Universidade do Minho
Escola de Economia e Gestão

Soraia Sofia Silva Lomba

Innovation incentives and reimbursement schemes in on-patent pharmaceutical markets

outubro de 2022

Innovation incentives and reimbursement schemes in on-patent pharmaceutical markets
Soraia Lomba
UMinho | 2022

Universidade do Minho
Escola de Economia e Gestão

Soraia Sofia Silva Lomba

Innovation incentives and reimbursement schemes in on-patent pharmaceutical markets

Dissertação de Mestrado
Mestrado em Economia Industrial e da Empresa

Trabalho efetuado sob a orientação do
Professor Doutor Odd Rune Straume

outubro de 2022

Acknowledgments

It is with great happiness and feeling of accomplishment that I stand here, reaching the end of yet another milestone in my academic and personal journey. Therefore, please know that words cannot express how grateful I am.

To begin with, I would like to thank the one professor who, not only for the positive impact of the course unit he taught me had on my academic path, but especially for his enthralling teaching method, made me develop a keen interest in economics of markets, professor Odd Rune Straume, my supervisor in the present dissertation. For you, a statement of unending gratitude, for all the crucial guidance, great patience, and dedication towards this project. I owe it to you.

A word of love and thankfulness to my family. To my mum, for giving me everything I need to become whoever I want to be. To my dad, for being such a sweetheart. To my granny, for all her love and wisdom. To my brother, for his unconditional love, support and for being the role model that I always looked up to. And to Rach, for being like a sister and a best friend, all in one.

A very special thanks to my beloved boyfriend, Filipe, for all the love, support, and immense patience throughout the development of this dissertation. Thank you for always encouraging me to be and do better, and specially, for being my best friend.

I also want to thank all my friends, for being the absolute best. Thus, I extend a special thanks to the amazing group of friends I met at this university, who I will take with me for life, Ângela, Bruna, Miguel, and Rita, they made it all worthwhile. Another special word to Matilde and Bé, for being my partners in countless hours in the library writing this dissertation, and for all our years of friendship. To Bárbara, Bia and Fii, thanks for all your love. And to those not mentioned, thank you.

As they say, it truly takes a village.

STATEMENT OF INTEGRITY

I hereby declare having conducted this academic work with integrity. I confirm that I have not used plagiarism or any form of undue use of information or falsification of results along the process leading to its elaboration.

I further declare that I have fully acknowledged the Code of Ethical Conduct of the University of Minho.

Resumo

A presente dissertação analisa de que forma o tipo de inovação escolhido por uma empresa farmacêutica para entrar no mercado, depende da forma como os pacientes são reembolsados pelo regulador nesse setor. A escolha do método de reembolso por parte do regulador afeta a elasticidade preço da procura e por isso os preços praticados. Assim, através de um modelo de duopólio estilizado com base no modelo de Hotelling e partindo da comparação de dois métodos de reembolso, cosseguro simples e preço de referência terapêutico, um resultado principal é que o grau de diferenciação terapêutica é menor neste último cenário. Essencialmente, os nossos resultados sugerem que o preço de referência fomenta a inovação incremental e não a inovação drástica, o que contradiz a literatura existente.

Palavras-chave: Cosseguro simples; Inovação; Mercados farmacêuticos; Preço de referência terapêutica; Sistemas de reembolso.

Abstract

The present dissertation analyses the extent to which the type of innovation a pharmaceutical company chooses to enter the market with, depends on the way patients are reimbursed by the regulator within this sector. The regulator's choice of reimbursement method affects the price elasticity of demand and so the prices charged. Thus, through a stylized model, that assumes a duopoly, based on Hotelling's model, and building on the comparison of two reimbursement methods, simple coinsurance and therapeutic reference pricing, a main result is that the degree of therapeutic differentiation is lower under the latter scenario. Essentially, our results suggest that reference pricing fosters "me-too" innovation rather than drastic innovation, which contradicts the existing literature.

Keywords: Innovation incentives; Pharmaceutical markets; Reimbursement schemes; Simple coinsurance; Therapeutic reference pricing.

Table of contents

List of abbreviations and acronyms

GDP – Gross domestic product

GRP – Generic reference pricing

OECD – Organization for Economic Co-operation and Development

R&D – Research and development

RP – Reference pricing

TRP – Therapeutic reference pricing

WHO – World Health Organization

List of tables

1. Introduction

The pharmaceutical industry, responsible for researching, developing and producing medicines and their active compounds, exhibits an oligopolistic market structure, i.e., this sector of the economy has a restricted number of competitors for a pronounced demand, whose products offered may be, to some extent, differentiated and with a strongly innovative slant.

The regulator's choice of reimbursement method is crucial not only for the patients but for pharmaceutical companies, as it affects the price elasticity of demand and thereby the equilibrium prices within the market in which they compete. Accordingly, it impacts the profitability of innovating with either a close substitute or a more differentiated product, what might benefit so-called "me-too" innovation over drastic innovation, or the other way around.

The main aim of this thesis is to understand how the decision made by the regulator of which regulation scheme to use in on-patent pharmaceutical markets can indeed affect the incentives for innovation – a noteworthy departure from the earlier literature, commonly overlooking these incentives –, through a theoretical analysis. In this context, there are two reimbursement schemes, the simple coinsurance and the therapeutic reference pricing (henceforth TRP), and the focus will be on the latter, because although it is less common, it is the most relevant for on-patent drugs.

The methodology used to obtain the intended answers, and subsequently compare it with the published literature, is game theory - a stylized model that describes a strategic behaviour in which the outcome of each player is influenced not only by his actions but also by the actions of other players -, in particular, different games based on the Hotelling model (Hotelling 1929). For this purpose, two players are considered, one incumbent drug producer and one entrant, in a therapeutic market for on-patent prescription drugs.

In brief, and as a result, for a given location of the new drug, prices, profits, copayments and total drug expenditures are lower under TRP than under simple coinsurance, for both drugs. Similarly, when innovation incentives are considered, patients are also better off under TRP, and in fact, the difference is even greater between the two scenarios considered. Equally, the regulator does better under TRP, as it is the scenario in which total patient utility minus total drugs expenditures are maximized. Additionally, the degree of therapeutic differentiation is found to be lower under therapeutic reference pricing, when comparing both settings, fostering "me-too"

innovation. It follows that the optimal choice to reimburse patient's drug expenditures is through TRP.

The dissertation's remaining sections are organized as follows. Chapter 2 provides the institutional background, where key concepts, relevant descriptions, and real-world statistics, for the overall understanding of the topics under analysis, are presented. Afterwards, Chapter 3 reviews and discusses the existing economics literature on drug reimbursement and drug innovation, both theoretical and empirically. Next, Chapter 4 presents and displays the stylized model to be conducted in order to answer the research questions outlined beforehand. Chapter 5 follows up on the model, by solving it as far as the post-innovation scenario is concerned, under simple coinsurance and therapeutic reference pricing. Following, Chapter 6 solves the model, again under both assumptions, but this time when innovation incentives are taken into account. Still in this chapter, the effects of therapeutic reference pricing on innovation incentives are addressed, and at the end of Chapter 6 the optimal drug reimbursement policy is found. Lastly, Chapter 7 underlines some concluding remarks.

2. Institutional Background

This chapter presents an overview of the drug patent system and other types of regulations, including different types of drug reimbursement.

Chemicals with therapeutic properties are produced and distributed by the pharmaceutical industry. Undoubtedly, pharmaceuticals are a crucial component of health-care services in general, to the extent that 2020 OECD data shows that the country with the highest ratio of pharmaceutical spending as a percentage of total health spending is Bulgaria at 32.5%, followed by Greece with 30.2%, and Hungary with 25.6%; among the countries taken into consideration, the one presenting the lowest ratio is the Netherlands at 6.0% (OECD, 2021). Therefore, and to minimize inefficient substitution, drug policies must be tightly integrated with broader health policies (OECD, 2001).

The pharmaceutical industry being a high-tech, knowledge-intensive business, and supply-side large sunk costs linked to the discovery of new drug courses, highlights the relevance of patents (OECD, 2001) (Brekke, Königbauer and Straume 2007). In brief, a patent, or intellectual property right, is a government-guaranteed right that a producer holds to exclude others from making or using part of its innovation for a specified period (Hall, 2007). Fundamentally, patents have been designed to create a market for the knowledge that is intrinsically linked to them. Hence, the economic reasoning underlying patents arises from the fact that they exist to stimulate innovation because by creating a market for knowledge, they offer a bargain between science and the innovator itself, a kind of agreement. Wherefore the patent-holder in exchange for a certain limited period of exclusivity agrees to make his invention public knowledge afterwards, thus allowing the dissemination and creation of enhanced knowledge (Stoneman, 1995).

The drug patent system rewards pharmaceutical companies that innovate by guaranteeing a return on their investments. This system enables them to take advantage of their temporary monopolistic position in the market (Nawrat, 2019). Thus, patents, by allowing an entity, in the short term, to exclude all others from practicing and copying their invention, it gives them the opportunity to earn higher profits than if there were a free, uncontrolled and immediate entry into the same pharmaceutical market.

Nevertheless, a patent on a compound does not necessarily mean that there will be no competition, because there may be other compounds that address the same disease, with or without an associated patent, which if so would indicate that these drugs belong to one of the two possible therapeutic clusters in this case – those whose drugs feature chemically related active

ingredients and are thus pharmacologically equivalent (chemical related active), and those which, although neither chemically identical nor pharmacologically equivalent, have comparable therapeutic effects (Danzon & Keuffel, 2005) (Brekke, Königbauer and Straume 2007). Once patent protection ceases, the generic entry will inevitably take place, whilst frequently introducing vigorous competition on prices (Danzon & Keuffel, 2005). Still, how extensively generics are able to capture market share from the originally brand-named drugs depends mostly on the government's regulation policies and reimbursement practices (Scherer, 2000).

Innovation is a core component within the pharmaceutical industry - having totalled about 186 billion US dollars in R&D expenditures worldwide, an increase by approximately 27% since 2012, making it one of the leading research-intensive industries globally - and regarding the types of it, it is relevant to highlight two of them (Mikulic, 2020). Therefore, "me-too" innovation refers to the production of drugs resembling pre-existing ones, exhibiting identical clinical results to the rest, thereby generating negligible added value; and is commonly found in most drugs, being in fact that 60% of the World Health Organization's list of essential pharmaceutical drugs for a healthcare system for 2020 consists of me-too drugs (Hollis, 2004)(Aronson & Green, 2020). Conversely, the outcome of drastic innovation are drugs that are effectively differentiated from all others and with fairly substantial added value (Doganoglu & Inceoglu, 2014).

Having innovated, developed, and established the medicine on the market, the prices to be charged are defined. As far as drug prices are concerned, there are two control mechanisms enforced by the regulator of the market under consideration so that disparities are avoided – mostly caused by a substantial monopolistic power that stems back to patents, first-mover advantages and the scarcity of suitable substitutes for the new drugs – the "price caps", and the reference pricing (Scherer, 2000).

The "price caps" method is used to restrain the exploitation of market power by pharmaceutical companies, by setting a maximum price for a given market, so they cannot be overpriced. The other method is reference pricing (RP), in which drugs are clustered according to similar therapeutic effects, and a reference price is determined by the regulator by taking into account the prices of all drugs within that cluster, generally the chosen price is the cheapest of them all (Brekke, Königbauer and Straume 2007). The latter method is often used to instigate competition by increasing the price elasticity of demand and lowering medical expenditures, and 2017 data listed 30 out of 45 surveyed countries from the World Health Organization for Europe were using it (WHO, 2018).

Thereupon, regarding reference pricing, it is relevant to distinguish two types. The one directly related to price regulation is international reference pricing, also known as external reference pricing, and uses the functions of the prices of the same drugs in other comparable countries to determine the price cap. Meanwhile, internal reference pricing relates to the regulation at the level of reimbursement, which can be divided into two main types: generic reference pricing (GRP) and therapeutic reference pricing (TRP) (Brekke, Königbauer and Straume 2007).

Generic reference pricing is applicable in therapeutic clusters of products featuring the same active chemical ingredients, i.e. it mainly entails unpatented drugs and their generic substitutes, meaning that it can only be addressed in off-patent markets (Brekke, Königbauer and Straume 2007). In fact, within the 30 WHO European countries previously mentioned as being reference pricing system users, 18 of them were specifically following the GRP. In comparison, therapeutic reference price can be extended to both the chemical related active cluster and the cluster of drugs with comparable therapeutic effects, thereby being able to include on-patent drugs. Indeed, the remaining 12 countries, among the 30 referenced by the survey, were using TRP (WHO, 2018).

All things considered, for on-patent drugs, the regulator has two means by which to control medical expenditures, namely prices, both directly through price regulation and indirectly through therapeutic reference pricing, via reimbursement schemes.

Pharmaceutical spending is expanding at a sharper pace than the overall health-care expenditures throughout many OECD countries. Resultantly, policy concerns have shifted towards strategies that limit pharmaceutical expenditures (OECD, 2001). As an illustration of these expenditures, OECD data from 2018, suggests that the European country with the highest percentage of GDP spent on pharmaceutical drugs is Bulgaria with 2.60%; whereas Luxembourg figures as the country with the lowest percentage of GDP spent on pharmaceuticals, only 0.60%. If, however, these expenditures are analysed by measuring the public per capita spending on pharmaceuticals in European countries using purchasing power parity, the country with the strongest performance is Germany, accounting for 884 US dollars, and the country with the poorest performance is Denmark, which accounts for 339 US dollars (OECD, 2019).

In order to control the pharmaceutical market and correct potential failures and imperfections, governments may intervene, for instance through reimbursement schemes - schemes whereby the government bears part of the cost of medicines, and thus reimburses a portion of what patients spend - to manage the medical expenditures in a given country, namely

by (i) simple coinsurance or (ii) therapeutic reference price (Danzon & Keuffel, 2005). These market imperfections can reduce the price sensitivity of demand, allow the suppliers a certain range of market power, and they also lead to demand curves that fail to represent true social benefits (López-Casasnovas and Puig-Junoy 2000).

Simple coinsurance entails that patients only must pay a fixed percentage of the price when buying a medicine, and that the regulator covers the remaining costs. Similarly, therapeutical reference pricing works like the method described previously, but only if the patient chooses a drug that is priced at or below the reference price. However if they choose a drug that is priced above the reference price, they will additionally have to pay the full difference between the price of the drug and the reference price (Brekke, Königbauer and Straume 2007).

With regard to off-patent drugs, they face competition from their generic substitutes and have consequently a lower associated price. GRP thus emerges as a vehicle to intensify this generic competition (Brekke, Königbauer and Straume 2007). Moreover, TRP intensifies price competition in the market for therapeutically similar drugs by grouping them in the same cluster, which leads to expectedly lower prices charged. However, and since the maximum reimbursable price is determined on the drug with the best cost-effectiveness ratio, this may put some patients in a position where they must choose between paying more or switching to a less suitable drug. There is, then, a trade-off associated with this method between the fees charged and the health risks for patients (Marđetko & Kos, 2018).

Unquestionably, the choice of reimbursement type is of great importance to pharmaceutical companies insofar as it affects the price elasticity of demand and thus the equilibrium prices into the market. Therefore, such a choice affects the profitability of innovating through a "me-too" procedure or something more drastic.

3. Literature review

The main objective of this chapter is to review both theoretical and empirical papers mainly concerning innovation and regulation in pharmaceutical markets, and the effects of different types of reimbursement schemes, in off-patent and on-patent markets, the latter being the most relevant for this dissertation. Literature on the effects of therapeutic reference pricing in on-patent markets, along with the effects of reimbursement schemes on innovation incentives will also be addressed in this chapter. The present dissertation builds on and relates to the theoretical literature on reference pricing in pharmaceutical markets, as existing literature pertaining to this research subject mainly analyses the effects on prices, expenditures, patient utility and welfare, without considering the incentives for innovation.

Through the theoretical model by Brekke, Königbauer and Straume (2007) that provides a comparison between generic reference pricing (GRP), therapeutic reference pricing (TRP), and the scenario of no reference princing (NRP), it follows that it is TRP that exhibits the lowest equilirium prices for every drug in the therapeutic market, since it is the one that fosters stronger competition. Conversely, NRP accounts for the highest equilibrium prices for all drugs in the considered market. Moreover, the mismatch costs and drug expenditures are also minimised under TRP, making GRP the scenario that most distorts patients' choices. As far as TRP is concerned, these results are consistent with the findings obtained in our model. However, the authors concluded that reference pricing, particularly TRP, might discourage both therapeutic substitues and generic entry, which does not match our insights. Accordingly, theoretically, the model developed by Brekke, Canta and Straume (2016) that has as its scope the effect of reference pricing on generic entry also demonstrates that reference pricing always deters the entry of generic products, despite the policy makers' intent, by encouraging the brand-name drug producer to set more aggressive prices.

Additionally, in line with Brekke, Königbauer and Straume (2007), and concerning the trade-off between fees charged and health risk for patients, although TRP may put patients in a position where they need to choose a less suitable drug in order to avoid extra co-payment, exposing them to health risks, it is GRP that is shown to be distorting drug choices the most, thus exposing them to greater health risks. This might be explained because in patented medicines the demand is less elastic than its competitors, which allows the patent holder a more leeway to charge higher

prices, leading some consumers to choose the drugs under GRP, which despite being less suitable, have a lower co-payment.

Furthermore, Miraldo (2009), by analysing how reference pricing reimbursement impacts firms' pricing strategy within a horizontal differentiation model that accounts heterogeneous qualities, verifies that in regards to the no-reimbursement setting, reference pricing drives demand up, inducing higher prices, as consumers' price sensitivity is reduced when their financial burdens is reduced, giving firms a greater market power. It should be noted that this does not counteract what is being advocated by the aforementioned authors, rather it is a different status-quo. Additionally, the same model states that the usage of reference pricing, as an indirect pricing control strategy does not always result in lower expenditure.

Further regarding expenditures, and as argued by López-Casasnovas and Puig-Junoy (2000), the reference price effectively contributes to a reduction of expenditures over the short-term, although this contribution is not substantial in the long-term savings. Pricing has a downward tendency under this reimbursement system, as held by other authors already mentioned. Thus, the findings by the mentioned authors point towards the degree of substitutability being higher under RP, but the stimulus of competition by both horizontal and vertical differentiation is capable of lessening price competition.

Ghislandi (2011), aiming to investigate how the optimal pricing strategies under reference pricing are impacted by competition, presents a two-staged model that contains more than one generic firm. The author concludes that the market for generic drugs must be competitive for the reference pricing scheme to be efficient per se. It has also been noted that through competitiveness, collusive behaviour may be brought about, and in order to disrupt these tendencies regulators are essential, as they have the leverage to increase the profitability of the incumbent drugs via competition. Additionally, concerns are raised about the lengthy viability of reference pricing when price-sensitive patients and reference pricing schemes engage together, thereby suffocating the generics market.

A thorough theory by Gonçalves and Rodrigues (2018) compares, resembling our model, the same two reimbursement methods, namely reference pricing and fixed percentage reimbursement, which is simply another denomination for simple coinsurance. This model, distinguishing it from other including ours, – in our model, total demand is completely price inelastic, due to the assumption that all patients always choose drug treatment, so total demand is constant (and equal to 1) regardless of the drug prices –, assumes that total demand is in fact

price sensitive, and therefore depends on the copayment rate. Indeed, the authors point out that drug prices rise in line with the copayment rate. Some other authors who differ from this line of thought are Brekke, Königbauer and Straume (2007), who sustain that no such correlation between prices and copayment rate does occur. Moreover, Gonçalves and Rodrigues (2018) conclude that on welfare matters, reference pricing is preferred over simple coinsurance, matching our result.

Using a novel policy experiment form Germany, Pavcnik (2002), looked into the correlation between potential patient out-of-pocket expenses and the pricing behaviour of pharmaceutical firms, by analysing the before and after drug prices, across multiple therapeutic groups, concerning the replacement of the reimbursement system of simple coinsurance by the reference pricing, held in 1989. According to this empirical study, pharmaceutical companies' pricing practices are highly sensitive to possible patient out-of-pocket costs. The results also suggest that the price decline is more pronounced for brand-name products that face more generic competition. The author further argues that the fact that RP leads to lower prices may discourage pharmaceutical firms from investing in R&D since they might not be able to earn it back, which meets the discussion in our research.

Empirically, in an attempt to understand the effects of replacing price cap regulation with reference pricing, in a practical context, Brekke, Grasdal and Holmås (2009) used the Norwegian market where this transition took place in 2003, which made it possible to observe the before and after of regulation on brand-names versus generic drug competition, for a subset of off-patent drugs. The results demonstrate that RP substantially decreases prices for both types of drugs inside the reference group, but with higher impact on brand-names, implying that RP is more effective than price regulation in lowering prices, regarding the consequences for policy. Additionally, a detrimental cross-price impact on therapeutic alternatives excluded from the RP system was discovered. The outcomes have implied that this cross-price effect concerns one about the use of patents. Along the same point of investigation, and still taking the Norwegian example, the natural experiment studied by Brekke, Holmås and Straume (2011), also found that with the introduction of RP, not only did prices drop significantly for both type of drugs - approximately 33% and 22%, respectively -, but it also resulted in considerably lower brand-name market shares. Thus, and according to the same authors, despite the additional surcharges under RP, this type of regulation has a considerable negative impact on average molecular pricing, indicating significant cost reductions and a drop in patient copayments.

This time, using Denmark as the focus of the empirical analysis, and by analysing the shift, in 2005, from external to internal reference pricing, Kaiser, Mendez, Rønde and Ullrich (2014) came to the conclusion that retail pricing, reference prices, and patient co-payments were all significantly reduced, as a result of the mentioned reform, along with overall producer revenues and health care costs, which is consistent with our findings. Notwithstanding, regarding consumer welfare, the authors consider that it depends on if one considers or not the perceived quality differences.

Aiming to better understand empirically the effects of therapeutic reference pricing as a reimbursement system, the example of Slovenia was studied by Marđetko and Kos (2018). Initially, Slovenia adopted the GRP as its reimbursement system in 2003, and only in 2013 the TRP was introduced, driven by the global financial crisis and the subsequent need to control expenditures in this regard. It must be noted that the Slovak government does not cover the entire financial burden of health care, so patients rely on extra health insurance, which still does not keep them from having to co-pay on their own to get access to certain medicines. Overall, the results of the introduction of TRP, although slightly different in each therapeutic cluster analysed, reflect a reduction in drug expenditures, in the maximum reimbursable price, and in costs - suggesting that this is an effective system for cost containment. In addition, the expenses bearable by patients have increased, yet the trend in drug consumption has remained unchanged.

A work that includes both theoretical and empirical studies, that it is important to mention, is the one by Galizzi, Ghislandi and Miraldo (2011), that presents a thorough and comprehensive review of the relevant studies on the effects of the introduction of reference pricing regulation in OECD member nations. Several common patterns were acknowledged at an empirical level, including that nearly every country that has adopted GRP has had their drug prices drop, with a steeper decline in sub-markets where generic competition was already present prior the introduction of this reimbursement method, which has also been claimed by some of the authors already mentioned. Another shared topic, this time with regards to cost savings, is that throughout the early years of usage, TRP and GRP have both been linked with significant and sustained savings, whereby being tendentially higher under TRP than under GRP, but not sufficiently high to self-finance the extensive R&D costs heavily associated with the pharmaceutical industry, which is in line with what is stated by some authors such as López-Casasnovas and Puig-Junoy (2000), among others in the theoretical literature. On another note, the theoretical part highlights that GRP and TRP might both weaken patent protection and make R&D investments less profitable, what can

lessen the motivation to invest in pricey breakthrough medications and, thus, have a negative effect on health results, discouraging "me-too" innovation; which is an interesting result in terms of our analysis.

For the most part, the empirical outcomes seen in the several presented studies have effectively proven that reference pricing enhances the stimulation of competition, prompting price responses in the market, by lowering them, as has been described in the theoretical literature. With respect to the reductions in medical expenditures, these studies also substantiate, with some shortcomings, what has been theoretically said, to the effect that this system is initially effective in the short term, but less so in the medium to long term. Nonetheless, and as stated by López-Casasnovas and Puig-Junoy (2000), it should be noted that in spite of the inevitable differences between the economic, financial, and social backgrounds of each country, the international reference price systems also exhibit substantial differences in market coverage, as well as in the extent to which on-patent drugs may or may not be included. Meaning that due to the variability of reference pricing policy and the pharmaceutical environment, empirically, it is difficult to extend the findings regarding the impact of reference pricing on a certain nation to the others (Puig-Junoy, 2005).

Furthermore, and on to literature that has a stronger focus on innovation in pharmaceutical markets, the theoretical literature is relatively scarce, although "Innovation is a process that contributes both to cost inflation and cost reduction. While the current health policy debate has focused on the control of short-term effects, (...), much more attention should be devoted to the role of innovation and its long run consequences" (Bardey, Bommier and Jullien 2010).

Seeking to understand the reason why in recent years pharmaceutical companies increasingly have chosen small improvements rather than drastic innovation, Ganuza, Llobet and Domínguez (2009), have established that, theoretically and through a stylized model, this pattern may be driven by the low sensitivity of the demand to certain segments of the market. Additionally, they also conclude that these small innovations are linked to larger rewards, which increases the companies' profitability through this kind of innovation. Another relevant finding to note is that, according to them, innovation can benefit in the long run from the recent emergence of regulatory policies designed to regulate pharmaceutical expenditures. Certainly, and based on Roberts (1999), innovation insures that, overall, firms retain a high performance position, regardless of the fact that returns on each innovation back to the firms may diminish over time.

Similarly, and a few years later, another theoretical framework, by González, Macho-Stadler and Pérez-Castrillo (2016), again aiming to contribute to the ongoing discussion about how pharmaceuticals frequently focus their R&D towards "me-too" drugs instead of breakthrough drugs, by means of a model that allows drugs that are both horizontally and vertically differentiated, and in a market with an established drug and one that is entering the market as the result of an innovative process, draws the conclusion that the two firms' price competition will be more intense the closer the horizontal distance between the two drugs is. This implies that, under price competition, it is more rewarding for firms to pursue drastic innovation. Moreover, it is also pointed out that if the resources are tight, pharmaceuticals are more likely to explore incremental innovation methods, which may decrease the incentives to invest in pioneering drugs.

Antoñanzas, Juárez-Castelló and Rodríguez-Ibeas (2011), by looking at how a producer of a brand-name drug, whose patent is about to expire, chooses to release an upgrade product through innovation before it encounters generic competition, at a theoretical level, were able to point to the fact that, it is ideal for the incumbent drug to compete for the price-sensitive physicians when the drug presents great level of innovation, whereas the incumbent drug prefers to take advantage of the loyal physicians and charge the monopolistic price for low levels of innovation.

The existing theoretical literature on innovation incentives is unanimous, but now referring to the work of Brekke, Königbauer and Straume (2007), about the negative effects that are generated towards it whenever on-patent drugs are regulated by reference pricing. Thus, as advocated by Gagnon (2013), financial incentives for innovation may also engender business models that promotes noxious practices. In fact, and as stated by Galizzi, Ghislandi and Miraldo (2011), both generic and therapeutic forms of RP hold the power to reduce patent protection and the profitability of investing in R&D, potentially discouraging more expensive innovations and affecting medical outcomes. Admittedly, as per Brekke, Königbauer and Straume (2007), TRP is capable of eliminating patent protection and further repressing innovation in therapeutic markets because it provides considerably lower profits for the patent holder, which does not set a favourable environment for innovation and subsequent market entry of a new drug. Whereas GRP, only being applied to markets with off-patent drugs, is seen as having minimal effect on innovation incentives.

Consequently, and to overcome the aforementioned effects, López-Casasnovas and Puig-Junoy (2000), assume that pharmaceutical companies tend to reinforce investments into developing more drastic innovative drugs, not yet regulated by the reference pricing. Notwithstanding this, and refuting what has been argued by the theoretical literature, findings by

Brekke, Königbauer and Straume (2007) point out that even though exempted from this reimbursement system, a patent-holding pharmaceutical company may be still adversely affected by the RP, since in order to avoid losing market share, when GRP increases price competition, the patent-holding company must also reduce the price of its drug. This price reduction for non-included drugs is due to the fact that the drugs are strategic substitutes as they are therapeutically equivalent, and also because prices are strategic complements. As a result, and according to the same authors, there has been considerable disagreement over whether or not to include on-patent drugs in reference pricing systems, both theoretically and empirically.

Proceeding to papers that focus on empirical literature on pharmaceutical innovation, which is broader than the theoretical, a recent one by Shaikh, Del Giudice and Kourouklis (2021), whose purpose was to further analyse the link between price regulation and pharmaceutical R&D investment by looking at data of the top ten European and US greatest pharmaceutical innovators from 2000 to 2017, states that when company effects are taken into account, price regulation is inversely correlated with R&D intensity, cash flow, and profitability; and in order to better understand these correlations, firm differences and business strategies are crucial, because different firms respond differently to price regulation. Likewise, Golec, Hegde and Vernon (2010), who had previously tried to find empirical potential connections between pharmaceutical price control and business R&D spending, but using "Clinton Administration's Health Security Act" of 1993 to test it, had also found this inverse correlation, whereby higher price regulation translates into a drop in the amount spent on R&D associated with the regulated drugs. Eger and Mahlich (2014), taking the European market, which is more regulated than the previous example taken, and following a similar methodology, and using the top 20 leading pharmaceutical companies in the time span from 2000 to 2008, attested, once again, regulation's negative impact on business incentives for R&D investment. Thus, it follows that the empirical literature is unanimous as to the extent that price regulation discourages innovation. Still regarding the United States, specifically Pennsylvania, an empirical study conducted by Bryce and Cline (1998), further suggests a positive correlation between the degree of competition in the market and the inherent predisposition to innovation.

Conclusively, the paper that is more closely related to the analysis herein, is the one that, upon the change of the regulatory scheme to reference pricing, and aiming to theoretically assess the long-term effects of reference pricing on pharmaceutical innovation, health, and expenditures, in which drug companies, consumers and the regulator are the three sorts of agents that are built

on a dynamic game, is carried out by Bardey, Bommier and Jullien (2010). One of the main conclusions of this model, that correlates regulatory policies, namely pricing policies, and innovation in the pharmaceutical industry, is that reference pricing stimulates drastic innovation rather than "me-too" innovation, which contradicts the outcome of our analyses. This inconsistency of results is related to the way that the two types of innovations at issue are defined and modelled, being that, while in the paper of the mentioned authors, drastic innovation is taken to mean that the innovator will enjoy a monopoly position without any therapeutic competitors, in our analyses it is assumed that the innovator will always face some degree of therapeutic competition. Thus, the notion of drastic versus "me-too" innovation, means in effect, less versus more therapeutic competition. Therefore, our analysis complements the work of Bardey, Bommier and Jullien (2010), and our results offer theoretical support for it, as far as reference pricing gives an incentive for innovators to avoid therapeutic competition altogether, by developing drastic innovations that yields a monopoly position, which is their result, but if this is not possible, so that innovation always implies some degree of therapeutic competition, it is shown by us that reference pricing in this case has the opposite effect, in the sense that it gives incentives for innovations that are closer therapeutic substitutes to existing drugs.

4. Model

Consider a therapeutical market for patented prescription drugs, where consumers/patients are heterogenous - meaning that an existing medicine can be effective for some - but less effective for others - and uniformly distributed on a line of length 1. Accordingly, the total consumer mass is normalized to 1. There are two drugs available in the market, one incumbent drug, located at 0, and one entrant drug, the latter being positioned at $a > 0$. The distance between the two drugs, given by a, indicates how close therapeutic substitutes the two drugs are, giving an insight into the type of innovation taken by the new drug in the market. Likewise, the distance between drugs and patients determines the effectiveness and suitability of that same drug for that patient.

Each patient in the market demands one unit of drug treatment and chooses (or is prescribed) the drug that yields the highest utility. For a patient located at x and being prescribed drug i located at z_i, utility is

$$U = v - [c_i + t\,(z_i - x)^2], \qquad (1)$$

where v is the gross utility of the drug treatment, c_i is the patient copayment for drug i, $t > 0$ is a mismatch cost parameter, and the total mismatch costs are t times the square of the distance between the patient's location and the drug's location on the line. Given that drug 1 is the incumbent (old) drug, located at 0, and drug 2 is the entrant (new) drug, located at a, a patient located at x will have a utility of $v - (c_1 + tx^2)$ if consuming drug 1 and utility $v - [c_2 + t(a - x)^2]$ if consuming drug 2. Having the patient who is indifferent between the two drugs located at

$$\hat{x} = \frac{c_2 - c_1 + ta^2}{2ta}, \qquad (2)$$

all patients located to the left of $\hat{x}$ will be prescribed drug 1, while all patients to the right of $\hat{x}$ will be prescribed drug 2.

Following this, the demand for drug 1 and 2 are $D_1 = \hat{x}$ and $D_2 = 1 - \hat{x}$, which can be written as follows:

$$D_1 = \frac{c_2 - c_1 + ta^2}{2ta}, \tag{3}$$

$$D_2 = \frac{2ta - c_2 + c_1 - ta^2}{2ta}. \tag{4}$$

The sum of utilities of all patients in the market is therefore given by

$$U = \int_0^{\hat{x}} (v - c_1 - tx^2)\, dx + \int_{\hat{x}}^1 (v - c_2 - t(a-x)^2)\, dx. \tag{5}$$

So, the total patient utility can be simplified as

$$U = v - \hat{x}c_1 - (1-\hat{x})\, c_2 - t\left(\frac{1}{3} - a\,(1-\hat{x})\,(1-a+\hat{x})\right). \tag{6}$$

The objective function of the regulator is to maximize total health benefits minus total drug expenditures. Formally, this is given by

$$W = U - (p_1 - c_1)\,\hat{x} - \left(p_2 - c_2\right)(1-\hat{x}), \tag{7}$$

where p_1 and p_2 are the prices of drug 1 and 2, respectively. Using the expression for U, the regulator's objective can be written as

$$W = v - t\left(\frac{1}{3} - a\,(1-\hat{x})\,(1-a+\hat{x})\right) - p_1\hat{x} - p_2(1-\hat{x}). \tag{8}$$

The first two terms are the total health benefits, while the last two terms are the total drug expenditures ($p_1D_1 + p_2D_2$), partly paid by patients and partly paid by the government.

Both producers of drugs 1 and 2 aim to maximize their profits. For simplification purposes, it is assumed that once a drug is developed and approved in the market, the drug production costs are zero.

5. Therapeutic competition

In this section, the case of price competition in the post-innovation game (i.e., for a given location of the new drug) will be addressed, wherein the two drug producing companies are already present in the market, and in which they will simultaneously choose the price they intend to practice, under two different assumptions regarding the reimbursement scheme, namely *simple coinsurance* and *therapeutic reference pricing*.

5.1. Simple coinsurance

Under simple coinsurance, the patient copayment is a fixed percentage of the drug price, and given by

$$c_1^{SC} = \alpha\, p_1, \tag{9}$$

$$c_2^{SC} = \alpha\, p_2, \tag{10}$$

where $\alpha \in (0,1)$ is the coinsurance rate. Therefore, the profit-maximization problems that the producers of drugs 1 and 2 face are, respectively,

$$max_{p_1}\, \pi_1^{SC} = p_1 \times D_1 = \; p_1 \times \left(\frac{\alpha p_2 - \alpha p_1 + ta^2}{2ta}\right), \tag{11}$$

$$max_{p_2}\, \pi_2^{SC} = p_2 \times D_2 = \; p_2 \times \left(\frac{2ta \; - \; \alpha p_2 \; + \; \alpha p_1 \; - \; ta^2}{2ta}\right). \tag{12}$$

The best response functions of producer 1 and 2 are, respectively,

$$p_1 = \frac{ta^2 \; + \; \alpha p_2}{2\alpha}, \tag{13}$$

$$p_2 = \frac{-ta^2 \; + \; 2ta \; + \; \alpha p_1}{2\alpha}. \tag{14}$$

As these expressions imply, prices are strategic complements, meaning that the optimal price of each producer is increasing in the price of the other drug. If one producer increases the price charged, the profit-maximizing strategic response of the other producer will be to increase its price as well. This strategic complementarity builds on the fact that, all else equal, if for instance firm 2 increases the price (p_2 goes up), this triggers a shift in demand from drug 2 to drug 1, which has now become relatively cheaper. If the demand for drug 1 increases, this will result in a lower price elasticity of demand for that same drug, which in turn means that the profit-maximization price rises. Thus, it explains the reason why a higher price in either firm, results in a higher price for the other firm as well.

Simultaneously solving the pair of best-response functions yields the following equilibrium prices:

$$p_1^{SC} = \frac{ta\,(a+2)}{3\alpha}, \tag{15}$$

$$p_2^{SC} = \frac{ta\,(4-a)}{3\alpha}. \tag{16}$$

Substituting the equilibrium prices into the demand function of each firm yields

$$D_1^{SC} = \frac{1}{3} + \frac{a}{6}, \tag{17}$$

$$D_2^{SC} = \frac{2}{3} - \frac{a}{6}. \tag{18}$$

As theoretically expected, drug 2 has the highest price in equilibrium, which can be accounted for by the locational advantage that this drug has because it gets positioned later in the market, meaning that it will take up a position closer to the midpoint of the line, thereby also prompting drug 1 to practice lower prices in order to attract more demand. Subsequently, if drug 1 is located at 0, and drug 2 at $a < 1$, drug 2 will have higher demand, i.e. market share, if the prices are equal. All else equal, higher demand makes demand less price elastic, so the firm with the locational advantage will have an incentive to set higher prices.

Equilibrium profits are given by

$$\pi_1^{SC} = \frac{ta\,(2+a)^2}{18\alpha} \tag{19}$$

and

$$\pi_2^{SC} = \frac{ta\,(4-a)^2}{18\alpha}. \tag{20}$$

Drug 2 is more profitable than drug 1, as it commands both higher prices and market share.

Inserting the equilibrium values into the expression for total patient utility yields

$$U^{SC} = v - \frac{1}{3} - \frac{ta\left(8 + a\,(20-a)\right)}{36}, \tag{21}$$

while total drug expenditures, are given by

$$E^{SC} = \frac{ta\,(a^2 - 2a + 10)}{9\alpha}. \tag{22}$$

The relationships between the new drug's location and prices, demands and profits are given by

$$\frac{\partial p_1^{SC}}{\partial a} = \frac{2ta + 2t}{3\alpha} > 0, \tag{23}$$

$$\frac{\partial p_2^{SC}}{\partial a} = \frac{-2ta + 4t}{3\alpha} > 0, \tag{24}$$

$$\frac{\partial D_1^{SC}}{\partial a} = \frac{1}{6} > 0, \tag{25}$$

$$\frac{\partial D_2^{SC}}{\partial a} = -\frac{1}{6} < 0, \tag{26}$$

$$\frac{\partial \pi_1^{SC}}{\partial a} = \frac{3ta^2 + 8ta + 4t}{18\alpha} > 0, \tag{27}$$

$$\frac{\partial \pi_2^{SC}}{\partial a} = \frac{3ta^2 - 16ta + 16t}{18\alpha} > 0. \quad (28)$$

For both drugs, prices are positively impacted by a, which means that the greater a, that is the further away the new drug is positioned from the incumbent, the higher both prices will get. Conversely, the lower is a, meaning that the two drugs are closer substitutes, the lower are the prices, due to the intensified price competition. Additionally, if a increases, the profits for both drugs also increase.

Expectably, and with regard to the demand for the two drugs, while D_1^{SC} increases in a, D_2^{SC} is negatively affected by the same variable. In other words, whenever a increases, demand for drug 1 increases, whilst demand for drug 2 decreases.

The differences between prices, demands, profits, and copayments, can be formalized by

$$p_2^{SC} - p_1^{SC} = \frac{-2ta^2 + 2ta}{3\alpha} > 0, \quad (29)$$

$$D_2^{SC} - D_1^{SC} = \frac{1 - a}{3} > 0, \quad (30)$$

$$\pi_2^{SC} - \pi_1^{SC} = \frac{-2ta^2 + 2ta}{3\alpha} > 0, \quad (31)$$

$$c_2^{SC} - c_1^{SC} = \frac{-2ta^2 + 2ta}{3} > 0. \quad (32)$$

Proposition 1. Under simple coinsurance, a lower value of a increases the market share of the new drug but leads to lower prices and profits for both drugs.

To put it differently, the new drug's location determines the degree of horizontal differentiation, i.e. how close substitutes the two drugs are, which in turn determines the intensity of competition. The

intensity of price competition increases with the proximity between the two drugs, which lowers drug prices and profits.

5.2. Reference pricing

Under therapeutic reference pricing, the patient pays a share α up to the reference price, given by r, plus the entire price difference between p_i and r if the price of the drug is higher than r. Thus, the copayment for drug i depends on whether the price of drug i is below or above the reference price r. On the one hand, if $p_i < r$, the copayment is $\alpha\, p_i$. On the other hand, if $p_i > r$, the copayment is $\alpha r + (p_i - r)$. In many cases, the reference price is endogenously defined as the lowest price in the market. Since drug 2 has a locational advantage over drug 1, i.e. it is a better therapeutic match than drug 1 for a majority of the patients, the price of drug 1 will be lowest in equilibrium. Thereby, defining $r = p_i$, the copayments under therapeutic reference pricing are given by

$$c_1^{TRP} = \alpha\, p_1, \tag{33}$$

$$c_2^{TRP} = \alpha\, p_1 + (p_2 - p_1). \tag{34}$$

The profit-maximization problems that the producers of drugs 1 and 2 face are, respectively,

$$max_{p_1}\ \pi_1 = p_1 \times D_1 = p_1 \times \left(\frac{p_2 - p_1 + ta^2}{2ta}\right), \tag{35}$$

$$max_{p_2}\ \pi_2 = p_2 \times D_2 = p_2 \times \left(\frac{2ta - p_2 + p_1 - ta^2}{2ta}\right). \tag{36}$$

In consequence, the best responses from each producer will be

$$p_1 = \frac{ta^2 + p_2}{2} \tag{37}$$

and

$$p_2 = \frac{-ta^2 + 2ta + p_1}{2}. \quad (38)$$

As under simple coinsurance, prices are strategic complements also under reference pricing, precisely based on the same rationale.

Simultaneously solving the best-response functions, the equilibrium prices are given by

$$p_1^{TRP} = \frac{ta\,(a+2)}{3}, \quad (39)$$

$$p_2^{TRP} = \frac{ta\,(4-a)}{3}. \quad (40)$$

By substituting the equilibrium prices into the demand function of each firm, the market shares are found to be

$$D_1^{TRP} = \frac{1}{3} + \frac{a}{6}, \quad (41)$$

$$D_2^{TRP} = \frac{2}{3} - \frac{a}{6}, \quad (42)$$

which are identical to the case of simple coinsurance. Thus, drug 2 once more has both higher prices and market shares, a point of reasoning owing to the locational advantage still held by this particular drug.

Consequently, the expressions stating the profits are given by

$$\pi_1^{TRP} = \frac{ta\,(2+a)^2}{18}, \quad (43)$$

$$\pi_2^{TRP} = \frac{ta\,(4-a)^2}{18}. \quad (44)$$

Given the calculations, taking a greater market share, and practicing higher prices, it seems logical that once again drug 2 has higher profits than drug 1.

Total patient utility equals

$$U^{TRP} = v - \frac{1}{3} - \frac{ta\,(12\,(2+a)\,\alpha - (4-a)^2)}{36}, \tag{45}$$

while total drug expenditures are

$$E^{TRP} = \frac{ta\,(a^2 - 2a + 10)}{9}. \tag{46}$$

As before, the effects of drug location on prices, market shares and profits are given by

$$\frac{\partial p_1^{TRP}}{\partial a} = \frac{2ta + 2t}{3} > 0, \tag{47}$$

$$\frac{\partial p_2^{TRP}}{\partial a} = \frac{-2ta + 4t}{3} > 0, \tag{48}$$

$$\frac{\partial D_1^{TRP}}{\partial a} = \frac{1}{6} > 0, \tag{49}$$

$$\frac{\partial D_2^{TRP}}{\partial a} = -\frac{1}{6} < 0, \tag{50}$$

$$\frac{\partial \pi_1^{TRP}}{\partial a} = \frac{3ta^2 + 8ta + 4t}{18} > 0, \tag{51}$$

$$\frac{\partial \pi_2^{TRP}}{\partial a} = \frac{3ta^2 - 16ta + 16t}{18} > 0. \tag{52}$$

Differences between prices, demands, profits, and copayments, are formally expressed as

$$p_2^{TRP} - p_1^{TRP} = \frac{-2ta^2 + 2ta}{3} > 0, \tag{53}$$

$$\pi_2^{TRP} - \pi_1^{TRP} = \frac{-2ta^2 + 2ta}{3} > 0, \tag{54}$$

$$c_2^{TRP} - c_1^{TRP} = \frac{-2ta^2 + 2ta}{3} > 0, \tag{55}$$

$$D_2^{TRP} - D_1^{TRP} = \frac{1-a}{3} > 0. \tag{56}$$

Regarding the effects of the new drug's location on prices, market shares and profits, Proposition 1 is equally valid under therapeutic reference pricing.

A comparison of the two reimbursement schemes with respect to equilibrium prices and profits yields

$$p_1^{TRP} - p_1^{SC} = -\frac{(1-\alpha)\,(ta^2 + 2ta)}{3\alpha} < 0, \tag{57}$$

$$p_2^{TRP} - p_2^{SC} = -\frac{(1-\alpha)\,(-ta^2 + 4ta)}{3\alpha} < 0, \tag{58}$$

$$\pi_1^{TRP} - \pi_1^{SC} = -\frac{(1-\alpha)\,(ta^3 + 4ta^2 + 4ta)}{18\alpha} < 0, \tag{59}$$

$$\pi_2^{TRP} - \pi_2^{SC} = -\frac{(1-\alpha)\,(ta^3 + 4ta^2 + 4ta)}{18\alpha} < 0, \tag{60}$$

$$c_1^{TRP} - c_1^{SC} = -\frac{(1-\alpha)\,(ta^2 + 2ta)}{3} < 0, \tag{61}$$

$$c_2^{TRP} - c_2^{SC} = -\frac{(1-\alpha)\,(ta^2 + 2ta)}{3} < 0. \tag{62}$$

Proposition 2. Prices, profits, and copayments are lower for both drugs under TRP than in the simple coinsurance scenario, while market shares are equal under both reimbursement schemes.

Notice that, for $\alpha = 1$, the equilibrium outcomes are identical under the two different reimbursement schemes. Thus, the effect of TRP on prices is the same as if all patients had to pay the full drug price under simple coinsurance. The rationale underlying the comparatively lower prices under TRP than in simple coinsurance stems back to the fact that, under TRP, the marginal coinsurance rate is 1 above the reference price, because patients have to pay the full price difference between the drug price and the reference price for drugs that cost more than the benchmark price. This increases the price elasticity of the demand for the high-priced drug, allowing the drug producer to optimally lower its price. Since prices are strategic complements, the producer of the low-priced drug will respond by also lowering its price.

As prices are lower while market shares are unaffected, the profits of both firms are also lower under TRP. For the same reason, total drug expenditures are also lower under TRP.

All patients are better off under TRP, since copayments are lower for both drugs and every patient is prescribed the exact same drug under both reimbursement schemes, as the location of the indifferent patient remains unchanged. Even if the patients who are prescribed the more expensive drug have to pay a larger share of the price under TRP, their copayment is nevertheless lower because of the drop in the drug price.

6. Drug innovation

In this section, the drug innovation incentives are analyzed by considering the following two-stage game. In the first stage, the entrant decides which type of drug to develop and to enter the market with. The cost of drug innovation is assumed to depend on the therapeutic distance to the existing drug in the market, in the sense that it is more costly to develop a drug that is more therapeutically differentiated from the existing drug. In the second stage, the two drug producers will compete in prices, as studied in the previous section.

The entrant will be facing a trade-off, because given the assumption that the cost of innovation depends on the distance to the existing drug in the market, on the one hand if it chooses to produce a drug that is very similar to the pre-existing one, it will naturally be cheaper, but will also lead to tough price competition. On the other hand, although it is more expensive, by developing a more differentiated medicine, it will entail additional benefits for patients and lead to less intense price competition. The main aim of the analysis is to examine how this trade-off depends on the reimbursement scheme. As in the previous section, we consider in turn the cases of simple coinsurance and therapeutic reference pricing.

Both producers are profit maximisers, and as for the producer of drug 1, the profits are $\pi_1 = p_1 D_1$, where D_1 is the demand for drug 1. Meanwhile, for the producer of the new drug, it is imperative to distinguish between profits before and after innovation. After the new drug has been developed and approved, the profits are $\pi_2 = p_2 D_2$, where D_2 is the demand for drug 2 (the total demand being equal to 1, it can be noticed that $D_2 = 1 - D_1$). However, before the drug is developed, profits are given by $\Pi_2 = \pi_2 - ka^2 = p_2 D_2 - ka^2$, where the term ka^2 measures the costs of developing the drug, and $k > 0$ is a cost parameter. In short, at the pre-innovation stage, producer 2 chooses a to maximize Π_2, while in the post-innovation stage, producer 2 chooses p_2 to maximize π_2.

6.1. Simple coinsurance

Under simple coinsurance, the profit-maximization problem that the producer of drug 2 faces at the first stage of the game is given by

$$max_a \Pi_2^{SC} = \pi_2^{SC} - ka^2, \tag{63}$$

where

$$\pi_2^{SC} = \frac{ta\,(4-a)^2}{18\alpha} \tag{64}$$

is the equilibrium second-stage profits, as derived in the previous section. The first-order condition is given by

$$\frac{\partial \Pi_2^{SC}}{\partial a} = \frac{\partial \pi_2^{SC}}{\partial a} - 2ka = 0. \tag{65}$$

The first term is the marginal revenue, i.e., the marginal effect of therapeutic differentiation on second-stage profits, and the second term is the marginal cost. Using the expression for the second-stage profits, the marginal revenue of therapeutic differentiation is given by

$$\frac{\partial \Pi_2^{SC}}{\partial a} = \frac{(4-a)(4-3a)t}{18\alpha} > 0, \tag{66}$$

meaning that, all else equal, a higher degree of differentiation increases second-stage profits.

Accordingly, the optimal solution of the first-stage profit-maximization problem of drug 2 is

$$a_{SC}^* = \frac{2}{3t}\left(4t + 9k\alpha - \sqrt{9k\alpha\,(8t + 9k\alpha) + 4t^2}\right). \tag{67}$$

The second-order condition is given by

$$\frac{\partial^2 \Pi^{SC}}{\partial a^2} = \frac{t\,(3a-8)}{9\alpha} - 2k < 0, \tag{68}$$

which holds for all $a \in (0,1),$ implying that the first-order condition defines a maximum.

The equilibrium prices in the post-innovation game are then found by inserting a^* into the relevant expressions previously derived.

6.2. Reference pricing

Under reference pricing, the first-stage profit-maximization problem that the producer of drug 2 faces is given by

$$max_a \Pi_2^{TRP} = \pi_2^{TRP} - ka^2, \tag{69}$$

where

$$\pi_2^{TRP} = \frac{ta\,(4-a)^2}{18} \tag{70}$$

is the equilibrium second-stage profit. The first-order condition is given by

$$\frac{\partial \Pi_2^{TRP}}{\partial a} = \frac{\partial \pi_2^{TRP}}{\partial a} - 2ka = 0, \tag{71}$$

where

$$\frac{\partial \Pi_2^{TRP}}{\partial a} = \frac{(4-a)(4-3a)t}{18} > 0. \tag{72}$$

The explicit expression for the optimal solution of the profit-maximization problem of drug 2 is

$$a^*_{TRP} = \frac{2}{3t}\left(4t + 9k - \sqrt{9k\,(8t + 9k) + 4t^2}\right). \quad (73)$$

The second-order condition is given by

$$\frac{\partial^2 \Pi^{TRP}}{\partial a^2} = -\frac{t\,(8 - 3a)}{9\alpha} - 2k < 0, \quad (74)$$

which holds for all $a \in (0,1)$, entailing that the first-order condition defines a maximum.

As before, the equilibrium expressions in the second-stage game are obtained by substituting a^* into the relevant expressions derived earlier.

6.3. The effects of therapeutic reference pricing on innovation incentives

At the pre-innovation stage, and through the condition that defines the optimal solution of the profit-maximization problem of drug 2 – the optimal location (a^*) for drug 2 to be placed - it is clear that while marginal costs are the same under simple coinsurance and under reference pricing, marginal revenue differs across the two reimbursement schemes.

Through the comparison of the two first-order conditions in each scenario, it follows that

$$\frac{\partial \pi_2^{SC}}{\partial a} > \frac{\partial \pi_2^{TRP}}{\partial a} \quad (75)$$

for all $\alpha < 1$, which implies that

$$a^*_{SC} > a^*_{TRP}, \quad (76)$$

meaning that the incentives to differentiate are stronger under simple coinsurance than under therapeutic reference pricing.

Note that, for any of the reimbursement schemes, the equilibrium prices are increasing in the degree of therapeutic differentiation:

$$\frac{\partial p_i^j}{\partial a} > 0\,, j = TRP, SC. \quad (77)$$

Furthermore, when switching from simple coinsurance to reference pricing, for a given a, equilibrium prices will be lower:

$$p_i^{TRP}(a) - p_i^{SC}(a) < 0. \qquad (78)$$

Coupled with that, reference pricing also entails that a is lower, which leads to even lower prices, in comparison. Consequently,

$$p_i^{TRP}(a_{TRP}^*) - p_i^{SC}(a_{SC}^*) < 0. \qquad (79)$$

This difference – when a is optimally chosen – will be higher than the one shown in equation (78), in absolute value. These results can be summarized by Proposition 3.

Proposition 3. The equilibrium degree of therapeutic differentiation (a^*) is lower under TRP than under simple coinsurance, which in turn amplifies the price-reducing effects of TRP.

In brief, for any value of a, switching from simple coinsurance to therapeutic reference pricing effectively makes the incumbent drug relatively more expensive for patients, which is advantageous for the new drug, all else equal. Overall, this reduces the benefits of therapeutic differentiation for the new drug, so the optimal location will be closer to the old drug. All of which makes the difference between prices in simple coinsurance and TRP even more substantial once innovation incentives are taken into account.

Furthermore, and since there are now two counteracting effects towards patients, being that TRP lowers prices, which is beneficial for them, but simultaneously leads to less product differentiation, hence increasing aggregate mismatch costs, which in turn does not benefit patients as it reduces patient utility, it is important to clarify how this impacts them. These effects are evaluated by a set of numerical examples.

Table 1 – Simple coinsurance with $\alpha = 0,2$

	t=1			k=1		
	k = 1	**k = 2**	**k = 3**	**t = 1**	**t=2**	**t=3**
a^*_{SC}	0,77	0,56	0,44	0,77	0,96	1
p_1	3,53	2,37	1,79	3,53	9,42	15
p_2	4,13	3,20	2,62	4,13	9,70	15
c_1	0,71	0,47	0,36	0,71	1,88	3
c_2	0,83	0,64	0,52	0,83	1,94	3
D_1	0,46	0,43	0,41	0,46	0,49	0,50
D_2	0,54	0,57	0,59	0,54	0,51	0,50
π_1	2,22	1,01	0,73	2,22	4,64	7,5
π_2	1,63	1,83	1,55	1,63	4,92	7,5
U	$v - 0,82$	$v - 0,62$	$v - 0,54$	$v - 0,82$	$v - 1,73$	$v - 2,58$
E	3,85	2,85	2,28	3,85	9,57	15
W	$v - 3,90$	$v - 2,90$	$v - 2,37$	$v - 3,90$	$v - 9,38$	$v - 14,58$

Table 2 – Reference pricing with $\alpha = 0,2$

	t=1			k=1		
	k = 1	**k = 2**	**k = 3**	**t = 1**	**t=2**	**t=3**
a^*_{TRP}	0,31	0,18	0,13	0,31	0,49	0,61
p_1	0,24	0,13	0,09	0,24	0,82	1,60
p_2	0,39	0,23	0,17	0,39	1,15	2,07
c_1	0,05	0,03	0,03	0,05	0,16	0,32
c_2	0,19	0,13	0,10	0,19	0,50	0,79
D_1	0,39	0,36	0,35	0,39	0,42	0,44
D_2	0,61	0,64	0,65	0,61	0,58	0,56
π_1	0,09	0,05	0,03	0,09	0,34	0,70
π_2	0,24	0,15	0,11	0,24	0,67	1,17
U	$v - 0,26$	$v - 0,29$	$v - 0,30$	$v - 0,26$	$v - 0,16$	$v - 0,07$
E	0,33	0,20	0,14	0,33	1,01	1,87
W	$v - 0,46$	$v - 0,39$	$v - 0,37$	$v - 0,46$	$v - 0,81$	$v - 1,35$

Table 3 – Simple coinsurance with $\alpha = 0,5$

	t=1			k=1		
	k = 1	**k = 2**	**k = 3**	**t = 1**	**t=2**	**t=3**
a_{SC}^{*}	0,49	0,31	0,23	0,49	0,70	0,82
p_1	0,82	0,48	0,34	0,82	2,51	4,62
p_2	1,15	0,77	0,58	1,15	3,07	5,21
c_1	0,41	0,24	0,17	0,41	1,26	2,31
c_2	0,58	0,39	0,29	0,58	1,54	2,60
D_1	0,42	0,39	0,37	0,42	0,45	0,47
D_2	0,58	0,61	0,63	0,58	0,55	0,53
π_1	0,34	0,19	0,13	0,34	1,13	2,17
π_2	0,67	0,47	0,36	0,67	1,69	2,76
U	$v - 0,57$	$v - 0,46$	$v - 0,41$	$v - 0,57$	$v - 1,17$	$v - 1,95$
E	1,01	0,66	0,49	1,01	2,82	4,93
W	$v - 1,07$	$v - 0,79$	$v - 0,66$	$v - 1,07$	$v - 2,57$	$v - 4,42$

Table 4 – Reference pricing with $\alpha = 0,5$

	t=1			k=1		
	k = 1	**k = 2**	**k = 3**	**t = 1**	**t=2**	**t=3**
a_{TRP}^{*}	0,31	0,18	0,13	0,31	0,49	0,61
p_1	0,24	0,13	0,09	0,24	0,82	1,60
p_2	0,39	0,23	0,17	0,39	1,15	2,07
c_1	0,12	0,07	0,05	0,12	0,41	0,80
c_2	0,26	0,17	0,12	0,26	0,74	1,27
D_1	0,39	0,36	0,35	0,39	0,42	0,44
D_2	0,61	0,64	0,65	0,61	0,58	0,56
π_1	0,09	0,05	0,03	0,09	0,34	0,70
π_2	0,24	0,15	0,11	0,24	0,67	1,17
U	$v - 0,34$	$v - 0,33$	$v - 0,33$	$v - 0,34$	$v - 0,41$	$v - 0,55$
E	0,33	0,20	0,14	0,33	1,01	1,87
W	$v - 0,47$	$v - 0,39$	$v - 0,38$	$v - 0,47$	$v - 0,82$	$v - 1,35$

Through the analysis of the tables relating the numerical examples, one concludes that, within the scenario of simple coinsurance, as the coinsurance rate (α) increases, all else being equal, the new drug's optimal location (a_{SC}^*) is bound to decrease, i.e., drug 2 will be brought closer to drug 1, meaning less product differentiation. As a result, the prices of both drugs drop, as price competition increases. Naturally, copayments follow this downward price trend. Simultaneously, and as expected, demand for drug 1 decreases while demand for drug 2 increases. In spite of this, profits on both drugs decrease. On the whole, under simple coinsurance, an increase in the coinsurance rate triggers an increase in total patient utility, and an accompanying decrease in total drug expenditures.

By contrast, and under therapeutic reference pricing, an increased coinsurance rate, all else being equal, does not have any impact on the optimal location of the new drug, a_{TRP}^* remains constant. Likewise, the prices for both drugs stay unaffected as well, yet their copayments increase. Accordingly, demand for the two drugs remains the same, which coupled with the aforementioned, also leads to unchanged profits. All in all, in the reference pricing scenario, an increase in the coinsurance rate translates into a decrease in total patient utility, and no change in overall drug expenditures.

Upon examining the effect that the mismatch cost parameter (t) has on the equilibrium, all else constant, it can be perceived that as this variable increases, for both scenarios, the optimal placement of drug 2 is also set to increase, thereby pushing both prices up, as well as the copayments. In turn, and once again in the two settings, demand for drug 1 increases, so demand for drug 2 decreases, although both drugs see their profits increase. All things considered, under simple coinsurance, an increase of the mismatch cost parameter, results in an overall reduction of total patient utility. Whereas, under reference pricing, an increase in the mismatch cost parameter only increases total patient utility if the coinsurance rate is sufficiently low. This is because a lower coinsurance rate for the patient translates into higher cost coverage by the government, which eases the burden on patients, mitigating the native effect of the increased t, because if not, total patient utility is decreased instead. At last, the result in both scenarios, when the mismatch cost parameter is increased, is an increase in total drug expenditures.

Now with regards to the effect of the cost parameter (k) in the equilibrium, everything else constant, it can be established that the increase of this variable has a diminishing effect on the location that drug 2 takes on in both simple coinsurance and reference pricing settings,

meaning that it fosters less innovation, which in turn leads to lower prices for drug 1 and 2 since price competition increases. This also leads to a reduction in the demand for drug 1, and an enlargement in demand for drug 2. Thus, under the same conditions, copayments also decrease. Hence, as for the profits, while drug 1 sees its profits diminished in both scenarios, drug 2 also sees them decreased, except when, in simple coinsurance, the coinsurance rate is so reduced that it prevents this to happen, showing no pattern in this case. In short, under simple coinsurance, the increase of the cost parameter makes total patient utility increase, and under reference pricing this increase in total patient utility only happens when the coinsurance rate is high enough, otherwise it decreases total patient utility. Concerning total drug expenditures, these are decreased, in both settings, by the increase in the cost parameter.

Finally, regarding the welfare trade off, which consists in maximizing health benefits while incurring the minimum expenditures as possible, it is important to address the patient utility across the two reimbursement schemes. Therefore, by means of these numerical examples, it can be perceived that the reduction in copayments, due to price reductions, always more than outweighs any increase in mismatch costs for the patients. Hence, patients always benefit from TRP, at least in these particular examples. To sum up, the regulator consistently prefers TRP over simple coinsurance, since the effects of lower prices always outweigh the effects of higher mismatch costs.

6.4. Optimal drug reimbursement policy

Under the assumption that is possible for the policy maker to commit to a particular reimbursement scheme as a long-term decision prior to the drug innovation decisions being made, for each set of parameter values of the previously presented numerical examples, the optimal policy – therapeutic reference pricing or simple coinsurance – is found by a comparison of the objective function of the regulator (W) across the two regimes. It is also supposed that the government is interested in maximizing total health benefits net of drug purchasing costs. To put it differently, it is reasonable to assume that the regulator is not concerned by the profits of the drug companies, which is a realistic assumption for most countries that lack a significant pharmaceutical industry.

According to the comparative analysis, it can be concluded that, given these conditions, the optimal choice to reimburse patient's drug expenditures is through therapeutic reference pricing, as it is the one that maximizes total patient utility minus drug expenditures. This can be

further explained, as stated previously, also by the effects of lower drug prices that ultimately counterbalance the impacts of greater mismatch costs. Consequently, due to the diminishing benefits of therapeutic differentiation linked to TRP, the optimal location for the new drug to take in the market will be closer to the existing one, meaning that the most suitable type of drug to enter the market with would be more along the lines of “me-too” innovation, rather than breakthrough innovation.

7. Conclusion

Innovation incentives and reimbursement schemes decisions by the market regulator were analyzed, focusing on pharmaceutical markets, with greater emphasis on those with a patent-protected drug. In this context, the reimbursement schemes being compared were the simple coinsurance and the therapeutic reference pricing, with the latter being the subject of attention since, despite being less frequent, it is the most significant for on-patent drugs. Regarding innovation, these effects might benefit "me-too" innovation over drastic innovation, or the other way around. Additionally, the outcomes of prices, patient welfare and pharmaceutical expenditures were also addressed.

It should be noted that we considered a market for prescription drugs, in which an on-patent drug is already in place, and where patients are heterogeneous. It was also held that there is another firm that tries to innovate and develop a new drug for this market. Thus, the new drug can either be quite similar to the existing one, or it can be more differentiated. Our findings suggest that, regardless of this choice, the prices of both drugs are strategic complements, meaning that if one producer raises the price, the other producer will follow suit as a profit-maximizing strategic maneuver.

Additionally, when comparing simple coinsurance and therapeutic reference pricing (TRP), it was verified that it is TRP that delivers the lowest prices, profits, copayments and total drug expenditures for both drugs, which is in line with the work by Brekke, Königbauer and Straume (2007), as quoted in the literature review. Unquestionably, as far as we are concerned, all patients are better off under TRP. Further regarding the copayments, and as per our insights, even the patients who are prescribed the costlier drug, and therefore have to pay a larger share of the price, their copayment is still lower under TRP, because of the price drop.

Correspondingly, when innovation incentives are taken into consideration, patients are expected to be even better under TRP, since TRP's price-lowering effects are amplified by the fact that the equilibrium degree of therapeutic differentiation is found to be lower under TRP than under simple coinsurance. This being the most significant finding, and the one that disagrees with the existing literature previously discussed. Thus, this dissertation builds on the work by Bardey, Bommier and Jullien (2010), as we demonstrate that reference pricing in this case has the opposite

effect, in that it encourages innovations that are closer therapeutic substitutes to those that are already available, whereas reference pricing typically gives innovators an incentive to avoid therapeutic competition altogether by developing drastic innovations that yield a monopoly position, which is their result.

As far as the regulator's incentives are concerned, and since the regulator seeks to maximize total patient utility minus drug expenditures, it faces a trade-off. On the one hand, if the innovating firm enters the market with a drug that is substantially similar to the drug already on the market, drug expenditures are minimized because this translates into strong price competition between the firms. On the other hand, the health advantages to patients are greater if the innovating company enters the market with a more distinctive product. As such, when innovation incentives are taken into account, our results indicate that the effects of lower pricing always outweigh the drawbacks of higher mismatch costs, hence the regulator consistently prefers TRP over simple coinsurance.

In the final analysis, and with regard to the optimal drug reimbursement policy, and presuming it is possible for the policy maker to commit to a specific reimbursement plan in the long run before decisions about drug innovation are taken, our insights indicate that "me-too" innovation, rather than breakthrough innovation, would be the most optimal type of drug to introduce to the market.

On a concluding note, it was possible, through the idealized and developed model, to address the intended subject of analysis. Also worthy of mention is the fact that some of the aforementioned results regarding optimal policy were obtained through numerical instances, which may make them somewhat less general.

References

Antoñanzas, F., Juárez-Castelló, C., & Rodríguez-Ibeas, R. (2011). Innovation, loyalty and generic competition in pharmaceutical markets. *Journal of the Spanish Economic Association*, *2*(1), 75–95. https://doi.org/10.1007/s13209-010-0032-5

Aronson, J. K., & Green, A. R. (2020). Me-too pharmaceutical products: History, definitions, examples, and relevance to drug shortages and essential medicines lists. *British Journal of Clinical Pharmacology*, *86*(11), 2114–2122. https://doi.org/10.1111/bcp.14327

Bardey, D., Bommier, A., & Jullien, B. (2010). Retail price regulation and innovation: Reference pricing in the pharmaceutical industry. *Journal of Health Economics*, *29*(2), 303–316. https://doi.org/10.1016/j.jhealeco.2009.11.015

Brekke, K. R., Canta, C., & Straume, O. R. (2016). Reference pricing with endogenous generic entry. *Journal of Health Economics*, *50*(2016), 312–329. https://doi.org/10.1016/j.jhealeco.2016.04.003

Brekke, K. R., Grasdal, A. L., & Holmås, T. H. (2009). Regulation and pricing of pharmaceuticals: Reference pricing or price cap regulation? *European Economic Review*, *53*(2), 170–185. https://doi.org/10.1016/j.euroecorev.2008.03.004

Brekke, K. R., Holmås, T. H., & Straume, O. R. (2011). Reference pricing, competition, and pharmaceutical expenditures: Theory and evidence from a natural experiment. *Journal of Public Economics*, *95*(7–8), 624–638. https://doi.org/10.1016/j.jpubeco.2010.11.015

Brekke, K. R., Königbauer, I., & Straume, O. R. (2007). Reference pricing of pharmaceuticals. *Journal of Health Economics*, *26*(3), 613–642. https://doi.org/10.1016/j.jhealeco.2006.11.003

Bryce, C. L., & Cline, K. E. (1998). The Supply and Use of Selected Medical Technologies. *Health Affairs*, *17*(1), 213–224. https://doi.org/10.1377/hlthaff.17.1.213

Danzon, P. M., & Keuffel, E. (2005). *Regulation of the Pharmaceutical Industry*. The Wharton School, University of Pennsylvania.

Doganoglu, T., & Inceoglu, F. (2014). Licensing of a drastic innovation with product differentiation. *Manchester School*, *82*(3), 296–321. https://doi.org/10.1111/manc.12025

Eger, S., & Mahlich, J. C. (2014). Pharmaceutical regulation in Europe and its impact on corporate R&D. *Geography and Natural Resources*, *4*(1), 1–9. https://doi.org/10.1186/s13561-014-0023-5

Gagnon, M. A. (2013). Corruption of pharmaceutical markets: Addressing the misalignment of financial incentives and public health. *Journal of Law, Medicine and Ethics*, *41*(3), 571–580. https://doi.org/10.1111/jlme.12066

Galizzi, M. M., Ghislandi, S., & Miraldo, M. (2011). Effects of reference pricing in pharmaceutical markets: A review. *PharmacoEconomics*, *29*(1), 17–33. https://doi.org/10.2165/11537860-000000000-00000

Ganuza, J. J., Llobet, G., & Domínguez, B. (2009). R&D in the pharmaceutical industry: A world of small innovations. *Management Science*, *55*(4), 539–551. https://doi.org/10.1287/mnsc.1080.0959

Ghislandi, S. (2011). Competition and the Reference Pricing Scheme for pharmaceuticals. *Journal of Health Economics*, *30*(6), 1137–1149. https://doi.org/10.1016/j.jhealeco.2011.08.010

Golec, J., Hegde, S., & Vernon, J. A. (2010). Pharmaceutical R&D spending and threats of price regulation. *Journal of Financial and Quantitative Analysis*, *45*(1), 239–264. https://doi.org/10.1017/S0022109009990512

Gonçalves, R., & Rodrigues, V. (2018). Reference Pricing with Elastic Demand for Pharmaceuticals. *Scandinavian Journal of Economics*, *120*(1), 159–182. https://doi.org/10.1111/sjoe.12207

González, P., Macho-Stadler, I., & Pérez-Castrillo, D. (2016). Private versus social incentives for pharmaceutical innovation. *Journal of Health Economics*, *50*, 286–297. https://doi.org/10.1016/j.jhealeco.2015.12.003

Hall, B. H. (2007). Patents and patent policy. *Oxford Review of Economic Policy*, *23*(4), 568–587. https://doi.org/10.1093/icb/grm037

Hollis, A. (2004). *Me-too drugs: is there a problem ?* (pp. 1–8). University of Calgary.

Hotelling, H. (1929). Stability in competition. *The Econonomic Journal*, *39*(153), 41–57. https://doi.org/https://doi.org/10.2307/2224214

Kaiser, U., Mendez, S. J., Rønde, T., & Ullrich, H. (2014). Regulation of pharmaceutical prices: Evidence from a reference price reform in Denmark. *Journal of Health Economics*, *36*(1), 174–187. https://doi.org/10.1016/j.jhealeco.2014.04.003

López-Casasnovas, G., & Puig-Junoy, J. (2000). Review of the Literature on reference pricing. *J. Puig-Junoy / Health Policy*, *54*(00), 100–107. www.elsevier.com/locate/healthpol

Marđetko, N., & Kos, M. (2018). Introduction of therapeutic reference pricing in Slovenia and its

economic consequences. *European Journal of Health Economics*, *19*(4), 571–584. https://doi.org/10.1007/s10198-017-0903-9

Mikulic, M. (2020). *Global pharmaceutical R&D spending 2010-2024*. https://www.statista.com/statistics/309466/global-r-and-d-expenditure-for-pharmaceuticals/

Miraldo, M. (2009). Reference pricing and firms' pricing strategies. *Journal of Health Economics*, *28*(1), 176–197. https://doi.org/10.1016/j.jhealeco.2008.09.006

Nawrat, A. (2019). *Exploring companies' manipulation of pharma patents*. From Evergreening to Thicketing: Exploring the Manipulation of Pharma Patents. https://www.pharmaceutical-technology.com/features/pharma-patents-manpulation/

OECD. (2019). *Health resources - Pharmaceutical spending*. https://data.oecd.org/healthres/pharmaceutical-spending.htm

OECD. (2021). Pharmaceutical spending. In *Health at a Glance 2021* (Issue November). https://doi.org/10.1787/19991312

OECD. (2001). Competition and Regulation Issues in the Pharmaceutical Industry. *Competition and Regulation Issues in the Pharmaceutical Industry*, *4*(3), 1–59. https://doi.org/10.1787/clp-v4-art10-en

Pavcnik, N. (2002). Do Pharmaceutical Prices Respond to Potential Patient Out-of-Pocket Expenses? *The RAND Journal of Economics*, *33*(3), 469. https://doi.org/10.2307/3087468

Puig-Junoy, J. (2005). What is required to evaluate the impact of pharmaceutical reference pricing? *Applied Health Economics and Health Policy*, *4*(2), 87–98. https://doi.org/10.2165/00148365-200504020-00003

Roberts, P. W. (1999). Product innovation, product-market competition and persistent profitability in the U.S. pharmaceutical industry. *Strategic Management Journal*, *20*(7), 655–670. https://doi.org/10.1002/(sici)1097-0266(199907)20:7<655::aid-smj44>3.0.co;2-p

Scherer, F. M. (2000). The pharmaceutical industry. In J. P. Culyer, Antonhy J.; Newhouse (Ed.), *Handbook of Health Economics* (Vol. 1, pp. 1297–1336). Elsevier B.V. https://doi.org/10.1016/S1574-0064(00)80038-4

Shaikh, M., Del Giudice, P., & Kourouklis, D. (2021). Revisiting the Relationship Between Price Regulation and Pharmaceutical R&D Investment. *Applied Health Economics and Health Policy*, *19*(2), 217–229. https://doi.org/10.1007/s40258-020-00601-9

Stoneman, P. (1995). Markets for Technology: Knowledge, Innovation and Appropriability. In *Handbook of the economics of innovation and technological change* (pp. 100–106). Oxford.

WHO. (2018). *Medicines reimbursement policies in Europe*. WHO.