TOTAL	1,634	7,645	16,696	38,667	164,801	268,325	274,197	**771,965**

Table 3.1: Sofosbuvir R&D Expenditures. The coloured squares divide the origination of such expenditures: light yellow for Pharmasset, light brown for Gilead. The green colour indicates mixed expenses taken by Pharmasset, but they are not completely linked to developing of Sovaldi. Source: US Senate Committee on Finance and 114th US Senate, 2015, Appendix F (our elaboration).

To conclude, depending on when one starts countring "the degree of public contribution is either overwhelming or quite modest"[246] but it appears safe to state that Gilead exploited the research of Pharmasset, and use it for ultra-maximize its profit from HCV patients, *de facto* making 'paying-twice' the US general public. In the next chapter, we will try to solve the 'paying-twice' problem thorugh a policy model that allows governments and pharmaceutical companies to minimize the deadweight loss that appears with the 'paying-twice'.

3.2 SARS-CoV-2 Vaccines: Pfizer and AstraZeneca

In the next line, we will outline the cases of Pfizer and AstraZeneca's vaccine against Covid-19, a disease responsible to the pandemic situation that we are incurring at the time writing. We have to point out, however, that there is no trace in literature nor a complete report on the matter and most of the documents related with the matter are or protected by NDAs or not publicly available. Moreover, the pandemic is still on-going, and it is therefore possible that information, events, and/or data are not exactly nor precise at the time reading.

We have already treated the Covid-19 Pandemic in Chapter I, especially from a social-economical point of view. In this paragraph we will analysis the vaccines marketized from the point of view of the 'paying-twice', trying to established if the prices of the vaccines are considering the funding from public bodies. At this regard,

[246] Silver and Hyman, 2020, pg. 10.

we will focus on AstraZeneca vaccine and Pfizer/BioNTech (later for brevity, Pfizer) vaccine against the SARS-CoV-2. The reason behind the choice can be traced back to the pricing strategy of AstraZeneca and Pfizer: while the former distributed its vaccine at a lower price, Pfizer decided to price it higher than AstraZeneca.

The paragraph will be organized as follow: a subparagraph regarding the Oxford-AstraZeneca Covid-19 Vaccine, a subparagraph on the Pfizer Vaccine and a subparagraph of discussion on the 'paying-twice' critique and its links with the vaccines. We also have to point out again that the information in this paragraph is subject to changes with the evolution of the pandemic and the information contained in them is to consider right at time writing.

The protagonists of this case are numerous, but for now we will focus on the private entities: AstraZeneca, Pfizer and BioNTech. Instead, among the public or quasi-public bodies, there are the University of Oxford, the British Government, the US Federal Government and the European Union (with all its member states).

Moreover, contrary to the US Senate Committee on Finance Investigation on Gilead behaviour for Sovaldi pricing, there is no investigation yet on the pricing strategies of Covid-19 vaccines. Therefore, it is not possible to know which and what strategies these two companies undertook in order to set the price of their vaccines: what we could do is to make assumptions on the information in our possession and publicly available.

3.2.1 Oxford-AstraZeneca Covid-19 Vaccine

AstraZeneca is a multinational pharmaceutical company that focuses its pipeline of products on cardiovascular, renal and metabolic diseases, oncological drugs and treatments, respiratory and immunology, neuroscience, and vaccines. It sells a conspicuous number of products: among them, Tagrisso (an oncological drug), Symbicort and Brilinta are products that have the most revenues, respectively 3.2 billion of US Dollars, 2.5 and 1.6 billion. [247]

Astra has been founded in 1913 in Sweden by a pool of numerous doctors and apothecaries in order to compete with the harsh and strong German and Swiss pharmaceutical companies' competition. Its first successful product was Xylocaine (lidocaine), marketized after the Second World War in all the west countries, especially USA. Astra has been acquired by Zeneca, a chemical company demerged by the Imperial Chemical Industries in the 1998 for 35 billion of US Dollars, forming the now called AstraZeneca. [248] With the merger, AstraZeneca became the fourth largest pharmaceutical company in the world with a value of 67 billion of US Dollar.

With the outbreak of Covid-19, AstraZeneca began a collaboration with the Jenner Institute (Oxford University's body) and Vaccitech, a spin-off from University of Oxford financed by Oxford Sciences

[247] AstraZeneca 2020
[248] AP NEWS 1998

Innovation, Google Ventures and Sequoia Capital. Vaccitech is a clinical stage biopharmaceutical company, founded by professors Sarah Gilbert and Adrian Hill – both professors at the Jenner Institute. In the early stages of the outbreak, the Jenner Institute began a collaboration with Advent Srl, an Italian company based in Pomezia (Italy) for the production of a small batch of candidate for the vaccine.

Contrary to any public believes, the vaccine was developed on a fair and equal access basis. Jenner Institute and the other players agreed to sign an agreement which stated that no involved parties should profit from selling the product and they chose to aid the developing through the partnership with a large pharma provider. Hence, the UK Government urged Oxford University to work with AstraZeneca PLC, also because of the possible setbacks in case the Institute would have decided to work with US company based, due to regulatory rules.[249]

However, the technology behind the Covid-19 vaccine of AstraZeneca and Oxford was not new: the Jenner Institute, indeed, had been working on another vaccine against a similar coronavirus, the virus that causes Middle East Respiratory Syndrome (or MERS). To this regard, it is interesting what prof. Sarah Gilbert had declared in the initial phase of the developing of the vaccine:

> "Novel pathogens such as nCoV-19 [*sic.; WHO did not yet release the official designation: SARS-CoV-2]* require rapid vaccine development. By using technology that is known to work well for another coronavirus vaccine we are able to reduce the time taken to prepare for clinical trials. Advent *[Advent Srl]* are working with us to move as rapidly as possible (University of Oxford 2020)."[250]

Some sources reported that the R&D for the Oxford/AstraZeneca vaccine (with the trade name of Vaxzevria) has been funded for the 97% by public bodies, European and American institutes and the European Union. The matter has been then analysed by Cross et al. (2021) in a working paper titled 'Who funded the research behind the Oxford-AstraZeneca COVID-19 vaccine? Approximating the funding to the University of Oxford for the research and development of the ChAdOx vaccine technology' that discovered a pull of different public bodies which funded the basic research of the MERS technology vaccine then reapplied against the SARS-CoV-2 and which funded the clinical trials of the ChAdOx vaccine. The pool of research had request different FOIs (Freedom of Information requests) to the University of Oxford, discovering that only the 3% of the total research funds has been sponsored by private entities and by other entities not individuated (See figure 3.6 for details). The UK Government has sponsored both the basic research and applied research for the total amount of 38.8 million of British Pounds (the 37.3%), while overseas governments (including the European Union) for the total amount of 26.2 of British Pounds.[251]

[249] OSI 2020
[250] University of Oxford 2020, pg. 1.
[251] Safi 2021; Cross et al. 2021.

Funder type	ChAdOx technology (to S.G. and A.H. only)	Oxford-AstraZeneca vaccine	**Total**
U.K. government	£5,511,316 (8.0%)	£33,354,469 (95.5%)	**£38,865,785 (37.3%)**
Overseas government	£26,252,085 (37.9%)	£0 (0.0%)	**£26,252,085 (25.2%)**
Charity	£21,468,904 (31.0%)	£1,217,835 (3.5%)	**£22,686,739 (21.8%)**
PPP	£12,943,763 (18.7%)	£272,286 (0.8%)	**£13,216,049 (12.7%)**
Research institution	£0 (0.0%)	£68,106 (0.2%)	**£68,106 (0.1%)**
Industry	£1,970,370 (2.8%)	£0 (0.0%)	**£1,970,370 (1.9%)**
Other	£1,166,941(1.7%)	£0 (0.0%)	**£1,166,941 (1.1%)**
Total	**£69,313,380**	**£34,912,696**	**£104,226,076**

Figure 3.5: Funds distribution for ChAdOx technology and Oxford/AstraZeneca Vaccine against Covid-19. Source: Cross et al. 2021, 10.

It is safe to state that "public founding [*account*] for 97.1-99% of the funding towards the R&D of the ChAdOx technology and its application for SARS-CoV-2."[252] Therefore, the research and the developing of the AstraZeneca vaccine has been funded quasi-completely by public entities: additionally, the US Federal Administration has awarded around 125 million of US Dollar for the clinical trials of AZD-7442 – the candidate for the vaccine in the R&D phase – and more than 1.2 billion for manufacturing and distributing doses around the US; regarding this last point, we should note that the upfront payment cannot be characterized and split in various sub-payments and we are not entitled to access the unredacted contracts between DoD-ASPR-BARDA and AstraZeneca. However, from what we can infer in the redacted contract between the US Army Contracting Command and AstraZeneca Pharmaceutical LP (the parenting AstraZeneca firm in USA), the US Government had sponsored the pharmaceutical company in the clinical trials, especially in phase III of them for an unknown amount. [253]

[252] Cross et al. 2021, pg. 12.
[253] AstraZeneca and Us Army Contracting Command 2020

	Amount for ChAdOx technology	Amount of AZD-7442 funding	Total
UK Department of Health and Social Care	£0.00	£31,179,621.00	**£31,179,621.00**
European Commission	£23,545,255.00	£31,179,621.00	**£54,724,876.00**
Wellcome Trust	£14,144,606.00	£1,217,835.00	**£15,362,441.00**
CEPI	£12,098,260.00	£272,286.00	**£12,370,546.00**
UK Medical Research Council	£3,080,837.00	£2,174,848.00	**£5,255,685.00**
Foundation for NIH (US)	£5,729,292.00	£0.00	**£5,729,292.00**
Innovate UK	£2,403,678.00	£0.00	**£2,403,678.00**
European & Developing Countries Clinical Trials Partnerships	£2,209,747.00	£0.00	**£2,209,747.00**
Bill and Melinda Gates Foundation	£1,595,006.00	£0.00	**£1,595,006.00**
Other	£4,506,697.00	£68,106.00	**£4,574,803.00**

Figure 3.6: Distribution of funding per each funder and per each objective. Source: Cross et al. 2021

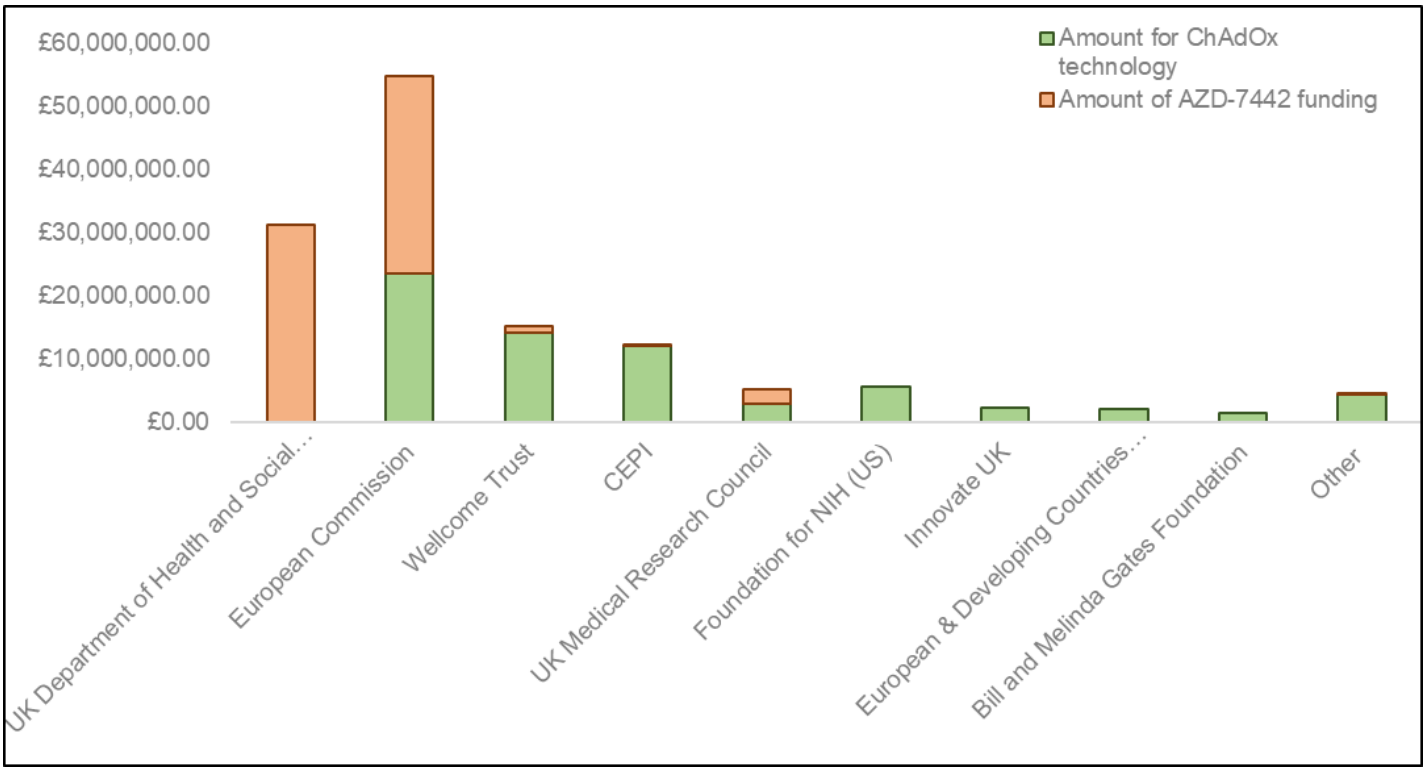

Figure 3.7: Graph with the distribution of funding for each entity. Our elaboration. Data Source: Cross et al. 2021.

As we were saying few lines above, Oxford University together with all the partners and AstraZeneca signed an agreement stating that none of the parties involved should profit from the sale of the pharmaceutical product. Later, however, AstraZeneca declared that it has reserved the right to waive this agreement and to declare the pandemic phase over, gaining from the selling of vaccines in later stages.[254]

The Oxford-AstraZeneca vaccine has been priced in a different way compared to Pfizer and J&J vaccines. Since the agreement between all the players involved, the pricing strategy was set towards the direction of 'cost of manufacturing = price to the public': therefore, the prices set in the agreements between European Union and the manufacturing company has set the price on around 3 € per dose. Among a leak of official documents involving the European Union, and then published by the TV show Report (Rai – Italy), it is possible to see the advance purchase agreement (or APA) between European Commission and AstraZeneca AB for a first batch of 300 million of vaccine doses.[255] The APA at the art. 9, number 1 states that

> "AstraZeneca shall manufacture and supply to the Participating Member States the Initial Europe Doses at a price equal to their total Cost of Goods, with no profit or loss for AstraZeneca, which, as of the Effective Date, is estimated at 870,000,000 Euros, of which 336,000,000 Euros Shall be paid by the Commission and 534,000,000 Euros by the Participating Member States (European Commission and AstraZeneca 2020)"[256]

The APA characterized the meaning of 'Cost of Goods', meaning that the European Union and MSs shall pay the reasonable direct and indirect costs that consist of:

- "Direct labour costs.
- Direct materials.
- A fair and reasonable allocation of operating of facilities and equipment.
- Quality, release and in-process control costs.
- Charges for reasonable spoilage, scrap or rework costs.
- Amounts that are paid to a third party (without mark-ups).
- […]
- Costs and expenses for pharmacovigilance directly incurred for, or fairly allocable to, the Vaccine.
- Regulatory filing fees for the Vaccine and other regulatory costs and expenses.
- Supporting functions and the cost of working capital (European Commission and AstraZeneca 2020)."[257]

Therefore, the operation involved AstraZeneca, Member States and the European Union that paid 2.9 € (2.18 US Dollars) per each dose. According to different sources,[258] the price is the minimum price per dose that

[254] Dyer 2021
[255] European Commission and AstraZeneca 2020
[256] European Commission and AstraZeneca 2020, pg. 19.
[257] European Commission and AstraZeneca 2020, pg. 4-5.
[258] Dyer 2021; Terry 2021; The Week 2021.

AstraZeneca has applied. Indeed, in other countries, the Oxford-AstraZeneca vaccine has slightly higher prices, with the UK at 3.00 British Pound per dose, USA at 4.00 US Dollars per dose and South Africa at 5.25 US Dollars.

However, AstraZeneca has incurred in different polemics around the non-observance of the APA signed with European Union, especially on the delivery timing and on the amount of each delivery. Moreover, EMA and each Member States' pharmaceutical regulatory agency began to administer the vaccine to specific segments of population (over 60s) due to its adverse reactions in younger segments. Additionally, some of these agencies came to not distribute the AstraZeneca vaccines to their vaccinal hubs, forbidden the distribution due to regulatory preoccupation around the safety of the vaccine. For example, Denmark has ditched the AstraZeneca serum stating that "*[w]*e must weigh this against the fact that we now have a known risk of severe adverse effects from vaccination with AstraZeneca, even if the risk in absolute terms is slight."[259] At the same time, due to unmet clauses, in the early part of 2021 the former Italian Prime Minister Giuseppe Conte declared that Italian Government would proceed with legal actions against AstraZeneca behaviour.[260]

3.2.2 Pfizer/BioNTech Covid-19 Vaccine

The second vaccine we are going to treat is the one manufactured by Pfizer and BioNTech, called Comirnaty (or BNT162b2). The companies in play are two: Pfizer Inc. (later Pfizer) and BioNTech SE (later BioNTech).

Pfizer Inc. is a research based, global biopharmaceutical company, founded in the 1849 in New York by the Charles Pfizer and Charles Erhart: the former was a German chemist and entrepreneur and the latter a confectioner. The new-company has an immediate success with a flavourful form of santonin (an anthelmintic drug for treating intestinal worms – common in the mid-1800s). With the wars that USA has undergone, especially the American Civil War and the Second World War, Pfizer reached high level of revenues with its disinfectants, preservatives and painkillers. During WWII, Pfizer was the only pharmaceutical company to mass-produce penicillin. After the WWII, the company began its expansion with the acquisition of Taito (a Japanese company) in 1983 – after a long partnership in producing antibiotics – and in 1971 the acquisition of Mack Illertissen, a chemical and pharmaceutical producer. In 2003 and 2009, Pfizer acquired respectively Warner-Lambert, Pharmacia Corporation and Wyeth.

Instead, BioNTech is a biotechnology company, founded in Mainz (Rhineland-Palatinate, Germany) by Ugur Sahin, Ozlem Tureci and Christoph Huber: three researchers from the Johannes Gutenberg University in Mainz. Prior to the foundation of BioNTech, the three researchers had founded Ganymed Pharmaceuticals

[259] BBC I 2021. *Statement of the General Director of the Danish Health Authority Soren Broström.*
[260] BBC II 2021. "[…] Such delays in deliveries represent serious contractual violations, which cause enormous damage to Italy and other countries […]."

(2001) which developed the monoclonal antibody Zolbetuximab. The company has been sold to Astellas Pharma for around 850 million of Euros.[261]

BioNTech has been founded aiming to develop cancer vaccine through a technology that was developing in the early 10s of XXI Century. According with the company website, Sahin and Tureci are among the few experts in medicines with messenger ribonucleic acid technology (mRNA). Since the creation of BioNTech, Sahin has been the CEO, Tureci the Chief Medical Officer and Huber a member of the board. At the time writing, the scope of the company is focus on four distinct drug classes: mRNA therapeutics, cell therapies, antibodies and small molecule immunomodulators. Being a young company, only in 2019 BioNTech has been quoted in the NASDAQ Global Select Market and one month prior, Bill and Melinda Gates Foundation contributed to the company with a capital of 55 million of US Dollars. In the years BioNTech has been sponsored by different public bodies for its research and development of cancer vaccines. In December 2019, BioNTech has received a sponsorship (50 million of Euros) by the European Investment Bank for the cancer immunotherapies that BioNTech is developing.

In the initial phase of the outbreak of Covid-19, BioNTech CEO and founder commenced research on a vaccine against the new coronavirus, basing his hypothesis on the first complete genetic sequence of the SARS-CoV-2. From the proprietary mRNA platform, BioNTech assembled a consortium of partners including Pfizer – with which BioNTech has had a partnership for the developing of a flu vaccine – and Fosun Pharma (a Chinese pharmaceutical company)[262]. Among over 20 candidates for the vaccine, BNT16b2 had been chosen for the preclinical studies in late April 2020. Between July and November 2020, Pfizer and BioNTech commenced and terminated the Phase III Clinical Studies for the vaccine. On the 21st of December 2020 after less than a year from the first candidate vaccine, EMA approved the MAA of the vaccine of BioNTech Manufacturing GmbH with the product number EMEA/H/C/005735. On the 11th of December 2020, FDA authorized Pfizer-BioNTech vaccine for the emergency use on individuals 16 years of age and older.

The BNT162b2 has been funded by different bodies, both public and private. In particular, the mRNA technology – as already stated above – is not the most recent technology. Martin and Lowery[263] in a recent paper have undergone a thorough analysis on the IPs of mRNA technology, identifying that half of the patents on the vaccine technology are owned by a bunch of biotechnology companies, in particular BioNTech, Moderna, CureVac and GlaxoSmithKline (GSK).

[261] AG 2016
[262] Reuters 2020
[263] Martin and Lowery 2020

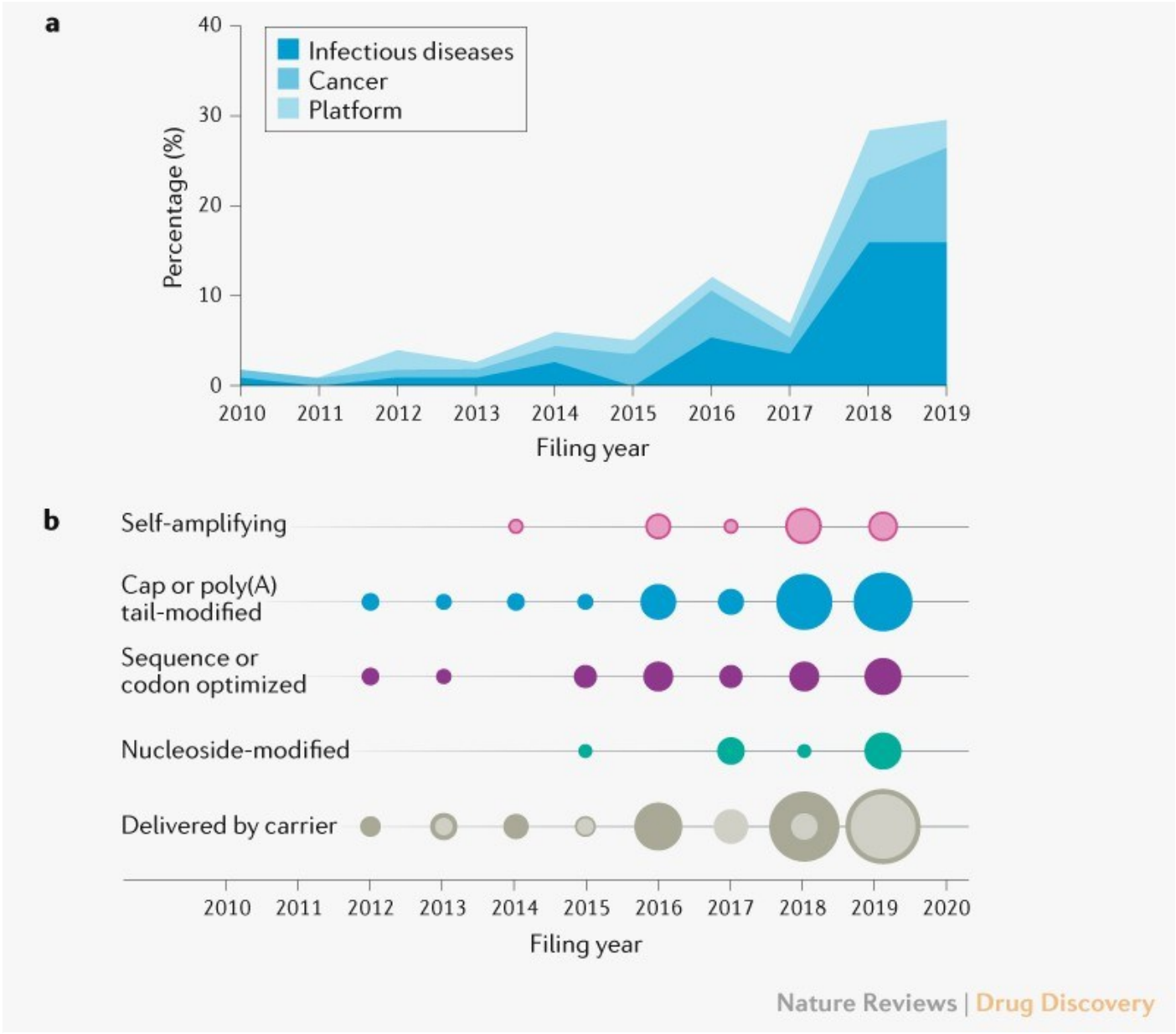

Figure 3.8: Distribution in time (a) and for type (b) of patents with mRNA technology. Source: Martin and Lowery, 2020.

Since the technology is fairly allocated to few companies, it does not come to a surprise the existence of few vaccines with mRNA technology – for now, only Pfizer-BioNTech and Moderna, even though Sanofi with Translate Bio is developing a new SARS-CoV-2 vaccine with this technology. The funding, however, is not clear as for the AstraZeneca case. BioNTech has been founded prior to the outbreak of Covid-19 by the EIB and Bill and Melinda Gates: but with the arise of Covid-19 and the relative research and development on a future vaccine, the EIB agreed to a 100 million Euros debt financing in order to support the development of the vaccine. Moreover, through its partnership with Fosun Pharma, BioNTech received a 135 million of US Dollars investment in exchange for 1.58 million shares. [264]Contrary to Mike Pence and Donald Trump

[264] EIB, 2020; Reuters (I) 2020.

believes, BioNTech has never received any funding by Operation Warp and the NIH, instead the German Government has conspicuous funded from the partnership with 445 million of US Dollars.[265]

Additionally, according to Pfizer Inc, the operation of R&D had a total expenditure around 1 billion of US Dollars: 50% of this amount paid and sponsored by German Government and EIB, and the other part from private entities. [266]

3.2.3 Price and 'paying-twice' critique

With the outbreak of SARS-CoV-2, the pharmaceutical industry began to research (or conclude different new research) and develop new vaccine against the virus. We have already seen in the early chapters how this move has affected and still affects the industry and the population in general. Among different research and candidates, at the time writing there are 6 vaccines authorized to marketisation by different agencies: FDA and EMA have authorized for emergency use or with a regular MAA/NDA four vaccines (Pfizer-BioNTech, Oxford-AstraZeneca, Johnson&Johnson and Moderna), in China and Russia there are two other vaccines (CoronaVac and Sputnik), while others are in clinical trial phases (Sanofi-GSK vaccine, Sanofi-Translate Bio, CureVac, etc). The problem for this type of new technology and new developments is the pricing strategies: indeed, we chose these two vaccines as cases for their differences in prices – although we know that these are the manifestations of distinct technologies.

AstraZeneca vaccines is priced at the Cost of Good, thanks to an agreement between Oxford University and the pharmaceutical company. With their pricing strategy, they provided vaccines to European Union and the ROW at a low price. Pfizer-BioNTech did not choose the road of the 'Cost of Good' for their vaccine: instead, they applied different pricing technique in order to profit from the distribution of the vaccines. We cannot thoroughly elaborate on the strategy because there are no documents publicly available on the matter, nor there has been an investigation on the matter (even though we hope that the matter will be taken into consideration due to the abnormous differences on prices).

Pfizer-BioNTech vaccine, indeed, has been priced following the agreement on the batches to be distributed: that is, the price has changed in the years following the distribution of the batches of vaccines. According to a policy report of Oxfam Italy,

> "Pfizer/BioNTech have been charging governments between 6 and 24 times the estimated cost of producing its vaccines. Its lowest reported price was charged to the African Union at $6.75 per dose, still nearly 6 times more than the estimated cost of production (Marriott and Maitland 2021)."[267]

[265] Riley and Armstrong, 2020.
[266] Kaplan and Wehrwein 2021.
[267] Marriott and Maitland 2021, pg. 5.

Comirnaty has been averagely priced for 19.50 US Dollars per dose in USA and 14.76 US Dollars per dose in EU (with a percentage difference equals to -32.1%).[268] According to the APA signed between Pfizer-BioNTech and European Union, the pricing strategy has been developed on a volume basis: the first 100 million doses are priced at 17.50 € per dose, from 101 to 200 million doses the price is lowered to 13.50 € per dose. Any additional order placed within three months form the signature of the APA has been priced for 15.50 € per dose, while any other order over this period of time and the termination of the APA has been priced for 17.50 € per dose. [269]

It is evident that the pricing strategy is the exact opposite of the one chosen by AstraZeneca. The profits from the distribution of the vaccines for Pfizer are equal to 3.5 billion of US Dollars only in Q1, according with the New York Times.[270] BioNTech profits are estimated to reach 18.7 billion of US Dollars only in 2021. [271] Therefore, from the one billion of expenditure in R&D estimated by Pfizer, both the companies have profited from the selling of the vaccines, while developing and developed countries struggled to contain the spread of the virus and the tremendous effects that SARS-CoV-2 was having on the population.

The rightness of the pricing strategy is not the objective of the thesis: what we should look at is the fairness of the whole picture. Pfizer and BioNTech have behaved worse than Gilead in the point of view of the 'paying-twice': while Gilead and Pharmasset had a small percentage of public funding for the developing of Sofosbuvir, Pfizer-BioNTech partnership has received more than 50% of funding for its vaccine, profiting from the distribution and selling of the products, and basically sponsoring also future research of both companies. Now, the discussion on the proposed pricing policy will be relegate to the final chapter of this thesis: however, it sounds fairly unequal to the population of the European Union to be 'charged' twice for the Covid-19 vaccine. The first charge is through general taxation collected by the State, and – for German citizens – distributed to BioNTech, while for European citizens, distributed to European Union and then to BioNTech and Pfizer. The second point of charge is the administration of the vaccine, where – depending on the healthcare system – the European citizens are charge another time, or trough general taxation or through the payment of a ticket (in Italy, for example, the dose is completely covered by the IT-NHS).

Therefore, is there any 'paying-twice' scenario with Pfizer-BioNTech vaccine? It is safe to reply with a positive answer: EU and German Government has funded the R&D of the vaccine and then paid for the distribution, with a conspicuous markup. Moreover, thanks to the revenues of the distribution of the vaccine, BioNTech has in mind to leverage them and become the "21st century immunotherapy powerhouse".[272] According with FiercePharma, BioNTech has declared to accelerate the pipeline of oncology drugs thanks to the boost in revenues of the distribution of the vaccines (especially, BNT111 and BNT113). [273]

[268] Ang 2021, data at pg. 2.
[269] European Commission, Pfizer Inc, and BioNTech SE 2020, art. I.7
[270] Robbins and Goodman 2021.
[271] Kansteiner 2021.
[272] Kansteiner 2021, pg.1, declaration of the BioNTech CEO
[273] Kansteiner 2021.

Here, the point becomes quite complex to solve: from one side we have BioNTech and Pfizer that leveraged the production of a vaccine – which is quite complex to store and manage – that has been funded partially by the European Union and German Federal Government; on the other, we have a source of revenues, linked to the vaccine, that will be used for the R&D on different innovative drugs. Therefore, there is a difficult-to-solve trade-off, between addressing the 'paying-twice' problem with a policy that hit the problem at its roots and a more laissez-faire solution that aims to aid the R&D of innovative drugs. This trade-off cannot completely solve by academics and scholars: instead, it has to be addressed politically with a medium-long term view balancing both the weight of the 'paying-twice' problem and of the innovativeness of the national/supranational pharmaceutical industry.

In this chapter, we have seen two cases in which we can see the 'paying-twice' critique arising. Gilead's sofosbuvir has been a difficult case for the US Senate, that has been called to investigate on the enormous price that Gilead had set for its breakthrough drugs, Sovaldi and Harvoni. The other case involves the two vaccines against Covid-19, manufactured by Oxford-AstraZeneca and Pfizer-BioNTech: in this situation, the 'paying-twice' critique arises way stronger and harsher than the previous case. The amount of public funding has been enormous and Pfizer-BioNTech have set a price much higher than the competitors: differences of technology has surely impacted the pricing strategies of both companies, but Pfizer-BioNTech failed to remember the violent and sudden nature of the outbreak and the enormous 'debt' that both have contracted towards the humanity, through their pricing strategies. In the next and last chapter, we are going to present a policy that can address the 'paying-twice' critique, the incentives for innovative drugs and a possible way to diminish the deadweight loss that arises with fixing prices too high.

Chapter IV

‘Paying-Twice’ Critique and Pricing Regulations: How To Address The Problem?

Pharmaceutical industry is a complex sector where different actors have enormous interests to defend: public players have the duty to empower the safety and the health of the population, health care providers have the duty and the interest to provide therapies that can cure illnesses, pharmaceutical companies – as well as other industries companies – have to address the interest of their shareholders, considering also the impact that their choices have on the general population, and therefore their business at large.

In this highly complex picture, IPRs regimes play an important role in the developing of new products and in the defence of inventors’ discoveries. We have seen the differences between Bayh-Dole Act regime and the Professor’s Privilege regime, but we have always postponed the debate on the solutions of the 'paying-twice' critique, that is the situation where the population find itself in paying a specific drug – or product at large – twice: once with the funding of the research, the other time with the purchasing of the drug developed by the company. Here, the 'paying-twice' is not confined to the simple double payment that the citizen makes with the general taxation and the following exchange of goods (money for drugs); the same, indeed, applies for healthcare providers – in case the healthcare expenditure is entirely covered by the State. Therefore, the problematic not only arises in those countries where the citizen has to pay for its health directly (and then reimbursed by the insurance schemes or directly by the State) but also in those countries where the State is the final purchaser.

Instead of proceeding with a change in IPRs – that, aside, we believe it would be a difficult move and a non-solution – the governments and the supranational/federal institutions can develop and impose a new model of pricing, whereas the State intervenes upstream with a funding sponsorship. In this way – as we will see – the 'paying-twice' critique can be unravelled and the problematic on the high prices can be calmed, with benefits on both side of the ‘river’.

Therefore, we will divide the chapter in three different parts: the first that will address the change in IPRs regimes, the second will address the consequences of a pricing policy that can diminish the deadweight loss, and – finally – a conclusion paragraph, where we will conclude and address future development of studies on this stream.

4.1 Public utility and IPRs regimes change: a non-solution

As we have explained in the Chapter II, Intellectual Property Rights are extreme important for the pharmaceutical industry for their protection of discoveries and innovations. Reminiscing what already explained in Chapter II, "patents provide exclusive rights to inventors of new, useful and nonobvious inventions. The patent law concerns hard technologies, including chemical, electrical and mechanical products and processes, as well as other pragmatic innovations in fields ranging from biotechnology to business methods." [274]

With the decades, two regimes established themselves in the world: the BDA and the PP. As we already saw, there are two huge differences between these two systems: with the BDA the control rights are held by the research entity (universities, colleges) while with the PP, the control rights are held by the researcher conducting the research. Moreover, with BDA the university has de jure the ownership of the IPRs, while under the PP, the university has not control on the IPRs.

With the outbreak of Covid-19, an old debate revamped: indeed, the IPRs set a protection level and a protection time for all recognized patents; however, every so often the governments can circumvent the allowed protection, and, *de facto*, make the patents entirely accessible to the public. In early part of 2021, there has been a boost around this debate with mainly two sides: one in favour, the other against, both brought to the table different sides of their proposal, guided by their differences in economic ideologies. If we have to divide the two sides with clear statements, the picture should be as follow: those in favour are brought to this conclusion by their believes on the fact that 'innovative science has to be public' or at large 'science has no barriers'; we can instead characterize those against as 'supporter of a total capitalist view of the world'.

Now, the problem should be solved around the feasibility of this proposal: is it possible to remove the barriers to science and make it forcibly public? Or, on the other way around, is it fair to forcibly publish patents that has been created by private entities? In one of his editorials, Ferruccio De Bortoli addressed the matter, making the example of Dr. Albert Sabin's actions with its breakthrough discovery.[275] Indeed, in 1957, after a terrible attempt of Jonas Salk in delivering a polio vaccine[276], Sabin released a new trivalent vaccine against all the three types of polioviruses: despite the high marketability and high profitability of such vaccine, Sabin refused to patent the discovery, *de facto* giving complete and free access to his vaccine to all the world.[277] Dr. Sabin

[274] Schechter and Thomas 2003, Ch. I, pg. 26.
[275] De Bortoli 2021
[276] *In the early 50s, Jonas Salk and his team from University of Pittsburgh declared to had created a vaccine against Polioviruses. In 1954, the Clinical Trials began and in 1955 the vaccine was licensed, and the vaccination mass campaign began: for an error in the production and inactivation of the live virus in the vaccine doses, at the end of 1955, 40.000 cases of Polio in vaccinated subjects were discovered, killing 10. The incident, together with other incidents, led to a decrease in confidence on the vaccine and a drop in vaccination rates.*
[277] *The matter will not address completely: for further information see Oshinsky, David M. Polio: An American Story. Oxford; New York: Oxford University Press, 2005; Fitzpatrick, Michael. 'The Cutter Incident: How America's First Polio Vaccine Led to a Growing Vaccine Crisis'. Journal of the Royal Society of Medicine 99, no. 3 (March 2006): 156; Juskewitch, B.A., Justin E., Carmen J. Tapia, B.A., and Anthony J. Windebank. 'Lessons from the Salk Polio Vaccine: Methods for and Risks of Rapid Translation'. Clinical and Translational Science 3, no. 4 (August 2010): 182–85. https://doi.org/10.1111/j.1752-8062.2010.00205.x.*

allowed the humanity to eradicate polioviruses (in 2020, there have been around one hundred registered cases of Polio disease), without economically benefiting from it. Besides the great ethic and altruistic value that this action brings, the absence of a registered patent on the vaccine against polioviruses posed a precedence. During the outbreak of Covid-19, the debate was developed on the possibility to exploit the art. 31 of the TRIPS[278]:

> "Where the law of a Member allows for other use (7) of the subject matter of a patent without the authorization of the right holder, including use by the government or third parties authorized by the government, the following provisions shall be respected:
>
> […]
>
> (b) such use may only be permitted if, prior to such use, the proposed user has made efforts to obtain authorization from the right holder on reasonable commercial terms and conditions and that such efforts have not been successful within a reasonable period of time. This requirement may be waived by a Member in the case of a national emergency or other circumstances of extreme urgency or in cases of public non-commercial use. In situations of national emergency or other circumstances of extreme urgency, the right holder shall, nevertheless, be notified as soon as reasonably practicable. In the case of public non-commercial use, where the government or contractor, without making a patent search, knows or has demonstrable grounds to know that a valid patent is or will be used by or for the government, the right holder shall be informed promptly."

According with different observers in the pharmaceutical industry, the article 31 of the TRIPS, if applied in the Covid-19 outbreak situation, would have posed an enormous threat to the innovation pace of the industry itself. Sergio Dompé – for example – declaring to the Economia of Il Corriere della Sera that "If there were no patents […] there would be no research, nor interest in doing it, nor public or private capital willing to risk disappearing completely *(sic)*"[279] failed to address the point of the problem: indeed, the debate was not on the rightness of the existence of patents, but on the need of wave capitalistic view and revenues view on the lives of the entire world. The celebration of the high technology and the high human capital that private entities have embodied in their organisations is at the mercy of public taken risks. Indeed, where the governments have sponsored the research on the vaccines or the research on the technology of the vaccines (we are referring to the mRNA basic research vaccines that were partially funded by public bodies), the same countries have seen prices for the vaccines shots which have hugely profited the pharmaceutical companies. Be aware, we are not against the remuneration of private entities works: here, the point should not be focused on the interventions of State in the economy but should be focused on unbalanced equilibrium that is pictured with the 'paying-twice', that finds citizens paying literally twice for drugs or vaccines where the amount of R&D is in full or partially funded by public bodies.

[278] TRIPS, Part II, Section 5, art. 31.
[279] Translated from"Se non vi fossero i brevetti […] non vi sarebbe ricerca, nè interesse a farla, nè capitali pubblici o privati dispoti a rischiare di svanire del tutto (sic)." De Bortoli, 2021, in Economia of Il Corriere della Sera, pg. 3.

Surely, this 'nuclear solution' is not feasible for the day-to-day business and, as stated by the art. 31, let. b – the 'seizure' of patents has to be exercised only in emergency cases. However, the revamped debate poses the urgency to address the problem at its own roots.

The modification of the discipline around patents and copyrights could be a feasible but utopic solution. Idealistically, the solution for addressing the 'paying-twice' critique and finally solve this long-standing problem should include decreasing the period of protection granted to the patentee. In theory, for what concern the pharmaceutical industry, this solution can favour competition and the entry of various generic pharmaceutical companies that in order to survive has to compete on prices and not on the leverage that the privilege of the patent grants to the patentee.

This solution solves the problem on the prices side via the modification of IPRs systems but has major and negative consequences. *De facto*, patents indirectly incentivise pharmaceutical companies to research, develop, and distributed the products of their R&Ds due to the protection granted by the states for a limited period of time. This protection allows companies to ensure a flow of profits after draining amount of money in researching, constructing manufacture equipment and marketize the drug. Sir Robin Jacob in a 2021 article well characterized the scenario of the debate we were treated just a few lines above. Sir Jacob explained that those in favour of the dismantle of the IPRs system think that in order to guide the innovation, "the direction of research should be dictated by a state-appointed body *(regarding this, see next paragraph and D'Amico [2021])* […] [*the aim]* should be mission oriented. Moreover, universities and research institutes should either dedicate their medical inventions to the public or at least license all-comers."[280]

Additionally, the modification on the IPRs systems can lead on the absence of innovative research by the pharmaceutical companies that would be incentive-sensitive: the states would grant funds to pharmaceutical companies which in turn they would behave as in a centralise economy.

The solution of modify patents system taking as cue the art. 31 of the TRIPS would be disastrous as to delete completely the protection granted by patents. Surely, the IPRs systems are not perfect, and it is advisable to reform them, but at this time a modification in the path of the seizure of patents is unpractical and may cause more harm than benefits.

4.2 A change in the pricing: the consequences

The main problematic around the prices regulation of pharmaceutical products is the difficulty to encapsule different policies in a law or in a set of rules that all countries have to follow. In this paragraph, we will outline the basis for a change in pricing strategies from the perspective of a legislator or a regulatory authority: it will

[280] Sir Jacob 2021.

focus on two cases, similar to those presented in Chapter III, with few assumptions in order to simplify the situation.

We have seen the various pricing techniques and models that pharmaceutical companies usually use in order to set the price for their products: among them, there are a bunch of strategies that only applies in the pharmaceutical industry (ERP, for example). At the same time, we have seen how difficult and risk-sensitive the process of researching and developing drugs and medical devices is (cfr. Chapter I). For a pharmaceutical company, the R&D phase can last a decade during which the company makes no profit and for which it takes the most risks. In this picture, public bodies have the duty to ensure innovation and incentives for the developing of new drugs or new health means for the population. Therefore, states and public agencies tend to focus their commitments to fund universities, laboratories and small firms which conduct basic research: it is fairly rare that public bodies fund applied research or even directly pharmaceutical product research. The reason can be retrieved in the attractiveness of the outcome: basic research is risky, does not have any assurance of working, and does not have an applied outcome; it is an elementary phase of the research on drugs, an elementary but ineluctable phase. At the contrary, applied research have more attractiveness for private entities because of their aspect of being close to a pharmaceutical product: therefore, it is more probable to have pharmaceutical companies sponsored applied research, or acquire small firms with a valuable outcome of applied research. The rarity of governments in funding applied research does not mean that it has never happened in the history of humankind: a great example (and we have treated in Chapter III) is the SARS-CoV-2 vaccines; the most funds of basic and applied research have come from public bodies.

In this situation, moral hazard behaviours and skyrocket prices are quite common, rising a dynamic where the population find themselves to pay twice for a drug. Therefore, how to minimize this 'paying-twice' or at least how to address the matter? Before, try to address a solution, we have unfortunately underlined a contradiction in the economical literature: few scholars and observers do not believe nor treat the matter according with the ‘gravity’ that follows it; indeed, they believe that the 'paying-twice' critique is a non-critique, a sort of rhetoric and stylistic exercise. Without deepening the social part of the matter, allow us to just underline a *fact*: there are double cash-outs, and it is myopic do not recognize them as cash-out and relinquish them in a sort of evil debate.

Coming back to the questions, how to minimize the 'paying-twice'? There a plenty of different solutions that can be applied to the market. However, the difficulty around the topic is extremely high-level. Weighing the value of public research fund in basic research is not an easy computation, weighing the impact of the funds on developing drugs is even more, weighing the value of the past funds on a product that is going into the market, capitalising them with the optic to extinguish the ‘double-payment’ that the population face purchasing the product of the R&D is close to be impossible.

The core of the dilemma is the situation *in*-se of 'paying-twice' a drug; in an economic sense, this scenario would be solved through a computation of a future value: ‘I lend you an amount in the past, now repay me for

each year at this particular interest rate'. However, in the pharmaceutical case, the amount of public research sponsorship is not a credit, it is instead close to a non-payable contributes: it does not earn an interest rate, and, therefore, cannot be computed a present value. Moreover, the funds usually sponsor basic research which is difficult to link with the applied research. Governments can change the legal formulation of public research funds, turning them into loan. It surely solves the 'paying-twice' critique, but at the same time it creates a turmoil: those institutions performing basic research that do not reach the market would be in debt towards the lending institution, and a simple solution would create even more negative consequences. Moreover, the 'lending' of public research funds would denaturalize the truth core of the funds, *i.e.,* incentivize innovation.

Therefore, how to capture this future value without turning funds into credits? The solution is merely on how to compute the future value of a non-payable contribution, without agreed interest rates, also considering the impact of the funds on the R&D process, the impact of the drug on the population and, especially, the small time window which pharmaceutical companies find themselves in launching products in (due to fixed terms in patents protection). Also, the computation has to address the intrinsic and extrinsic value of the drug: besides financial considerations, it has to focus on the benefits that such drug brings to the market and to the population. It is clear that such index has to be built addressing a variety of different aspects of the pharmaceutical industry and, mostly, it has to weigh each of these aspects accordingly between each other.

Now, let's suppose that a regulatory authority develops a policy that applies a percentage sale discount on each drug sold: a discount that *de facto* zeroes the 'paying-twice' dilemma calculated on the future value of the funds, weighing what we have already written a few lines above. Moreover, the policy has to be applied in a way that minimizes the risks of moral hazards by the pharmaceutical company. And this new price control strategy should only be applied by those States that has sponsored with a public fund the basic research or the applied research of the negotiating drug. In this situation, there would be different positive consequences. The 'paying-twice' scenario would be zeroed by the discounts for each dose, pill, etc. sold to that particular country, in a sort of paying-back action. Additionally, the policy would create a sort of vicious circle in which countries are incentivized by the prospect of having a discount for the drug (*ceteris paribus* the negotiations techniques and pricing control strategies already in play) in increasing the fund allocated to scientific research. The consequence of such increase would impact different macro-economic indices to increase: except – obviously – the total public spending, the measure would increase the GDP of the countries, the attractiveness for foreigner capitals; fundamentally, it would surely create an economical boomerang that would impact different areas of the economy, minimizing the deadweight-loss of the 'paying-twice' dilemma. The increase in public funding would require – of course – the creation of new funds distributor platforms or redesigning already existence agencies' organizational forms in order to counterbalance the distortions that rent-seeking countries/regions tend to pursue.[281]

[281] D'Amico, 2021.

The main problem of this reasoning is the absence of an index that captures and balances the sponsorship weights on the R&D expenditures of pharmaceutical companies. As already shown above, it is not effortless to compute all the variables in play in the pharmaceutical sector, plus all the variables that concur to make valuable the drug in development. Basically, the future value of the investment has to capture not only the financial side, but also the market side of the value itself: therefore, the value that the drug has in the target-population, the innovativeness shown by the drug (regarding this point, the computational difficulty arises considerably), the long-term impact on the population. Moreover, this measure has to properly assess in the market in order to not disrupt the equilibrium that the few public funds create in the industry.

From the creation of such index, there is also another main problematic, especially in the European region. There are some HTA bodies and regulatory authorities that tend to price new developed drugs with benchmarking systems (or solely with ERP), causing a domino effect that prices the drug according to specific countries baskets. Therefore, for example, if Italy applies discounts for counter-balance an underwritten sponsorship, pricing a drug accordingly, Croatia that – as per figure 2.5 and Toumi et al. 2014 – applies ERP strategies, would find itself pricing this particular drug with Italy, Slovenia and France as reference countries basket, capturing the discount that is not entitled to acquire. Surely, this point should solve during negotiation processes between Croatian regulatory authority and the pharmaceutical company, but still it has to be addressed at the European level for harmonization.

Now, an obvious question does arise, can be this measure seen as too much interventional in the economy? The answer depends on which country such actions are engaged: surely, in USA, a solution for the 'paying-twice' should be urgently addressed, but the economic culture and the ostracism towards any kind of economical interventions of the Federal State pose a consistent threat to the solution. The absence of control in pricing and the enormous amount of funds that NIH distributes to different entities are the ingredients for making pharmaceutical company wealthier and more influent: Moreover, the formalisation of lobbying organisations inside the Federal State alter and distort the reality of the economy, while more than ever the healthcare expenditure is rising. In the European Union and its MSs, the 'paying-twice' critique is not urgent as in US, the mechanisms of prices controlling and the existence of public reimbursability programs make the old country a ‘island of happiness’ where other problems are looming.

4.3 Conclusion

The pharmaceutical industry is a complex environment rules by a double-face nature: the main objective of a firm in the capitalistic system is the maximization of the profit and the costs minimization; this vision collides with the social importance of pharmaceutical products, together with main objective of the healthcare system. Therefore, the equilibrium is fairly precarious with different players pursuing different interests.

The situation has gotten more intricate thanks to the switch of model underlying the sector itself. Historically, large pharmaceutical companies were the driver in R&D: they researched and developed drugs from their origin. With the advance in technology and the increasing interest of the markets on the pharmaceutical

industry, various and different small and medium enterprises had begun researching and bringing drugs to the initial phase of clinical trials, waiting for bigger companies to acquire them or acquire the use/patent of the developing drug. However, most of the research on new drug formulations come from public/private universities, foundations, private laboratories and – surely – SMEs, funded by public sponsorships.

This picture is even more complicated by the existence of two different regimes on IPRs: a regime created from the basis of the Bayh-Dole Act (Us Law approved in the mid-80s), and another regime based on the Professor's Privilege criteria. These two regimes present different aspects that combined cancel each other out. In short, the Professor's Privilege regime is provided only in two countries (Italy and Sweden), while the BDA regime is provided in every other west country. The former was created with the scope of delegating the researchers to exploit the invention individually by becoming a professor-entrepreneur, while the latter provide that the ownership of the invention has to fall into the researcher's body for which carries out scientific research. Obviously, each regime has different consequences: in the debate around the BDA, various observers have pointed out that the Us regime favours mostly applied research, while basic research is excluded for profit targets. At the same time, the same applies to PP regime: the researcher will gain much more profit from applied research instead of from basic research. In scientific literature the debate has continued, reaching a consensus: Von Proff et al. (2012) and Czarnitzky et al. (2015), studying the German panorama have find out that with a change from a PP regime to a regime based on BD Act the number of university invention does not change. At the same time, in Denmark the data has shown a 14% reduction in patenting made by biotech firms. The worst case is Norway which have been subjected to a 50% decline "in the rate of new venture creation and patenting by university-based researchers after the reform and the quality of university start-ups and patents also appears to have declined".[282]

We should – however – point out that the causes of this decline in patents and inventions could be not completely caused by the regime itself. As mentioned in Darmsgaard and Thursby (2013), the relative advantage of the regimes depends on the opportunity-cost of time, the skill-set of the TLOs and "tacitness of the technology"[283], as well as on search costs and inventors' preferences and technology. Some models[284] have demonstrated that the probability of success in marketisation of an invention is higher with the PP than with the BDA, as "the inventor's effort level is not contractible, and the inventor has a lower take-home share under BDA". [285] It safely to state that there is no empirical evidence against or in favour on one of these two IPRs regimes. The only way to capture and describe which IPR is best suited for the academic world should be observing a country that changed the IPR regime from a BDA regime to a PP regime or vice versa and then, capture the change. At the time writing, nor Italy nor Sweden have on the policy plate a change in regime, and

[282] Astebro et al. 2019, pg. 7.
[283] Astebro et al. 2019, pg. 8.
[284] Darmsgaard and Thursby 2013; Hvide and Jones 2015.
[285] Astebro et al. 2019, pg. 8.

therefore it cannot be correctly estimated the weight of these regimes on the academic entrepreneurship structures.

The IPRs regimes debate – however – does not change the situation of the pharmaceutical industry. Most of these university basic research and applied research are sponsored by public bodies, in a run towards innovation. This characteristic arises a well-known problematic: the 'paying-twice' dilemma. Since most of the basic research are carried out in public laboratories and university, or by private entities with public funding, once the drug reaches the market, the general population find themselves to pay twice the same product: the first time through the general taxation that the government collects and the second time in the market (for OTC and class C drugs) or in hospitals/specialized pharmacies (for other classes). The 'paying-twice' debate is – however – treated differently in the literature: while different observers[286] recognize the existence of such dilemma, others unlink the creation of value from basic/applied research to the drug in the market, *de facto* classifying the debate – as we called it in 2.8 – as a 'child caprice'. The causes of such definition can be traced back to the economic and political culture that, since the Cold War, have interested different part of the Us society. The centralisation of economic power and the interventions of the State in the economy is still nowadays seen as 'far-left' turn (to give a perspective, Bernie Sanders in the last decade has been categorized as 'communist/socialist' (sic) just for the proposition of a universal and free-for-all health care system[287]).

The 'paying-twice' dilemma has been the engine for the addressing of the two most notorious cases of the exploiting public funding towards the profiting of private enterprise. In a weaker sense, Gilead has exploited the public funding for the Pharmasset's project to develop an HCV drug – Sovaldi (sofosbuvir) – that, once it reached the market, has been priced through a premium (μ), instead of considering the impact of the price on the population. After an 18 months investigation led by the US Senate Committee on Finance, Gilead has been shown to apply a markup price that gained to the firm around 25.000 US Dollars per therapy, causing the Federal Administration to spend around 9 billion of US Dollars only for Sovaldi and Harvoni (a parent drug used in combination with sofosbuvir). After the investigation, nor a march-in-rights nor an imposition in changing the price have been imposed to Gilead (that it is not new to this kind of pricing techniques[288]).

The other case treated is around the SARS-CoV-2 vaccines developed by Oxford-AstraZeneca and Pfizer-BioNTech partnerships. Both the R&D on these vaccines have been sponsored by public entities (AstraZeneca up to the 97% of the total in expenditure while Pfizer-BioNTech up to more than 50% on the declared expenditure). However, the pricing strategies of AstraZeneca vaccine differ completely with the Pfizer-BioNTech one: while AstraZeneca has sold doses at the Cost of Good (averagely in Europe at 2.9 Euros), Pfizer-BioNTech have set the price way higher at averagely 15.50 Euros per dose.

[286] Conti and David 2020; Eisenberg 1996; *partially,* Wolitz 2019.
[287] *Actually, the proposal has never been close to the system design of the UK and Italian NHS.*
[288] Mancini, Asgari, and Findlay 2021

Both the cases – Gilead and Pfizer-BioNTech – have exploited aids from the public authorities for profiting: while Gilead is known to non-considering the weight of different prices on the target population, Pfizer-BioNTech have priced the Comirnaty in a way that yield high revenues from the distribution. On the good side, BioNTech has declared that it will use the funds for advancing the drugs with mRNA technology (especially cancer vaccines), and we hope that the prices of such drugs will be set according with the funds that concurred to the R&D of mRNA vaccines. With the outbreak of Covid-19, the European Union had the chance to impose a joint strategy for all pharmaceutical companies distributing vaccines against SARS-CoV-2, but it failed to do so, in the fear of be cut out from the initial phases of distribution. Truthfully, we do not understand neither why EU Commission and each MS had not asked for reduction in prices after tremendous delays in deliveries, and prior to them, why they did not jointly impose a reduction in price through their regulatory authorities.

In the light of these findings, it appears evident that a measure or a pricing technique, that addresses the 'paying-twice' dilemma, does not exist. In the early part of this chapter, we have tried to outline two possible scenario that can change this situation. Firstly, we have focused on the IPRs regimes, reaching a non-solution: IPRs regimes are brittle equilibria that are formed on precarious conditions. We also have seen in the developing of this thesis how difficult is to assess the benefits of switching from a regime to another: the evidence from applied works is few and a minor change might cause bigger impacts. Secondly, we tried to present the scenario of a future-value-index that can solve the 'paying-twice' dilemma. The solution, that truthfully for now is beyond our reach, properly address the problem, solving – in theory – the core of the 'paying-twice'.

This last solution is – in our opinion – the optimum that regulatory authorities can pursue to regain equality and fairness to a mistreated market. Surely, the index has to be created – as already mentioned – considering the various intrinsic aspects of the industry and considering the weight of the drugs on the society, but in our believes is the right path.

It appears clear what future developments this thesis might have: the construction of the index, a forecast study on its functioning with historic data and a more thorough analysis on the impact of such index on the economy is imperative for proposing it as a policy.

Executive Summary

Pharmaceutical industry is a fundamental sector for the entire world: indeed, it provides communities with pharmaceutical products, "substance*[s]* or complex of substances which is administered to man or to animals in order to prevent, diagnose, alleviate or cure a disease, to relieve a symptom, or to modify bodily function in some way."[289] It is also a complex environment, ruled by an intrinsic double-face nature: the main objective of a firm in the capitalistic system is the maximization of the profit and the costs minimization; this vision collides with the social importance of pharmaceutical products, together with main objective of the healthcare system.

The situation has gotten more intricate thanks to the switch of model underlying the sector itself. Historically, large pharmaceutical companies were the driver in R&D: they researched and developed drugs from their origins, bringing into the markets. With the advance in technology and the increasing interest of markets into the pharmaceutical industry, various and different SMEs had begun researching and bringing drugs to the initial phase of clinical trials, waiting for bigger companies to acquire them or acquire the use/patent of the developing drug.

Moreover, pharmaceutical products do not follow the same life-cycle of general goods. The existence of drugs and medical devices are not only threatened by other ameliorative products, but also by generics: indeed, a drug is protected by market exclusivity for a fixed amount of time; after the expiration of this term, other pharmaceutical companies can recreate the former-patented-drug and launch it onto the market, competing not anymore on the values of the good but on the prices.

We can divvy the market into three submarkets characterized by different protagonists: one regroups the conventional side of the market where large companies produce conventional pharmaceutical products (such as the Humira [AbbVie], Eliquis [BMS/Pfizer], etc.); another one regroups the biotechnology firms, that is those companies that mix biology and technology in order to create products for the treatment of specific diseases (among them we can find Novo Nordisk A/S, Regeneron, etc); the last group represents those firms and businesses that cannot find an adequate position in the groups cited above. The outputs of these firms can vary from each other, and, now more than ever, the pharmaceutical products are much more diverse than in the past. Overall, we can individuate four different categories of outputs: biological/biosimilars products, generic drugs, over-the-counter drugs, and the traditional Chinese medicines (that hold a significant share in the Chinese market and, for the size of it, also in the global market).

[289] Dukes 2006

According with IQVIA,[290] the distribution of the total global pharmaceutical market sales is predominant in the USA with a slight increase from 2014 to 2019; the other markets have an equal percentage of global share, with Europe and emerging markets slightly equivalent.

Economically speaking, the US market has the biggest market share for pharmaceutical products globally: throughout the entire country, the most sold products are relative to oncology area, diabetes related illnesses, respiratory diseases, and HIV/AIDS. If we apply the Porter's five forces model on the Us pharmaceutical industry, the deviation from what we already presented in the last section is small. If we apply the Porter's five forces model on the Us pharmaceutical industry, the deviation from what we already presented in the last section is small. Main differences can be found in buyer power: indeed, bargaining power of buyers is strengthened by the development of oligopsony and by the free pricing regimes. We should notice that the Patient Protection and Affordable Care Act – also known as Obamacare – is still under severe pressure from Us Congress, causing the Us healthcare apparatus to move from a value-based pricing system to a formulation of prices based on the health outcomes of drugs.

The pharmaceutical industry in Italy is markedly dissimilar to the global and Us one, also for what concern the forces in play. Italian market accounts for the 10.3% of the European pharmaceutical market value, at the same level of United Kingdom: compared to other markets, Italy has not LMCs and big corporations, however it has different intermediate size firms and smaller firms. This facet can be trace back to the incumbent presence of Large Multinational Corporations, such as Pfizer, J&J, Novartis, etc. The presence of these abroad incumbents, together with small generics company battling for each drug approval makes the rivalry condition very strong. At the same time, the threats of new entrants are low due to the strict regulations forcibly applied in the market and due to the different regulation on the patents and intellectual property protection regimes that lower the likelihood of new entrants. According to MarketLine, "entering the Italian market is made harder by the 50% reduction drug are discounted by when used in a hospital. Doctors – continues MarketLine – are also banned (*sic*) from prescribing a brand name and must instead use the chemical formula name".[291] Another regulation barrier is the usage of restrictive formularies that limit the utilization of specific drugs to the specific treatment or disease: this facet causes "potential market for non-formulary drugs to be smaller than the size of the therapeutic class market." [292] Therefore, it is safe to state that the threats of new entrants are quite weak, if not absent.

Due to the double-face of pharmaceutical industry nature, the State has to intervene in the market for ensuring "the safety, efficacy, and quality of medicines, as well as the relevance and accuracy of product information."[293] These actions are performed by the so called regulatory authorities, scilicet, that body entitles

[290] IQVIA, 2020.
[291] MarketLine 2020 (II), pg. 16.
[292] MarketLine 2020 (II).
[293] Al-Worafi 2020, 21.

to develop and enforce pharmaceutical legislation and regulations.[294] Far from recalling the entire Theory of Regulation, it is useful to frame the reason why regulation authorities are needed in the market. Campbell citing Pigou states "that the pursuit of self-interest which motivates economic action can readily take unwelcome forms, such as mere appropriation by violence or deceit, and accepted without much argument the necessity of a legal framework which channelled self-interest into the beneficent form of exchange as an essential condition of market order."[295] In these words, it is possible to see the deeper motivation of regulation existence: in order to outcome the failures of the self-regulation of the markets (and of the actors in the markets), it is ineluctable to funnel the possible negative results on a social and beneficial paths. More operatively, the economic reasons for the existence of a regulatory agencies can essentially be linked to two failures of the market: the imperfection or absence of informative symmetry, and the patents and insurance-related moral hazard for price and reimbursement regulation.

In USA, the authority entitled to ensure the observation of the laws and regulation for pharmaceutical products is the Food and Drug Administration (FDA). The authority was founded in 1906 with the Pure Food And Drugs Act in order to control the interstates distribution of drugs, and regulated and publish the 'addictive or dangerous' components of drugs in the market. Throughout the decades, the US Legislator enhanced and enlarged the regulations around the two main scopes of FDA, from regulating the packaging of pharmaceutical products, controlling the distribution of possible abuse drugs, regulating the composing of certain food products, to improving the generics market and the competition inside the pharmaceutical industry. Indeed, in 1984 the Drug Price Competition and Patent Term Restoration Act (also known as Hatch-Waxman Act) was approved by the US Congress, expediting "the availability of less costly generic drugs by permitting FDA to approve applications to market generic versions of brand-name drugs without repeating the research done to prove them safe and effective."[296]

The European Union regulatory system is in a unique situation: contrary to the United States of America, European Union is not a federalisation of states, it has not any supranational bodies that can rule for every aspect of the lives of European citizens, and therefore, has precise borders of ruling. The Treaty of Lisbon has established the contents which the European Union, together with its legislative and regulative bodies, can act on. In this context, since the first treaties for the establishment of the Union, the pharmaceutical industry has been in the centre of different and complicated reform which aimed to found a cooperation between state-members on the regulation and protection of public and animal health, while ensuring the free circulation of medicines, according with the Treaty on free movement of people, goods, and money. Therefore, a decentralised regulatory authority has been created in the Nineties, the so-called EMA: being a decentralised agency, EMA does not entirely substitutes the activities that national authorities are entitled to perform. Indeed, the European agency performs human and veterinary pharmaceutical evaluations for the member states

[294] WHO 1999.
[295] Campbell 2018.
[296] FDA Office of the Commissioner 2021

in the context of approving the marketizations in the European market. However, there are specific drug class that are mandatory to be evaluated by the EMA: rare diseases drugs, HIV, cancer, neurodegenerative disorders, diabetes, auto-immune diseases, viral diseases, biotechnology drugs and those drugs that focus on gene therapy and monoclonal antibodies. For other class of drugs, the manufacturer or patent holder has the right and possibility to apply for the market authorization (MA) within the EEA, and therefore being able to market the drug in every European country, or he can apply to the national authority, limiting the sphere of marketisation within the State where it is applying to.

In almost every country, the regulatory authority also controls the prices of the pharmaceutical products via different techniques. Pricing in the pharmaceutical industry is an important step: it is the ground where hospitals and NHS plan their expenditures, where negotiations take place between Governments and companies. Nowadays, pricing of pharmaceutical products poses a major challenge for the world: the equilibria between equity, fairness and profit is always more precarious, where innovation – the real driver of the sector – is finding difficult ways to express itself and grasp the needs of the population. The market, indeed, appears to have an inelastic demand, where consumers of patented products cannot defer consumption and, therefore, accept the price as it comes in that particular moment of need. There are different models of pricing with different actors that take part of the negotiations. We will discuss of two extreme situations: the Italian scenario where different governmental bodies negotiate with companies the pricing of certain categories of pharmaceutical products following precise analysis and the other part of the spectrum, the Us system, where there is no regulatory intervention on the market and economic laws set the prices following the market criteria.[297]

Together with the usual pricing techniques that apply on every market, the pharmaceutical industry also is seen to perform fixed pricing, cost-effectiveness pricing, profit control pricing, reference pricing and ERP (External Reference Pricing). Among these, the two most interesting pricing techniques are profit-control pricing and ERP (which is a more complex version of the reference pricing).

The former is only applied in UK, through a scheme called Pharmaceutical Price Regulation Scheme (hereafter, PPRS), which "indirectly regulates the prices of branded pharmaceuticals sold to the National Health Service by setting profit limits."[298] The PPRS aims to balance reasonable price goals with incentives to UK pharmaceutical industry in order to be strong and profitable, while innovative and competitive. Those companies in this scheme have a profit cap equals to 21%, measured as a return on capital employed or return on sales: if a company exceeds its target, it can retain up to 40% of it permitted return; instead, when the company exceed the allowance cap, it must reduce profits by reducing prices or delaying or restricting previously agreed future price increases. The scheme failed to assure lower prices for pharmaceuticals, while

[297] Morgan et al. 2020.
[298] Mrazek 2002, pg. 458.

it allows a stable and certain regulatory environment and a level of R&D expenditure higher than the worldwide average.

The latter, instead, is basically a benchmark pricing: the Regulatory body applying this policy requires the pharmaceutical company to apply a price that has to be no more than a maximum value set by a basket of countries, called reference basket. The mechanism is not new in the policy making world: for example, the funding that the Italian Government gives to the Regions in order to operatively function the Regional Health System is calculated on the basis of a reference basket of virtuous Regions.[299] Aside this note, ERP was first created in Germany in 1989 and since then has been adopted by different countries in EU. According to Rémuzat et al.,[300] 28 European countries has applied the ERP (except UK and Sweden) and 23 of these countries make ERP the main policy in calculating prices. External reference pricing is either applied to all marketed drugs – like in Luxembourg – or to specific therapeutic area drugs, or to specific categories of drugs (OTC, prescription drugs, innovative medicines, etc). The calculations behind ERP are based on two criteria: lowest price and average price. Whenever the price has not been set yet, the country usually takes the lowest price of a single state if available, or, if a comparable drug exists, the price is set on the same price of that drug. In most cases, the reference price is set from the ex-factory price or from the pharmacy purchasing price (PPP): the pharmacy retail price is only used in two countries (Luxembourg and Malta). According to Rémuzat et al., Italy used ex-factory prices, PPP and PRP depending on which information has been provided by the pharmaceutical company.

The main problem associated to the ERP is the "path dependence": indeed, the price is influenced by the rules that the reference system has imposed itself which in turn is influenced by the same reference system – a process that feeds on itself. Moreover, the available prices in the reference countries are usually heterogenous, making the comparison of prices difficult and do not consider the managed entry agreements between governments and companies. Another problem of the ERP is the possible spill-over effects on other countries and the price convergence: indeed, "wide application of ERP, a low price for a new product in a given market *[let's say France]* might affect manufacturer's pricing strategies elsewhere and could lead to parallel trade".[301] On the contrary, literature[302] demonstrates that ERP has become an incentive for pharmaceutical companies to adopt international pricing strategies, launching in sequence their products to delay or avoid launching new drugs in those countries where lowest prices is applied.

In Italy, the pricing negotiations are performed by AIFA, together with the IT-MoH. In 2019, the Legislator has chosen to reform the pricing techniques of AIFA with the Decree of the 2nd of August 2019. The pricing determination is a mix of different strategies and assessment methods that include an economical and financial assessment of the future drug uses, an assess of the forecasted market share that the drug is forecasted to

[299] Distaso 2019.
[300] Rémuzat et al. 2015
[301] Rémuzat et al. 2015, pg. 9.
[302] Espin et al. 2011; Vogler et al. 2011; Cueni 2012. Iravani, Mamani, and Nategh 2020

acquire, the forecasts and budget variation that the IT-NHS has to undergo in case the proposed firm is accepted by AIFA (art. 2, comma 2, let. a-j). Moreover, the Decree requires that the pharmaceutical company and AIFA have to take into consideration the selling volumes, the availability of the drug to the IT-NHS, to every entity of the IT-Regional HS and the public funding (if any) that the Italian State had distributed in the early phase of the R&D phase (art. 4, comma 1, let. d). [303] The Decree also describes the mandatory process of negotiation between AIFA and the pharmaceutical company. The negotiation itself can be activated both by AIFA (in case the reimbursability would have a considerable impact to the NHS's budget) and the pharmaceutical company. The negotiation lasts for 180 days during which it can be halt once by AIFA, only in the case that it requires more solid and thorough document for the assessment; the pharmaceutical company can also halt the process once in order to provide other documents useful to the assessment.

AIFA also applies another technique, that is close to a bilateral agreement between State and pharmaceutical company, the MEA (Managed Entry Agreement). The scope of this agreement is to manage the uncertainty associated to an innovative drug and related to clinical benefit and cost-effectiveness, not completely proved by the market (since the 'early access'), and also it helps government agencies to control and manage the budget impact of such drug. Therefore, in this situation, MEA can prescribe different solutions in the reimbursement area, both in the means of expenditure cap and performance based terms. It appears evident that Italian Government through its agencies intervenes in the market in order to protect the population and to guarantee the safety (both in a health sense and in an economical sense) of the patients. The behaviour does not appear unexpected: historically and socially, Italian WS has been always centred on the interventions of the State in the economy with a profound regard to the universality of the Health Care system in place. Instead, Us Health Care system is the complete opposite of the Italian model.

Indeed, the US health care system, and in particular the pharmaceutical sector, does not have solid and massive interventions from the Us State. Therefore, the market is free to 'adjust' following its own practices, imposing prices higher enough to turn pharmaceutical products useless or inaccessible to the general public. There are no regulation strategies nor pricing methods imposed from the State nor negotiations (with some exceptions) around pharmaceutical products: the pricing strategies are decided by the pharmaceutical company and imposed in the market: a market with the same mechanism of other industries.

The Us pharmaceutical and healthcare chain is composed by producers, insurances and wholesalers, retailers and hospitals: producers sell to wholesaler and insurances, that resell the products to pharmacies and hospitals. In this context, pricing is decided through market laws, usually applying discount pricing to the first level of this chain and then using cost-based pricing. Moreover, since the surge in pharmaceutical products prices, different intermediate and end consumers start to pool resources and voices in order to have applied discounted prices: therefore, different consortia between hospitals start to rise in order to raise the purchase power and lower the prices. In any case, the end consumer (the patient) faces anyways the surge of prices in the day-to-

[303] Italian Minister of Health and Italian Minister of Finance 2019

day life: different patented-drugs, OTC and generics (epi-pens, insulins etc) have even higher prices of the Us neighbour, Canada. [304]

Linked with the pricing debate of the pharmaceutical products, there is also a matter around the IPRs regimes. In the west world, there are two main systems of intellectual property rights: a system based on the Bayh-Dole Act of the 80s and a system based on the Professor's Privilege. Before addressing the differences between these two systems, it is useful to give a context to the meaning of intellectual property. Intellectual property is an abstract proprietary interest addressing the intangible, that is the creation of the mind that has been embodied. There are different forms of Intellectual Property (later, IP): copyrights that protect artistic and literary works; patents, pertaining to pragmatic innovations; trademarks, protecting commercial symbols. We can define 'patents' with Schechter and Thomas's words: "patents provide exclusive rights to inventors of new, useful and nonobvious inventions. The patent law concerns hard technologies, including chemical, electrical and mechanical products and processes, as well as other pragmatic innovations in fields ranging from biotechnology to business methods." [305] Throughout international laws, there is no definition of *invention*, but it is correct to define it as 'solution of a technical problem', in order to counterpose it with the concept of discovery. Indeed, the invention "applies the natural laws in order to satisfy human needs: and for satisfying them with a serialized (technical) industrial production."[306]

The Patent and Trademark Law Amendments Act, also known as Bayh-Dole Act (Pub. L. 95-517, December 12, 1980), is an Act sponsored by two US Senators – Birch Bayh (D) and Bod Dole (R) – that modified the legislation on federal government-funded research. The scope of intervention of the Bayh-Dole Act (later, BDA) was to transfer the IPRs from the granting agency to universities that received federal funding for researching. The complete change in policy was aimed to increase and simplify the relationship between granting agencies and non-profit organisations/small-firms, and to increase the competitiveness of the US industries (as stated in 35 Us Code §Section 200).

However, two countries decided that the BDA was not the proper and rightful policy and adopted another method in administering patent policies: the Professor's Privilege. The Professor's Privilege is a policy adopted only by Italy and Sweden. In Italy, it is embodied in the art. 65 of the Codice di Proprietà Industriale (Code of Industrial Property). Basically, the article states that the researcher is the only owner of the rights resulting from the invention. The ratio behind this policy was to incentive professors and researchers to industrially exploit their invention, in this way choosing applied research over basic research: where basic research is far from an industrialization.[307]

[304] Wertheimer and Huang 2015.
[305] Schechter and Thomas 2003, Ch. I, pg. 26.
[306] Cetra and Cian, 2017, Ch. XVII, 281. *Translated from:* "*l'invenzione applica queste leggi naturali per soddisfare bisogni umani: e per soddisfarli attraverso una produzione industriale (tecnica) serializzata*".
[307] Lissoni et al. 2004.

These two systems have been thoroughly discussed among observers and scholars; a conspicuous number of countries decided to introduce policy and legislations similar to the BDA: the goal with this decision was to increase the competitiveness of the academic and innovation sector of those countries. This globalization of a policy, such as the BDA, were put in practice in Germany, Belgium, Denmark, Japan, Norway, Finland and China. However, in Germany, the increase in competitiveness have never shown: indeed, different studies[308] have shown that the number of university invention has remained unchanged or decreased. There are different papers and research in this branch, and it safely to say that there is no empirical evidence against or in favour on one of these two IPRs regimes. The only way to capture and describe which IPR is best suited for the academic world should be observing a country that changed the IPR regime from a BDA regime to a PP regime or vice versa and then, capture the change.

This brief discussion on regulation, prices, and IPRs regimes is propaedeutic to explain the 'paying-twice' critique. This critique is the follow:

> "where subsidies are present, prices are alleged to be too high because product research and development has been co-finance by taxpayers *[and this]* is often framed in terms of 'paying-twice' – first for the research and, second, through the above-market pricing of resulting privatized products (Wolitz 2019)."[309]

In other words, paying-twice in the pharmaceutical industry occurs in those situations where a State (via public agencies or direct funding) invests in pharmaceutical research and then, also pays the drug once is authorised to enter the market. The problem is cross-countries and cross-healthcare-systems: it occurs in Italy, as well as in the USA. However, the scientific literature around this topic covers only the US scenario and does not treat any kind of situation in Europe. Wolitz (2019) has undergone a thorough investigation of the meaning and principal aspects of the 'paying-twice' critique: we should also notice that the point of view of the paper cited is far from being objective. There are four features and question on the 'paying-twice': the first question that Wolitz addresses is the meaning of the 'paying-twice'. Unquestionably, the meaning is not literal (contrary to the provocation that Wolitz wrote in the paper): the final consumer does not pay double the amount of the products – in this context, pharmaceutical product. However, s/he pays twice: the first time by the State via taxes that the final consumer has paid to the Administration and the second time when s/he purchases the product. Surely, the process is not literal, but in reality, s/he ends to buy a product which has been funded through *their* taxations and practically 'paying it twice'.

Again, the 'paying-twice' critique depend on ideas about the normative relationship that ought to achieve amongst government funding and the pricing of products. This relationship can be structured on three possibilities: the gift view, the transaction view and the access view. The former relies on the assumption that the State should not intervene on the pricing of any resulting products: the relative funding, therefore, would

[308] Von Proff et al. 2012; Czarnitzki et al. 2015.
[309] Wolitz 2019, pg. 178.

be a plain gift to the private sector. A second structuring of this relationship can be viewed as "a complaint about transactional unfairness. It expresses the view that the terms of an arrangement between taxpayers and a private party with license or patent rights covering a medication are unfair."[310] This second perception does not strictly hit the pricing critique, but focuses on the unfairness of the game as "if US taxpayers are already funding university research to the optimal level, then adding patent rights to the incentive package gives an excessive reward."[311] Finally, the third view is focused on the fact of government funding: in other words, the critique is not on the unfairness of the transactions but is a "complaint based on inaccessibility and unaffordability in spite of government funding.

The 'paying-twice' critique is not a rhetoric and spoiled debate of researchers, observers and scholars. There are different real cases where we can see a pay twice by the general public. In the thesis, we have focused on two examples: Sofosbuvir (Sovaldi) and SARS-CoV-2 vaccines cases (Pfizer-BioNTech and Oxford-AstraZeneca).

Sovaldi case has arisen due to an investigation led by the US Senate Committee on Finance, after the Us Federal Administration had found out that only Sovaldi and Harvoni costed for the administration around 9 billion US Dollars for the year 2014, an excessive amount for an HCV pharmaceutical product. Sovaldi is the trade name, while the pharmaceutical product is called sofosbuvir and it is marketized in two solutions: Sovaldi 400mg film-coated tablets and Sovaldi 200mg film-coated tablets. Contrary to general believes, Sovaldi (sofosbuvir) is not a single pharmaceutical product that cure HCV: instead, it is a drug that has to be used combined with another drug (the medical doctrine suggests ribavirin) and, for specific genotype, with an additional one, that is the peginterferon-alfa. In the Sovaldi case, Gilead (the manufacturer) created Harvoni as additional drug. The original inventor of sofosbuvir, however, is not Gilead, but Pharmasset Inc., a company found by academic researchers as a spin-off of different research on HIV and HBV/HCV. Throughout the years, Pharmasset had received around 2 million of US Dollars as grants for research: thanks to these, Pharmasset had been able to synthetize a drug that can cure HCV in an efficient way than already marketed drugs. In 2011, Gilead acquired Pharmasset (and sofosbuvir) for 11.2 billion of US Dollars (137 $ per share).

After the classification of Sovaldi as breakthrough therapy by the FDA, Gilead in 2013 launched into the market the sofosbuvir with a nominal price of 84.000 Us Dollar per therapy cycle. The pricing strategy – that is deeply analysed in the Thesis – of Sovaldi had been set on the premium basis, in order to "allow Gilead to capture value for product without going to a price where the combination of external factors and payer dynamics could hinder patient access to uncomfortable levels."[312] The prices in other countries has been set out according with the figure EX.S.1., where most of the European countries had been able to negotiate lower prices (Norway around 53 thousand US Dollars per cycle).

[310] Wolitz 2019, pg. 184.
[311] Hemel and Ouellette 2017, pg. 7.
[312] US Senate Committee on Finance and 114th US Senate 2015, Appendix E, Ex. 28, 0014044.

Country	Price
Austria	$63,189.70
Canada	$50,525.00
Denmark	$56,449.40
Finland	$54,381.20
France	$72,508.00
Germany	$63,198.70
Luxembourg	$62,149.90
Norway	$53,043.90
Sweden	$51,453.60
Switzerland	$59,594.80
United Kingdom	$57,100.20

Source: *Gilead Sciences, Inc.*, Response to Chairman Wyden/Senator Grassley letter dated July 11, 2014, narrative answer to question 21, September 9, 2014 (Appendix F)

Figure EX.S.1. Pricing comparison in non-US markets for Sovaldi (treatment course). Source: US Senate Committee on Finance and 114th US Senate 2015.

In this picture, US HCV patients happen to be in a 'paying-twice' situation: where through general taxation the Federal Administration has sponsored the basic research behind the Sofosbuvir, *de facto* investing in a future product. Now, the question that we should pose is whether the Federal Administration granted the sponsorship aiming to invest in order to spoil after the outcome or trying to fill a failure of the market. The answer to this question is the key for the policy making. In both cases, the 'paying-twice' critique has to be addressed; however, the difference of each case hits the political perception of such intervention. To conclude, depending on when one starts countring "the degree of public contribution is either overwhelming or quite modest"[313] but it appears safe to state that Gilead exploited the research of Pharmasset, and use it for ultra-maximize its profit from HCV patients, *de facto* making 'payin g-twice' the US general public.

	Amount for ChAdOx technology	Amount of AZD-7442 funding	Total
UK Department of Health and Social Care	£0.00	£31,179,621.00	**£31,179,621.00**
European Commission	£23,545,255.00	£31,179,621.00	**£54,724,876.00**
Wellcome Trust	£14,144,606.00	£1,217,835.00	**£15,362,441.00**
CEPI	£12,098,260.00	£272,286.00	**£12,370,546.00**
UK Medical Research Council	£3,080,837.00	£2,174,848.00	**£5,255,685.00**
Foundation for NIH (US)	£5,729,292.00	£0.00	**£5,729,292.00**
Innovate UK	£2,403,678.00	£0.00	**£2,403,678.00**
European & Developing Countries Clinical Trials Partnerships	£2,209,747.00	£0.00	**£2,209,747.00**
Bill and Melinda Gates Foundation	£1,595,006.00	£0.00	**£1,595,006.00**
Other	£4,506,697.00	£68,106.00	**£4,574,803.00**

Figure EX.S.2: Distribution of funding per each funder and per each objective. Source: Cross et al. 2021

[313] Silver and Hyman, 2020, pg. 10.

In the same line, SARS-CoV-2 vaccines appear to have the same problematic. Oxford-AstraZeneca vaccine has been sponsored by public funding for 97% of the total expenditure in R&D, as per figure EX.S.2.[314]

At the same time, however, Oxford University and AstraZeneca had signed an agreement that provided to sell the batches of vaccines at the Cost of Good, also reported as follow in the APA between European Commission and AstraZeneca AB for the acquiring of 300 million of vaccine doses:

> "AstraZeneca shall manufacture and supply to the Participating Member States the Initial Europe Doses at a price equal to their total Cost of Goods, with no profit or loss for AstraZeneca […] (European Commission and AstraZeneca 2020)"[315]

Therefore, AstraZeneca and Oxford University has more than applied what the 'paying-twice' dilemma critiqued on, that is, selling at the cost of good what the general population have sponsored to create.

Of different results the Pfizer-BioNTech vaccine with mRNA technology; the problem around this case is the low number of documents around the expenditure and the funding of this vaccine. According with various sources, Pfizer-BioNTech vaccine has been sponsored for 445 million of US Dollars by the German Government and for 100 million of Euro from the EIB, for a total spending in R&D of 1 billion of US Dollars (as declared by Pfizer managers). Pfizer-BioNTech did not choose the road of the 'Cost of Good' for their vaccine: instead, they applied different pricing technique in order to profit from the distribution of the vaccines. We cannot thoroughly elaborate on the strategy because there are no documents publicly available on the matter, nor there has been an investigation on the matter (even though we hope that the matter will be taken into consideration due to the abnormous differences on prices).

Pfizer-BioNTech vaccine, indeed, has been sold following the agreement on the batches to be distributed: that is, the price has changed in the years following the distribution of the batches of vaccines. According to a policy report of Oxfam Italy,

> "Pfizer/BioNTech have been charging governments between 6 and 24 times the estimated cost of producing its vaccines. Its lowest reported price was charged to the African Union at $6.75 per dose, still nearly 6 times more than the estimated cost of production (Marriott and Maitland 2021)."[316]

It is evident that the pricing strategy is the exact opposite of the one chosen by AstraZeneca. The profits from the distribution of the vaccines for Pfizer are equal to 3.5 billion of US Dollars only in Q1, according with the New York Times.[317] BioNTech profits are estimated to reach 18.7 billion of US Dollars only in 2021. [318] Therefore, from the one billion of expenditure in R&D estimated by Pfizer, both the companies have profited from the selling of the vaccines, while developing and developed countries struggled to contain the spread of

[314] OSI 2020; Cross et al. 2021; Safi 2021.
[315] European Commission and AstraZeneca 2020, pg. 19.
[316] Marriott and Maitland 2021, pg. 5.
[317] Robbins and Goodman 2021.
[318] Kansteiner 2021.

the virus and the tremendous effects that SARS-CoV-2 was having on the population. Therefore, is there any 'paying-twice' scenario with Pfizer-BioNTech vaccine? It is safe to reply with a positive answer: EU and German Government has funded the R&D of the vaccine and then bought the batches, with a conspicuous markup for Pfizer-BioNTech.

To conclude, both the cases – Gilead and Pfizer-BioNTech – have exploited aids from the public authorities for profiting: while Gilead is known to non-considering the weight of different prices on the target population, Pfizer-BioNTech have priced the Comirnaty in a way that yield high revenues from the distribution. On the good side, BioNTech has declared that it will use the funds for advancing the drugs with mRNA technology (especially cancer vaccines), and we hope that the prices of such drugs will be set according with the funds that concurred to the R&D of mRNA vaccines. With the outbreak of Covid-19, the European Union had the chance to impose a joint strategy for all pharmaceutical companies distributing vaccines against SARS-CoV-2, but it failed to do so, in the fear of be cut out from the initial phases of distribution. Truthfully, we do not understand neither why EU Commission and each MS had not asked for reduction in prices after tremendous delays in deliveries, and prior to them, why they did not jointly impose a reduction in price through their regulatory authorities.

In the light of these findings, it appears evident that a measure or a pricing technique, that addresses the 'paying-twice' dilemma, does not exist. In the early part of this chapter, we have tried to outline two possible scenario that can change this situation. Firstly, we have focused on the IPRs regimes, reaching a non-solution: IPRs regimes are brittle equilibria that are formed on precarious conditions. We also have seen in the developing of this thesis how difficult is to assess the benefits of switching from a regime to another: the evidence from applied works is few and a minor change might cause bigger impacts. Secondly, we tried to present the scenario of a future-value-index that can solve the 'paying-twice' dilemma. The solution, that truthfully for now is beyond our reach, properly address the problem, solving – in theory – the core of the 'paying-twice'.

This last solution is – in our opinion – the optimum that regulatory authorities can pursue to regain equality and fairness to a mistreated market. Surely, the index has to be created – as already mentioned – considering the various intrinsic aspects of the industry and considering the weight of the drugs on the society, but in our believes is still the right path.

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