

# Pharmaceutical innovation, reference pricing and therapeutic classes <sup>1</sup>

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## **Abstract**

This paper is a first attempt to model the effects of reference pricing on the innovation effort of pharmaceutical firms. The model is based on a dynamic game involving three types of agents: pharmaceutical firms, consumers and a regulatory entity. The game includes research stages where the innovation efforts by the firms are determined and introductory stages where a price for a new medicament is fixed. We model the negotiation between the drug owner and the regulator to fix the price, first without legal constraint, second under the regime of reference pricing in therapeutic classes. We then solve the innovation game where the firms anticipate the results of the negotiation round on prices. We thus consider the effect of the therapeutic class regulation on both prices and the innovation pace. The final stage consists in calibrating the model with a small data on anti-statine in France and simulates the effect of the change in regulatory regime.

**Keywords:** innovation, mee-too, reference pricing, pharmaceutical laboratories.

**Jel codes:** I18, L11, L15, L51.

# 1 Introduction

Pharmaceutical expenditures have dramatically increased in most of developed countries during the two last decades. In United States for example, spending on outpatient grew at a rate of 17 percent in 1999 whereas total health expenditure only grew at a rate of 3.3 percent during the same year (Danzon and Pauly, 2002). As it is noticed by these two authors, this trend in drug spending is related to the growth in drug coverage. According to Weisbrod (1991), more health insurance coverage implies a higher rate of R&D and technological change in health sector that generates more health expenditures which increases the demand of coverage. Danzon and Pauly explain the relation between coverage and drugs spending by the reverse effect: the growth of drug spending comes from technological change in health sector and the extent of coverage.

Two main theories dealing with patients' overconsumption can explain the Danzon and Pauly's point of view. The first-one is the **ex post** moral hazard theory described by Pauly (1968), the fact that health care spending increases with health insurance coverage. The second theory that aims at explaining health care overconsumption is the supply induced demand (SID) revealed by Rice (1993). In this theory, it is postulated that health care consumption decisions come from physicians and do not really result from patients' choices. In despite of their opposite assumptions, recent models such as Ma and McGuire (1997) and Eggleston (2000) combine both effects **i.e ex post** moral hazard and SID behaviors. They show that incentives have to be splitted between physicians and patients, the latter having to pay some co-payments. Without separate the respective roles of patients and physicians, Danzon and Pauly (2002) estimate that **ex post** moral hazard behaviors explain between one-four and one-half of the increase in drug consumption. Nevertheless, inefficiencies generated by patients' overconsumption can be reduced by increasing the share of the health care expenditure through co-payment mechanisms.<sup>1</sup>

In this line of thought, over the last few years, several countries - starting with Germany - have adopted the principle of drug reimbursement based on therapeutic equivalence (TE). Simply put, drugs are divided into different

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<sup>1</sup>See for example Zeckhauser (1970), Manning and Marquis (1996) and Blomqvist (1997).

classes according to their active agents and the pathologies they are supposed to treat. All drugs within a given therapeutic class are reimbursed on the same basis. Thus, for any drug consumed, and whatever the price paid by the patient, the latter receives a reimbursement which depends solely on the therapeutic class to which the drug belongs. Manufacturers remain free to set their prices and the part of drugs consumption paid by policy holders is, under the traditional form of reference pricing, the difference between prices set by laboratories and the reference price (RP), multiplied by the copayment rate applied in their health insurance contract.<sup>2</sup> Obviously, the introduction of therapeutic equivalence explicitly aims at reducing public expenditure and more precisely inefficiencies generated by patients' health care overconsumption.

Prescriptions, especially prescriptions of high quality drugs, are clearly one way for physicians to induce patients' demand. To limit this kind of behaviors, RP is a manner to introduce additional copayments into patients' drugs consumptions, letting the couple patient-physician in front of a trade-off between cost / quality. Actually, RP allows to provide incentives for cost conscious use of resource (Danzon, 2003).<sup>3</sup> Indeed, Bardey and Lesur (2006) show how copayments influence physicians' ability to induce demand. Confronted to a RP mechanism, the couple patient-physician may choose cheaper drugs *i.e.* me-too products or generics in order to reduce patients' bills. In Germany, since 1997, physicians prescribing drugs with a price above the RP have to explain to their patients motivations of their prescriptions. In Germany, two-third of physicians admitted that they change their prescriptions after the introduction of RP and substitute more often brand-name products by generics. Obviously, in case of important vertical differentiation due to an imperfect substitution between drugs, such therapeutic referencing can be inefficient if patients do not take the best drugs available to treat their disease and moreover introduces some inequity aspects. Danzon and Liu (1996) explain that with this kind of regulation, the demand for drugs is kinked at the reference price. When they have to pay some copayments, patients demand is elastic for price above the RPs, the elasticity depending

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<sup>2</sup>See Lopez-Casanovas and Puig-Junoy (2000) for more details on RPs' characteristics.

<sup>3</sup>*Ex post* moral hazard phenomenon is sometimes presented as a contract incompleteness problem in the sense that health risk is too complex to plan some lump-sum payments in each state of nature. In response to this point, if we ignore quantity effects, RP can be viewed as a manner to introduce lump-sum payments for each pathology.

of drugs substitutability degrees, and inelastic for price below.

Obviously, physicians prescriptions and pharmaceutical firms strategies are linked. Confronted to a RP regulation or generics entry, manufacturers can have two possible reactions. The first-one is an increase of brand-name drugs prices. Scherer (1993) explains this phenomenon by a loyalty to brand-name drugs. Prices increase may be interpreted as a manner to increase the differentiation with mee-too products or generics.<sup>4</sup> Frank and Salkever (1992) show that prices increase if the reduced demands of brand-name drugs become more elastic. Nevertheless, in a vertical differentiation framework, Castello (2003) show that brand-name drugs prices decrease when a RP regulation is introduced. Besides, in countries which have introduced RP regulation, Danzon and Liu (1996) and Danzon (2003) observed that brand-name drugs prices have been reduced. Manufacturers reduces prices of their drugs to limit losses of market share due to generics' competition. Moreover, Rizzo and Zeckhauser (2005) revealed that even brand-name drugs prices increase, their average price diminishes thanks to a substitution effect toward the cheapest brand-name drugs.

In the long run, the existence of drugs cannot be considered exogenous. Drugs arrive on the market as a result of long and costly R&D processes which are undertaken only if the expected profits are sufficiently high. To resume the Weisbrod's point of view,<sup>5</sup> since the introduction of therapeutic equivalence reduces policy holders' coverage, it negatively affects R&D in pharmaceutical sector. Indeed, pharmaceutical companies' profits decreasing, it reduces their incentives to innovate, which means less medical research, less innovation, and ultimately fewer drugs. However, one should not conclude from this that drug supply will deteriorate in a uniform way. When pricing based on therapeutic equivalence is implemented, the overall level of incentives to innovate is of course reduced, but the structure of innovations is also profoundly changed. The introduction of therapeutic equivalence causes a decline in the intensity of research, but also a reorientation of research. In particular, pricing according to therapeutic classes could increase or decrease incentives to do research on drugs which are similar to those already

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<sup>4</sup>Mestre-Ferrandiz (1999) and Scherer (1996) explain this phenomenon in a horizontal differentiation framework whereas Cabrales (2003) obtains the same result in a vertical one.

<sup>5</sup>Weisbrod (1991).

present in the market, thereby increasing or decreasing incentives to conduct research on fundamental innovations which have the strongest effects on welfare. The literature is particularly ambiguous on this point, and conflicting arguments have been put forward. For example, one can argue that once a drug exists in a given therapeutic class, there is little incentive to innovate within that class, since the new drug would be reimbursed at the same rate as the old one (and would therefore hardly sell if it is more expensive). This effect is of course worsened when drugs in a therapeutic class are no longer protected by patents. There would thus be a disincentive to develop follower products, and a premium for very innovative drugs. But the opposite effect is also conceivable, in case the production of a follower turns out to be less costly than the production of an innovative drug, or if one takes into account that the introduction of a follower has a radically different effect on the sales of the older drug depending on whether or not reimbursement is based on therapeutic equivalence. Moreover, we have to take into consideration that therapeutic classes can be more or less broad. Drugs within the same therapeutic class may differ in quality and efficiency. Hence, reducing incentives for research on drugs which would be classified as belonging to an existing therapeutic class could in itself have a strong negative impact on medical innovation and welfare.

To sum-up, the literature reveals three potential effects of a regulation built on reference pricing: a quantity effect through a reduction of *ex post* moral hazard and SID behaviors, a price effect according to laboratories reactions and technological change. In this paper, we focus on the two last effects. More precisely, the goal of our modeling efforts described below is to determine the main effects of reference pricing on the structure of incentives to innovate according to the type of prices setting. Section 2 presents the hypothesis of the model. In Section 3, we analyze the negotiation between the drug owner and the regulator to fix the price, first without legal constraint, second under the regime of therapeutic classes. Section 4 is devoted to the innovation game where the firms anticipate the results of the negotiation round on prices without and with the therapeutic class regulation. Section 5 discusses welfare effects. In section 6 we present briefly the market for statins in France. We then show the results from numerical simulations. We finally concludes in section 7 and present some possible extensions of the model.

## 2 Model setting

Time is continuous from 0 to infinity. The three actors of the model are pharmaceutical firms (research laboratories and drugs producers), consumers and the regulator of the industry. These actors intervene differently at the two stages of the game. At the upstream stage, innovators invest in R&D and introduce new molecules or treatments. At the downstream stage, the regulatory agency and the producers negotiate to determine the price (the negotiation is modeled using the Nash bargaining solution concept where the [status-quo](#) corresponds to not introducing the new drug); knowing the prices, patients and doctors jointly determine the consumption of drugs. All this is done under the legal rules that have been set by the legislator, in particular the reference pricing system. We shall consider here an extreme form that represents the Italian version of RP.

To keep in line with the standard backward analysis, we first make explicit the hypothesis on the downstream agents and activities. Then we give details on the assumptions of the innovation stage.

### 2.1 The downstream stage: marketing

We focus on the case of a single pathology that can be treated with one of several medicaments. At each instant in time there is a population of size 1 of patients to be treated. We take account of patients' heterogeneity with respect to the various treatments by assuming that the effect of a given medication varies among patients in terms of efficiency, tolerance and side effects. A therapeutic class is a set of drugs that can be used to treat the pathology, and such that none unambiguously dominates the others. This does not mean that the drugs inside a given class are all perfectly substitutable, but that absent any specific information on the patient, a doctor would be indifferent between prescribing one or the other drug in the class: each has an equal chance to be effective. After examination of the patient, the doctor reaches an objective diagnostic which allows him to know what is the most adapted treatment.<sup>6</sup> We consider here a relation of perfect agency between the patient and the physician.<sup>7</sup> Then, they are viewed as a single agent, the consumer. As regards health expenses, we assume that the patient is fully reimbursed.

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<sup>6</sup>This assumption is based on the concept of *ex-post* differentiation as for instance in Gal-Or (1997 and 1999).

<sup>7</sup>We discuss in the conclusion what would change if we introduce SID effect.

This assumption allows to emphasize one of the main issue in the debate on price fixing for most European countries, namely the lack of price sensitivity.

Concerning the drugs consumed, we make a distinction between vertical and horizontal differentiation. Vertical differentiation is defined by levels. In order to simplify as much as possible the analysis, we assume that there are two levels indexed by  $k = 1$  or  $2$ , and that there are at most two drugs active in each level,  $i = 1$  or  $2$ .<sup>8</sup> We adopt a discrete choice model to represent the utility from consumption.<sup>9</sup> When consuming medication  $i$  in level  $k$ , the typical patient obtains an utility

$$U = V_k - \theta \tilde{x}_i^k - p + R$$

where  $p$  is the price paid and  $R$  is the reimbursement received. The patient being fully reimbursed, we have  $U = V_k - \theta \tilde{x}_i^k$ .<sup>10</sup> The term  $V_k$  represents the maximal value that a patient can derive from a drug in level  $k$ . We refer to it as the base value. Each patient receives the base value minus the disutility  $\theta \tilde{x}_i^k$ , where  $\tilde{x}_i^k$  is a random variable that is identically and independently distributed among all consumers and drugs. We assume that the distribution is uniform on the interval  $[-\frac{1}{2}, \frac{1}{2}]$  so that we can take the **ex-ante** value of a medication  $V_k$  as the reference value. Nevertheless, since doctors are able to identify the disutility component  $\tilde{x}_i^k$ , the **ex-post** value is  $V_k - \theta \tilde{x}_i^k$ , which differs from the reference value by a random term  $\theta \tilde{x}_i^k$ .

We assume that the base value takes the multiplicative form  $V_2 = v + V_1$ . In other words, introducing a drug in the superior level raises the base value by an amount  $v$ , with

**Assumption 1**  $v > \theta$ .

From the previous assumptions, we can derive the following demands for medications:

1. Only drugs in the highest level available are consumed.<sup>11</sup>

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<sup>8</sup>The extension to  $n$  is straightforward.

<sup>9</sup>See Anderson, de Palma and Thisse (1992) for a presentation of discrete choice models.

<sup>10</sup>We do not include the payment for tax and insurance premium, that are independent of consumption (at individual level).

<sup>11</sup>Indeed, consuming in class  $k$  and incurring the highest disutility is better than consuming in class  $k - 1$  and suffering from no disutility at all:  $kv - t > (k - 1)v$ .



2. The total demand for medication is equal to 1.
3. The demand is evenly spread between all the drugs in the same level of the therapeutic class.

Thus a therapeutic class contains at most two drugs that are effectively consumed, indexed by  $i \in \{1, 2\}$ , and a single level  $k = 1$  or  $2$ . Once the innovation process is successful, the cost of producing a drug is the same for all drugs, normalized to zero.

Knowing these characteristics of the demand and supply for drugs, the price is fixed during a negotiation round between the regulator and the drug owner detailed in section 2.

## 2.2 The upstream activity: R&D

The upstream part of the sector is composed of laboratories under the supervision of the regulator, whose role at this stage is limited to guarantee drug safety. There are  $N$  (large enough) laboratories active in the research sector of the pharmaceutical industry for the given pathology. Each laboratory is identified with a single project.<sup>12</sup> We assume that once a firm has innovated, it obtains a perfect patent of infinite duration. At that time, it exits the innovative sector to enter the downstream market where it becomes producer of the drug.<sup>13</sup>

The process of innovation is incremental. When a laboratory innovates, it can either discover a new product in the same level  $k$  as existing products (here, this occurs when there is only one product on the market), or it can discover a product in the superior level. The former will be referred to as horizontal innovation and the new drug as a **follower**. The latter is referred to as vertical innovation and the corresponding drug as a **pioneer**. When investing an amount  $I$  in R&D, the laboratory can devote an amount  $E$  to research for a superior quality drug, and an amount  $e = I - E$  to the search for a drug within the existing therapeutic class. If the current active level is

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<sup>12</sup>This assumption is here to avoid the problem of the management of projects and products portfolio. It also reflects the opinion among specialists that innovation by independent research unit is becoming standard in the pharmaceutical industry. Moreover, this assumption makes sense for a pathology given (see bullet iv in the conclusion).

<sup>13</sup>Another possibility is that the laboratory sells the patented innovation to a single producer.

$k$ , a laboratory investing in the vertical dimension can only have access to level  $k + 1$ .

As regards the innovation process, we adopt a deterministic innovation model according to which laboratories choose the time devoted to develop the new product. This time is known in advance and the development cost is a decreasing function of the discovery time. More precisely, the cost of bringing a vertical innovation to the market is

$$C(t) = Ce^{-\gamma t}$$

where  $t$  is the time length of the research process.

Similarly, starting the process after the introduction of the first drug in a given level  $k$ , the discovery of a new drug in the same level (horizontal innovation) has a cost

$$c(t) = ce^{-\gamma t}$$

with  $c < C$ .

At the competitive equilibrium three properties hold. First, the research projects start just after a new level  $k$  is created. Second, the time chosen for any active research project is the time that cancels the profit of the investor. Third, if no laboratory invests in horizontal innovation, the profit from doing so is non-positive. The pharmaceutical laboratories being far sighted, they anticipate correctly their future stream of income.

### 3 The price negotiation

We first consider the case where there is no legal constraint on the determination of the price in a negotiation round between the innovator who wants to maximize its profit and the regulator who protects consumers. The second subsection is devoted to the case where the negotiation is constrained by the therapeutic-class system.

#### 3.1 The base case

When a new drug is introduced in the market, the price is set by negotiation between the regulator and the laboratory who produces the new molecule.

The negotiation is depicted by the [Generalized Nash Bargaining Solution](#), with arbitrary bargaining power,  $\alpha$  for the regulator and  $1 - \alpha$  for the firm. This can be viewed as a bargaining process [a la](#) Rubinstein with different discount factors for the regulator and the firm. The negotiators only care about current consumers' surplus for the regulator and current profits for the firm, so that the resulting price maximizes the function:

$$\begin{aligned} & [W(\textit{with innovation}) - W(\textit{without innovation})]^\alpha \\ & \times [\pi(\textit{with innovation}) - \pi(\textit{without innovation})]^{1-\alpha} \end{aligned}$$

where  $W$  is the welfare as perceived by the regulator, and  $\pi$  represents the instantaneous profit generated by the sales of the drug. It is important to notice that the R&D expenses are sunk for all agents at the time of marketing. Therefore, they are not taken into account in the bargain. Hereafter, we assume that if the negotiation fails, the firm has no way to market its innovation anywhere so that it is as if it had no innovation at all and  $\pi(\textit{without innovation}) = 0$ .

We denote by  $i = 1$  the first drug introduced in level  $k$  and by  $p_k^1$  the price at which it is introduced. In all what follows we assume that one drug is already present in the level  $k = 1$  and take  $p_1^1$  as given by history:

$$p_1^1 = P$$

When a second drug is introduced in level  $k$ , it is denoted  $i = 2$  and its price is  $p_k^2$ . The welfare function is given by the aggregate utility of consumers net of the social cost of health expenses. If  $\lambda$  denotes the social cost of public funds,<sup>14</sup> we obtain

$$W = V_k - (1 + \lambda)p_k^1$$

in the case of a single product in the class. With a single drug in the highest level, all patients consume the same drug and welfare equals the reference value minus the social cost of the medicament. When there are two drugs in the highest level  $k$ , consumers are spread between the two drugs and the social

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<sup>14</sup>See Laffont-Tirole (1993) for a discussion of the concept of the cost of public funds.

value is the expectation of the highest value of treatment  $V_k - \theta \min\{\varepsilon_1, \varepsilon_2\}$  minus the social cost:

$$W = V_k + \frac{\theta}{6} - \frac{1}{2}(1 + \lambda)(p_k^1 + p_k^2)$$

in the case of two products.

Then introductory prices can be determined sequentially, as the function of previous introductory prices.<sup>15</sup> The outcome of negotiation depends on the actual state of the markets (drugs on the markets and prices) and on the nature of the innovation (vertical or horizontal). There are then three possible cases, when the current level is  $k$ .

We also assume that

**Assumption 2**  $P > (1 - \alpha)\frac{v}{(1+\lambda)}$ .

This amounts to say that the existing drug has replaced some previous one with a positive price and created a value  $V_1$  at least as large as  $v$ .

1) **First Case: introduction of a new drug in an existing level (follower).**

Here there is a drug  $i = 1$  in the level  $k$  with price  $p_k^1$ , and the innovator introduces another drug  $i = 2$  in the same level. This can occur at level  $k = 1$  or level  $k = 2$ . The consumer's gain from introduction is for a price  $p_k^2$  of the new drug:<sup>16</sup>

$$\begin{aligned} & \left[ V_k + \frac{\theta}{6} - \frac{1}{2}(1 + \lambda)(p_k^1 + p_k^2) \right] - [V_k - (1 + \lambda)p_k^1] \\ &= \frac{\theta}{6} + \frac{1}{2}(1 + \lambda)(p_k^1 - p_k^2) \end{aligned}$$

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<sup>15</sup> Although there are only two levels  $k = 1, 2$  in the model, we allow here for more levels ( $k = 1, \dots, K$ ) to highlight the nature of the negotiation process and of the dynamics of prices.

<sup>16</sup> Notice that given that demand is not sensitive to price, there is no incentive for the seller of the existing drug to reduce its price when an entry occurs.

The profit is now  $\frac{p_k^2}{2}$  as the new drug reaches half of the patients only. We thus solve the program

$$\max_{p_k^2} \left( \frac{\theta}{6} + \frac{1}{2}(1 + \lambda)(p_k^1 - p_k^2) \right)^\alpha \left( \frac{p_k^2}{2} \right)^{1-\alpha}$$

which yields

$$p_k^2 = (1 - \alpha) \left[ p_k^1 + \frac{\theta}{3(1 + \lambda)} \right]$$

Moreover

$$p_k^2 < p_k^1 \text{ whenever } \frac{1 - \alpha}{\alpha} \frac{\theta}{3(1 + \lambda)} < p_k^1.$$

Under our assumptions  $p_k^1 > (1 - \alpha) \frac{v}{1 + \lambda}$  so that this holds provided that  $\alpha > \frac{\theta}{3v}$ , in particular for  $\alpha > \frac{1}{3}$ .

We see that when the bargaining power of the regulator is high enough, horizontal innovation leads to a reduction in health expenses from  $p_k^1$  to

$$\frac{p_k^1 + p_k^2}{2} = \frac{(2 - \alpha)p_k^1 + (1 - \alpha) \frac{\theta}{3(1 + \lambda)}}{2}$$

## 2) **Second Case: introduction of a new drug at the superior level (pioneer) while the current level is incomplete.**

Here the first drug in level  $k + 1$  is introduced, while the second drug in level  $k$  is not discovered. According to our assumptions this means that there is one drug in level  $k$  (which sells at price  $p_k^1$ ). Then the new drug replaces the old one.

The consumers' gain is

$$\begin{aligned} & [V_{k+1} - (1 + \lambda)p_{k+1}^1] - [V_k - (1 + \lambda)p_k^1] \\ = & v - (1 + \lambda)(p_{k+1}^1 - p_k^1) \end{aligned}$$

so that we now solve

$$\max_{p_{k+1}^1} \left( v - (1 + \lambda)(p_{k+1}^1 - p_k^1) \right)^\alpha \left( p_{k+1}^1 \right)^{1-\alpha}.$$

The price of the new drug is then

$$p_{k+1}^1 = (1 - \alpha) \left[ p_k^1 + \frac{v}{(1 + \lambda)} \right]$$

Given that  $v > \theta$ , when there is only one drug in level  $k$ , the innovation to the superior level leads to an introductory price  $p_{k+1}^1$  larger than the introductory price  $p_k^2$  that would prevail for an horizontal innovation. Thus a vertical innovation generates higher prices than an horizontal innovation.

Notice also that  $p_2^1 > P$  when

$$\frac{1 - \alpha}{\alpha} \frac{v}{1 + \lambda} > P.$$

However, if the price is high enough, the new drug may be introduced at a lower price even if there is only one drug active in level 1.

**3) Third case: introduction of a new drug at a superior level (pioneer) while the current level is complete.**

The final case is when the first drug in level  $k + 1$  is introduced, while the second drug in level  $k$  has been discovered. There are thus currently two drugs in level  $k$  (which sells at prices  $p_k^1$  and  $p_k^2$ ) that are replaced by the new one. The consumers' gain is given by

$$\begin{aligned} & [V_{k+1} - (1 + \lambda)p_{k+1}^1] - \left[ V_k + \frac{\theta}{6} - (1 + \lambda) \left( \frac{p_k^1 + p_k^2}{2} \right) \right] \\ &= v - \frac{\theta}{6} - (1 + \lambda) \left( p_{k+1}^1 - \frac{p_k^1 + p_k^2}{2} \right) \end{aligned}$$

leading to maximize

$$\max_{p_{k+1}^1} \left( v - \frac{\theta}{6} - (1 + \lambda) \left( p_{k+1}^1 - \frac{p_k^1 + p_k^2}{2} \right) \right)^\alpha (p_{k+1}^1)^{1-\alpha}.$$

The price is then

$$p_{k+1}^1 = (1 - \alpha) \left[ \frac{p_k^1 + p_k^2}{2} + \frac{v - \frac{\theta}{6}}{(1 + \lambda)} \right].$$

We thus have in this case

$$p_2^1 = (1 - \alpha) \left[ \left(1 - \frac{\alpha}{2}\right) P + \frac{v - \alpha \frac{\theta}{6}}{(1 + \lambda)} \right]$$

Vertical innovation raises health expenditures for the given pathology whenever there are two products in the level 1 and  $p_2^1 > \frac{p_1^1 + p_1^2}{2}$  which amounts to

$$\frac{p_1^1 + p_1^2}{2} < \frac{1 - \alpha}{\alpha} \frac{v - \frac{\theta}{6}}{(1 + \lambda)}$$

Or,

$$P < \frac{(1 - \alpha)}{\alpha(2 - \alpha)} \left( \frac{2v}{(1 + \lambda)} - \frac{(1 + \alpha)\theta}{3(1 + \lambda)} \right)$$

### 3.2 Bilateral negotiation under reference pricing

We focus on a reference pricing system that has two characteristics. First all the drugs in the therapeutic class are sold at the same price. In particular, there are no drugs sold at prices above the official price. This corresponds for instance to the Italian system where the reimbursement is obtained only if the price is under the cap.<sup>17</sup>

Second, we maintain the assumption on the bargaining process. The bargaining is still bilateral between the producer of the new drug and the regulator. This means two things that are worth being noticed. Despite the fact that the producers of existing drugs are directly affected by the price negotiated (since they have to align their price), they are not part of the process. Thus there will be some incentives to "expropriate" these producers by setting a low price. Moreover, the bargaining weights  $\alpha$  and  $1 - \alpha$ , are not affected by the change in the bargaining environment. This fits with the view of a bargaining process a la Rubinstein (where the parties alternate offers, and the drug is introduced at the end).

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<sup>17</sup>The fact that drugs prices are identical is not specified by the regulator but is checked in equilibrium.

1) **First Case: introduction of a new drug in an existing level (follower).**

The consumers' gain from introduction is

$$\begin{aligned} & \left[ V_k + \frac{\theta}{6} - (1 + \lambda)p_k^2 \right] - [V_k - (1 + \lambda)p_k^1] \\ &= \frac{1}{6}\theta + (1 + \lambda)(p_k^1 - p_k^2) \end{aligned}$$

accounting for the fact that after introduction all the drugs in level  $k$  are sold at price  $p_k^2$ .

Solving

$$\max_{p_k^2} \left( \frac{1}{6}\theta + (1 + \lambda)(p_k^1 - p_k^2) \right)^\alpha \left( \frac{p_k^2}{2} \right)^{1-\alpha}$$

yields the price

$$p_k^2 = (1 - \alpha) \left[ p_k^1 + \frac{\theta}{6(1 + \lambda)} \right] < (1 - \alpha) \left[ p_k^1 + \frac{\theta}{3(1 + \lambda)} \right]$$

The follower is thus introduced at a smaller price when there is a single price for the therapeutic class. The reason is that the marginal benefit for the regulator of reducing the price is higher because the price reduction applies to all the drugs in the class. It is thus a "tougher" negotiator.

2) **Second Case: introduction of a new drug at a superior level (pioneer) while the current level  $k$  is incomplete.**

The therapeutic class doesn't change the pricing behavior, as a new level is reached and there is only one active drug. Consequently, the price is

$$p_{k+1}^1 = (1 - \alpha) \left[ p_k^1 + \frac{v}{(1 + \lambda)} \right]$$

like in subsection 2.1

3) **Third case: introduction of a new drug at a superior level (pioneer) while the current level is complete** (i.e. the second drug in level  $k$  exists).



Again the new drug takes all the market and the consumers' gain is given by

$$\begin{aligned} & [V_{k+1} - (1 + \lambda)p_{k+1}^1] - \left[ V_k + \frac{\theta}{6} - (1 + \lambda)\left(\frac{p_k^2}{2}\right) \right] \\ = & v - \frac{\theta}{6} - (1 + \lambda)(p_{k+1}^1 - p_k^2) \end{aligned}$$

We must solve

$$\max_{p_{k+1}^1} \left( v - \frac{\theta}{6} - (1 + \lambda)(p_{k+1}^1 - p_k^2) \right)^\alpha (p_{k+1}^1)^{1-\alpha}$$

that gives

$$p_{k+1}^1 = (1 - \alpha) \left[ p_k^2 + \frac{v - \frac{\theta}{6}}{(1 + \lambda)} \right]$$

Therefore the reference pricing system has no direct effect. However, the price is lower than in the base case provided that the price of a medication in the therapeutic class prior to the introduction of the innovation is lower than the average price that would prevail without reference pricing.

## 4 The dynamics of innovation

Knowing the prices that will be fixed at the marketing stage depending on the nature of the drug innovation, we can now solve the innovation game. Because of the assumption that a vertical innovation is drastic and captures the whole market, in any equilibrium, all levels will be discovered at some point in time. Thus, when looking at the dynamics of innovation there remains two questions. First, in which levels will there be an horizontal innovation? Second, what are the delays between subsequent innovations?

### 4.1 Innovation without reference pricing

Given that it is the last level, there will be eventually an horizontal innovation in level  $k = 2$ . The remaining uncertainty is whether there is an horizontal innovation or not in level 1 (prior to the discovery of the first level-2 drug).

This may thus yield two types of equilibria, corresponding to two different sequences of innovation.

To summarize, in any case the pioneer is introduced in every levels, and the follower in the level  $k = 2$  is introduced after some time. The difference comes from the follower in level  $k = 1$ . We thus define the two sequences:

**Sequence 1:** The follower of level  $k = 1$  is never introduced. The prices are then:

$$\begin{aligned}\bar{p}_2^1 &= (1 - \alpha) \left[ P + \frac{v}{(1 + \lambda)} \right] \text{ for the first drug in level 2;} \\ \bar{p}_2^2 &= (1 - \alpha)^2 \left[ P + \frac{v}{(1 + \lambda)} \right] + (1 - \alpha) \frac{\theta}{3(1 + \lambda)} \text{ for the last drug.}\end{aligned}$$

**Sequence 2:** The follower of level  $k = 1$  is introduced before the pioneer of level  $k = 2$ . The prices are then:

$$\begin{aligned}\hat{p}_1^2 &= (1 - \alpha)P + (1 - \alpha) \frac{\theta}{3(1 + \lambda)} \text{ for the second drug in level 1;} \\ \hat{p}_2^1 &= (1 - \alpha) \left( \left( 1 - \frac{\alpha}{2} \right) P + \frac{v - \alpha \frac{\theta}{6}}{(1 + \lambda)} \right) < \bar{p}_2^1 \\ &\text{for the first drug in level 2;} \\ \hat{p}_2^2 &= (1 - \alpha) \left( (1 - \alpha) \left( \left( 1 - \frac{\alpha}{2} \right) P + \frac{v - \alpha \frac{\theta}{6}}{(1 + \lambda)} \right) + \frac{\theta}{3(1 + \lambda)} \right) \\ &= (1 - \alpha)^2 \left( 1 - \frac{\alpha}{2} \right) P + (1 - \alpha)^2 \frac{v}{(1 + \lambda)} + (1 - \alpha) (2 - \alpha(1 - \alpha)) \frac{\theta}{6(1 + \lambda)} \\ &< \bar{p}_2^2 \text{ for the last drug.}\end{aligned}$$

In what follows we start the game at the date of introduction of the first drug in level 1. We derive the dynamics of innovation from that point in the absence of reference pricing. We then consider what occurs if the legislator impose a regulation built on reference pricing.<sup>18</sup>

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<sup>18</sup>This means that we implicitly assume that either the legislative change was not anticipated by the first innovator when choosing the introductory time of the first drug, or the first innovation is given by an exogenous process.

Let us denote  $\tau_2$  the delay between the creation of level  $k = 2$  and the introduction of the follower in level 2. For the sequence 2, we can also denote  $\tau_1$  the time of introduction of the follower in level 1. Let us denote  $t_2$  the delay between the creation of the level 1 and the introduction of the pioneer into level 2. Notice that the research on the follower and the research on the next level both start as soon as a pioneer is introduced. Indeed, there is no advantage from delaying the innovation. In particular in sequence 2, both  $t_2$  and  $\tau_1$  start from date 0.

Consider first the situation where the second level exists. The research focuses on the follower with an investment such that the discounted benefits are null, that is

$$ce^{-\gamma\tau_2} = e^{-r\tau_2} \frac{p_2^2}{2r}$$

where  $\frac{p_2^2}{2r}$  is the discounted value of serving half of the patients at price  $p_2^2$  for ever, with discount factor  $r$ . We assume that the drugs will be introduced in level 2 with some delays.

**Assumption 3**  $c > \frac{\bar{p}_2^2}{2r}$ ;  $C > \frac{\bar{p}_2^1}{2r}$ ;  $\gamma > r$ .

This yields an introductory delay

$$\tau_2 = \frac{1}{\gamma - r} \left( \ln(c) - \ln\left(\frac{p_2^2}{2r}\right) \right).$$

Consider now the situation where a pioneer has just been introduced in level 1, and an equilibrium leading to sequence 1 where laboratories focus on the vertical innovation only. In the vertical-only case, we must have  $\tau_2 = \bar{\tau}_2$  and  $t_2 = \bar{t}_2$  with

$$\begin{aligned} ce^{-(\gamma-r)\bar{\tau}_2} &= \frac{\bar{p}_2^2}{2r} \\ Ce^{-(\gamma-r)\bar{t}_2} &= \frac{\bar{p}_2^1}{r} \left( 1 - \frac{e^{-r\bar{\tau}_2}}{2} \right) = \frac{\bar{p}_2^1}{r} \left( 1 - \frac{1}{2} \left( \frac{\bar{p}_2^2}{c2r} \right)^{\frac{r}{\gamma-r}} \right) \end{aligned}$$

Here the formula accounts for the fact that once the drug is introduced, the seller will benefit from a monopoly position for a period of length  $\bar{\tau}_2$ . Thus

$$\begin{aligned}\bar{t}_2 &= \frac{1}{\gamma - r} \left( \ln(C) - \ln \left( \frac{\bar{p}_2^1}{r} \left( 1 - \frac{e^{-r\bar{\tau}_2}}{2} \right) \right) \right) \\ &= \frac{\ln(C)}{\gamma - r} - \frac{1}{\gamma - r} \ln \left[ \frac{\bar{p}_2^1}{r} \left( 1 - \frac{1}{2} \left( \frac{\bar{p}_2^2}{c2r} \right)^{\frac{r}{\gamma-r}} \right) \right]\end{aligned}$$

For this to be an equilibrium, it must be the case that there is no horizon that would yield a positive return on horizontal innovation. Such an innovation would allow to sell  $\frac{1}{2}$  at price  $\hat{p}_1^2$  as long as the new level is not introduced. Thus it must be the case that for all  $\tau_1 < \bar{t}_2$ :

$$ce^{-\gamma\tau_1} > \frac{\hat{p}_1^2}{2r} \left( e^{-r\tau_1} - e^{-r\bar{t}_2} \right)$$

Or,

$$ce^{-(\gamma-r)\tau_1} > \frac{\hat{p}_1^2}{2r} \left( 1 - e^{-r(\bar{t}_2 - \tau_1)} \right)$$

This amounts to say that there is no solution  $\Delta = \bar{t}_2 - \tau_1$  to the above inequality. Define

$$\Phi(\Delta) = \frac{ce^{(\gamma-r)\Delta}}{1 - e^{-r\Delta}}.$$

The condition of existence writes as

$$\min_{[0, \bar{t}_2]} \Phi(\Delta) \geq \frac{\hat{p}_1^2}{2r} e^{(\gamma-r)\bar{t}_2}$$

**Lemma 1** [There exists a threshold  \$\bar{t}\$  such that an equilibrium with sequence 1 exists if and only if  \$\bar{t}\_2 \leq \bar{t}\$ .](#)

**Proof.** see Appendix ■

Notice that  $\bar{t}$  is defined as the solution of

$$\frac{\hat{p}_1^2}{2\gamma} \left( \frac{\gamma - r}{\gamma} \right)^{\frac{\gamma-r}{r}} = ce^{-(\gamma-r)\bar{t}}.$$

Consider now the case of sequence 2 where innovators invest both in vertical and horizontal innovations. The follower is introduced with a delay  $\tau_1 = \hat{\tau}_1$  and the next level with a delay  $t_2 = \hat{t}_2 > \hat{\tau}_1$ . As mentioned above, the firm planning to introduce the next pioneer benefits from starting the research process immediately instead of waiting for the follower to emerge, since this minimizes the introductory delay and the follower doesn't generate R&D spillover. We then have:

$$\begin{aligned} ce^{-(\gamma-r)\hat{\tau}_1} &= \frac{\hat{p}_1^2}{2r} \left( 1 - e^{-r(\hat{t}_2 - \hat{\tau}_1)} \right) \\ Ce^{-(\gamma-r)\hat{t}_2} &= \left( \frac{\hat{p}_2^1}{r} \left( 1 - \frac{e^{-r\hat{\tau}_2}}{2} \right) \right) \\ ce^{-(\gamma-r)\hat{\tau}_2} &= \frac{\hat{p}_2^2}{2r} \end{aligned}$$

We obtain

$$\hat{t}_2 = \frac{\ln(C)}{\gamma-r} - \frac{1}{\gamma-r} \ln \left[ \frac{\hat{p}_2^1}{r} \left( 1 - \frac{1}{2} \left( \frac{\hat{p}_2^2}{c2r} \right)^{\frac{r}{\gamma-r}} \right) \right]$$

The existence condition is then  $\hat{t}_2 > \hat{\tau}_1$ . Said differently, there must exist a solution  $\Delta < \hat{t}_2$  to

$$\Phi(\Delta) = \frac{ce^{(\gamma-r)\Delta}}{1 - e^{-r\Delta}} < \frac{\hat{p}_1^2}{2r} e^{(\gamma-r)\hat{t}_2}$$

**Lemma 2** There exists an equilibrium with sequence 2 if and only if  $\hat{t}_2 > \bar{t}$ .

**Proof.** Same as above with revert inequalities. ■

Let us compare  $\bar{t}_2$  and  $\hat{t}_2$ . We have

$$\begin{aligned} Ce^{-(\gamma-r)\bar{t}_2} &= \frac{\bar{p}_2^1}{r} \left( 1 - \frac{\left( \frac{(1-\alpha)[\bar{p}_2^1 + \frac{\theta}{3(1+\lambda)}]}{c2r} \right)^{\frac{r}{\gamma-r}}}{2} \right) \\ Ce^{-(\gamma-r)\hat{t}_2} &= \frac{\hat{p}_2^1}{r} \left( 1 - \frac{\left( \frac{(1-\alpha)[\hat{p}_2^1 + \frac{\theta}{3(1+\lambda)}]}{c2r} \right)^{\frac{r}{\gamma-r}}}{2} \right) \end{aligned}$$

Define the function

$$\chi(p) = \frac{p}{2r} \left( 2 - \left( \frac{(1-\alpha) \left[ p + \frac{\theta}{3(1+\lambda)} \right]}{c2r} \right)^{\frac{r}{\gamma-r}} \right)$$

Then  $\bar{t}_2 < \hat{t}_2$  whenever  $\chi(\bar{p}_2^1) > \chi(\hat{p}_2^1)$ . For  $c$  large enough this holds, implying that the pioneer emerges faster if there is no horizontal innovation anticipated. The reason is that introductory prices are smaller if more drugs are present in the inferior class, the social benefit being smaller. In other words [horizontal innovations delay vertical innovations](#).

**Proposition 3** For  $c$  not too small, or for  $\gamma > 2r$ , an equilibrium exists. Three cases are possible:

- If  $\hat{t}_2 \leq \bar{t}$ , [sequence 1 is the only equilibrium](#).
- If  $\bar{t}_2 > \bar{t}$ , [there appears a level-1 follower before the level-2 pioneer](#).
- If  $\bar{t}_2 \leq \bar{t} < \hat{t}_2$ , [both sequences can emerge in equilibrium](#).

**Proof.** see Appendix ■

## 4.2 Innovation under a RP regulation

The model is still solved by backward induction, but using now the prices of subsection 2.2. As before, two equilibria can emerge corresponding to two different sequences of innovation.

**Sequence 1:** Prices are:

$$\begin{aligned} \bar{P}_2^1 &= \bar{p}_2^1 = (1-\alpha) \left[ P + \frac{v}{(1+\lambda)} \right]; \\ \bar{P}_2^2 &= (1-\alpha)^2 \left[ P + \frac{v}{(1+\lambda)} \right] + (1-\alpha) \frac{\theta}{6(1+\lambda)}. \end{aligned}$$

**Sequence 2:** Prices are:

$$\begin{aligned}
\hat{P}_1^2 &= (1 - \alpha)P + (1 - \alpha) \frac{\theta}{6(1 + \lambda)}; \\
\hat{P}_2^1 &= (1 - \alpha) \left[ (1 - \alpha)P + (1 - \alpha) \frac{\theta}{6(1 + \lambda)} + \frac{v - \frac{\theta}{6}}{(1 + \lambda)} \right] \\
&= (1 - \alpha)^2 P + (1 - \alpha) \frac{v}{(1 + \lambda)} - \alpha(1 - \alpha) \frac{\theta}{6(1 + \lambda)} < \bar{P}_2^1; \\
\hat{P}_2^2 &= (1 - \alpha)\hat{P}_2^1 + (1 - \alpha) \frac{\theta}{6(1 + \lambda)} \\
&= (1 - \alpha)^3 P + (1 - \alpha)^2 \frac{v}{(1 + \lambda)} + (1 - \alpha)(1 - \alpha(1 - \alpha)) \frac{\theta}{6(1 + \lambda)} < \bar{P}_2^2.
\end{aligned}$$

We partly repeat the discussion that precedes. Denote  $\varsigma_k$  the introductory delay of the follower, in class  $k = \{1, 2\}$ , and  $T_2$  the delay of introduction of the pioneer.

The delay for the follower in the second level is given by

$$\varsigma_2 = \frac{1}{\gamma - r} \left( \ln(c) - \ln\left(\frac{P_2^2}{2r}\right) \right).$$

Again two equilibria are possible, depending on whether there is or there is not an innovation in level 1.

When there is no follower in level 1 (sequence 1) we must have (with similar notations as above)

$$\begin{aligned}
C e^{-(\gamma-r)\bar{T}_2} &= \frac{1}{r} \left[ (1 - e^{-r\bar{\tau}_2}) \bar{P}_2^1 + \frac{1}{2} e^{-r\bar{\tau}_2} \bar{P}_2^2 \right] \\
c e^{-(\gamma-r)\bar{\varsigma}_2} &= \frac{\bar{P}_2^2}{2r}
\end{aligned}$$

The difference is that after delay  $\bar{\varsigma}_2$ , the pioneer not only loose half of the market but its price is reduced to  $\bar{P}_2^2$ .

And again this is an equilibrium if there is no solution  $\Delta$  to (introducing a follower is not profitable)

$$\Phi(\Delta) = \frac{c e^{(\gamma-r)\Delta}}{1 - e^{-r\Delta}} < \frac{\hat{P}_1^2}{2r} e^{(\gamma-r)\bar{T}_2}$$

between zero and  $\bar{T}_2$ .

**Lemma 4** There exists a threshold  $\bar{T}$  such that an equilibrium with sequence 1 exists if and only if  $\bar{T}_2 \leq \bar{T}$ .

**Proof.** Same as for Lemma 1. ■

In the second case we have delays  $\varsigma_1 = \hat{\varsigma}_1$ ,  $T_2 = \hat{T}_2 > \hat{\varsigma}_1$  and  $\hat{\varsigma}_2$ , with

$$\begin{aligned} ce^{-(\gamma-r)\hat{\varsigma}_1} &= \frac{\hat{p}_1^2}{2r} \left(1 - e^{-r(\hat{T}_2 - \hat{\varsigma}_1)}\right) \\ Ce^{-(\gamma-r)\hat{T}_2} &= \frac{1}{r} \left[ (1 - e^{-r\hat{\varsigma}_2}) \hat{p}_2^1 + \frac{1}{2} e^{-r\hat{\varsigma}_2} \hat{p}_2^2 \right] \\ ce^{-(\gamma-r)\hat{\varsigma}_2} &= \frac{\hat{p}_2^2}{2r} \end{aligned}$$

The existence condition is  $\hat{T}_2 > \hat{\varsigma}_1$ , or again there should exist a solution  $\Delta < \hat{T}_2$  to

$$\Phi(\Delta) = \frac{ce^{(\gamma-r)\Delta}}{1 - e^{-r\Delta}} < \frac{\hat{p}_1^2}{2r} e^{(\gamma-r)\hat{T}_2}$$

**Lemma 5** There exists an equilibrium with sequence 2 if and only if  $\hat{T}_2 > \bar{T}$ .

We have to compare  $\bar{T}_2$  and  $\hat{T}_2$  defined by

$$\begin{aligned} Ce^{-(\gamma-r)\bar{T}_2} &= \frac{1}{r} \left[ \left(1 - \left(\frac{\bar{P}_2^2}{c2r}\right)^{\frac{r}{\gamma-r}}\right) \bar{P}_2^1 + \frac{1}{2} \left(\frac{\bar{P}_2^2}{c2r}\right)^{\frac{r}{\gamma-r}} \bar{P}_2^2 \right] \\ Ce^{-(\gamma-r)\hat{T}_2} &= \frac{1}{r} \left[ \left(1 - \left(\frac{\hat{P}_2^2}{c2r}\right)^{\frac{r}{\gamma-r}}\right) \hat{P}_2^1 + \frac{1}{2} \left(\frac{\hat{P}_2^2}{c2r}\right)^{\frac{r}{\gamma-r}} \hat{P}_2^2 \right] \end{aligned}$$

We see that the conclusions are the same as for proposition 3, except that the thresholds take different values.

## 5 Welfare and health expenditures

The consumers' welfare is computed using the same discount factor as the firms  $r$ . Denote  $\tau_i$  the delay of introduction of a follower and  $t_2$  the delay



of apparition of the pioneer. If  $W_t$  is the consumers' surplus at date  $t$ , as defined above, the intertemporal surplus is defined as

$$r \int_0^{\infty} W_t e^{-rt} dt$$

If there were no innovation the intertemporal consumer welfare would be

$$V_1 - (1 + \lambda) P$$

Let  $s_i$  be the welfare gain compared to this reference level in sequence  $i$ . We can decompose this gain in two terms: the first-one is related to the gains in health whereas the second-one captures variations in expenditures. More precisely, we have

$$s_i = h_i - (1 + \lambda)e_i$$

where  $h_i$  is the aggregate gain in wealth and  $e_i$  the increase in medical expenditures.

In absence of reference pricing, and when innovation follows a sequence of type 1 we have

$$\begin{aligned} h_1 &= e^{-r\bar{t}_2} v + e^{-r(\bar{t}_2 + \bar{\tau}_2)} \frac{\theta}{6}; \\ e_1 &= \left( e^{-r\bar{t}_2} - e^{-r(\bar{t}_2 + \bar{\tau}_2)} \right) (\bar{p}_2^1 - P) + e^{-r(\bar{t}_2 + \bar{\tau}_2)} \left( \frac{\bar{p}_2^2 + \bar{p}_2^1}{2} - P \right) \\ &= e^{-r\bar{t}_2} (\bar{p}_2^1 - P) + e^{-r(\bar{t}_2 + \bar{\tau}_2)} \left( \frac{\bar{p}_2^2 - \bar{p}_2^1}{2} \right) \end{aligned}$$

For sequence 2, we have

$$\begin{aligned} h_2 &= e^{-r\hat{\tau}_1} \frac{\theta}{6} + e^{-r\hat{t}_2} \left( v - \frac{\theta}{6} \right) + e^{-r(\hat{t}_2 + \hat{\tau}_2)} \frac{\theta}{6} \\ e_2 &= e^{-r\hat{\tau}_1} \left( \frac{\hat{p}_1^2 - P}{2} \right) + e^{-r\hat{t}_2} \left( \hat{p}_2^1 - \frac{P + \hat{p}_1^2}{2} \right) + e^{-r(\hat{t}_2 + \hat{\tau}_2)} \left( \frac{\hat{p}_2^2 - \hat{p}_2^1}{2} \right) \end{aligned}$$

For the case where the regulator uses therapeutic classes, we obtain similar formulas for welfare:

$$\begin{aligned} S_1 &= H_1 - (1 + \lambda) E_1 \\ H_1 &= e^{-r\bar{T}_2} v + e^{-r(\bar{T}_2 + \bar{\tau}_2)} \frac{\theta}{6} \\ E_1 &= e^{-r\bar{T}_2} (\bar{P}_2^1 - P) + e^{-r(\bar{t}_2 + \bar{\tau}_2)} \left( \frac{\bar{P}_2^2 - \bar{P}_2^1}{2} \right) \end{aligned}$$

And,

$$\begin{aligned}
S_2 &= H_2 - (1 + \lambda) E_2 \\
H_2 &= e^{-r\hat{\tau}_1} \frac{\theta}{6} + e^{-r\hat{T}_2} \left( v - \frac{\theta}{6} \right) + e^{-r(\hat{T}_2 + \hat{\tau}_2)} \frac{\theta}{6} \\
E_2 &= e^{-r\hat{\tau}_1} \left( \hat{P}_1^2 - P \right) + e^{-r\hat{T}_2} \left( \hat{P}_2^1 - \hat{P}_1^2 \right) + e^{-r(\hat{t}_2 + \hat{\tau}_2)} \left( \hat{P}_2^2 - \hat{P}_1^2 \right)
\end{aligned}$$

The introduction by the legislator of a *RP* regulation has two potential effects:

- First expenses are affected through two channels:
  - the new price applies to all drugs when an innovation occurs
  - the regulator negotiates different prices (lower prices)
- Second, the dynamics of innovation is affected:
  - within a sequence, introductory delays changes
  - the sequence may change, for instance the follower in level 1 may be introduced without *RP* but not with *RP*.

When the legislator changes the regulatory regime to *RP*, for a fixed innovation paths expenses are reduced but the final impact depends on the effect on innovation. The changes in the pattern of innovation will affect both the health level and the expenses. Moreover, it is worth noticing that there may be countervailing effects on expenses due to different delays.

As seen above, under reasonable assumptions, horizontal innovations reduces total expenses. Thus a delay in the introduction of followers would be detrimental to expenses. Intuition suggests that *RP* may generate such effects, since it raises delays for the follower in level 2, at fixed date of introduction of the level 2 pioneer, it also raises the delay for the follower in level 1.

However the introductory time of the pioneer in level 1 is also affected in a non-trivial way. Indeed, there are two conflicting effects. On one hand, the profitability of a pioneer is reduced because its price decreases when the follower is introduced. On the other hand, the delay of introduction of the

follower increases, allowing the producer of a pioneer to generate larger sales. The global effect of imposing  $RP$  is thus ambiguous.

Notice that as the prices of followers are smaller with therapeutic classes, it is true that  $\bar{T} > \bar{t}$ . Everything being equal ( $t_2$  fixed in both sequence 1 and 2), the number of followers is smaller with  $RP$ , meaning that sequence 2 appears under more stringent conditions. This suggests that  $RP$  may eliminate the apparition of the follower 1, which we can anticipate having a negative impact on health expenditures.

The impact on health is ambiguous. On one hand, for a given sequence, one can expect that  $RP$  has a negative impact on health by delaying innovations. On the other hand, moving from sequence 2 to sequence 1 would have an ambiguous effect as one innovation never occurs and the pioneer occurs after a smaller length of time.

## 6 Numerical results

In order to obtain more insight on the impact of the change of regime on the dynamics of innovation and on consumers welfare, we develop some numerical simulations. We use the market for statins as a way to benchmark some parameters of the model and to get some insight on the likely impact of  $RP$  on the dynamics of this type of medicaments.

### 6.1 The statins

Statins are the most effective drugs to reduce the LDL – cholesterol in blood. In France, the market for statin was born in 1989 with the introduction of Simvastatin (20 mg). In the following 15 years, new products have been regularly introduced. In 2004 there were five available substance, with Simvastatin, Pravastatin (introduced in 1991), Fluvastatin (introduced in 1996), Atorvastatin (introduce in 1998) and Rosuvastatin (introduced in 2004). The first generic appeared in year 2005, and should be followed by another one (for Pravastatin) in year 2006. Each substance is now available in 2 to 4 dosages.<sup>19</sup>

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<sup>19</sup>We than Pfizer France and Jean-François Guichard for providing these data. Prices are for a 4 weeks treatment. Percentage reduction are derived from Etude BMJ 2003.326.7404.1423 par MR Law, NJ Wald et AR Rudnicka, ‘Quantifying effect of statins on LDL cholesterol, ischaemic heart disease and stroke : systematic review and meta-

These molecules have different performance levels, in particular in term of percentage reduction achieved for a given daily dose. They also differ on the nature of the secondary effect generated by each molecule, but we don't have data on this aspect. For a daily dose of  $20mg$ , the mean percentage reduction in "bad" cholesterol achieved are 32 % for Simvastatin, 24 % for Pravastatin, 21 % for Fluvastatin and 43 % for Atorvastatin. The last drug, Rosuvastatin obtains a reduction of 48 %. Differences are significant at a 95% confidence interval, except between Pravastatin and Fluvastatin, and Atorvastatin. and Rosuvastatin. Similar patterns occur for higher doses ( $40mg$  or  $80mg$ ).

This shows a clear difference between the first three molecules and the last two. Indeed this difference has allowed the producers of Atorvastatin and Rosuvastatin to launch products at daily doses of  $10mg$ , while the others stay above  $20mg$ . The corresponding reductions in cholesterol are 37 % and 43 %, above the level achieved by the others at 20%.

The expansion in the supply came along with a very rapid growth of statin consumption. In economic terms, if we add all product together, the sales value grew at more than 17 % per year over the period, despite of regular price reductions. The average growth rate during the last 4 years, is still at 15 %. Even the oldest drug (Simvastatin 20mg) continues being sold in growing quantities, despite the fact that it now suffers from the concurrence of other statins on the market. There has been in fact an extraordinary growth of the demand for statins, which benefited to all statins, and which is also the source of an increase of expenditure for the health care system in France.

In figure 1 we depict the evolutions of market shares of each molecule. The market share have been changing very importantly over time (see Figure 1). Simvastatin, the first statin to be introduced remained leader until 2000 where it lost the first position to Pravastatin and Atorvastatin. Fluvastatin has expanded very little, and Rosuvastatin still has a very short history. For most substance there is dosage that appears much more popular than the others and that sell about twice as much as the second dosage of the same substance.

Prices went down along all the period. Simvastatin 20mg which was first sold at 30,05 Euros is no sold at 19,34. The other drugs experimented similar decline (see the table in figure 2). A particularity of the market, is that entrants were market at price that were lower than those of older drugs, even if they were recognized to have a greater efficiency. This is the case for

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analysis'

example of Atorvastatin 10mg which was first sold at 20.62, and was then therefore cheaper than the oldest Pravastatin and Simvastatin, although it is known for generating greater a decrease in cholesterol.

## 6.2 Simulations

We use the above data to get some insights on relevant parameters. First as pointed above Fluvastatin had only a marginal impact on the market, and Rosuvastatin just emerges. We thus decided to focus on the three main medicaments, Simvastatin, Pravastatin and Atorvastatin. In each molecule some dose seems to be determinant, in particular 20mg doses for the first two are largely dominant. From the data above, we decided to include the first two molecules in one level, and to classify Atorvastatin as a vertical innovation as defined in our model.

Our model has little to say about volumes and in any case demand in increasing over time.<sup>20</sup> So we use prices as a benchmark. We face however a difficulty because molecules are available at different doses and we don't know which is the relevant one. Should we consider Atorvastatin at 10mg which is above but not too far from Simvastatin 20mg in terms of reduction in cholesterol, or is it the dose that matters under our modelling assumptions in case we should consider Atorvastatin at 20mg. Given that tolerance is related to doses, we opted for the second option.

The second issue relates to the fact that we observe a general trend in decreasing prices that is not accounted for in the model. This means that we can not directly compare directly introductory prices. To avoid the issue we choose the prices of a given year as a benchmark, namely 2004.

The data thus corresponds to a sequence of type 1 with an horizontal innovation in level 1. We have 3 prices available namely 20.75 for Simvastatin, 18.92 for Pravastatin and 32.76 for Atorvastatin. Prices allow to calibrate the equation of bargaining between the regulators and the innovator. However for prices, 3 parameters matter  $\alpha$ ,  $\frac{v}{1+\lambda}$ ,  $\frac{\theta}{1+\lambda}$ . We thus calibrated the last two as a function of  $\alpha$ . We present the predicted prices for each possible trajectories for  $\alpha = 0.2$ . patterns are similar for other values:

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<sup>20</sup>Notice that our model can easily accomodate a time trend in demand, but adjusting the discount factor. Indeed increasing demand is formally equivalent to reducing  $\delta$ .

|                 |         |         |         |
|-----------------|---------|---------|---------|
| $\alpha = 0.2$  | $p_1^2$ | $p_2^1$ | $p_2^2$ |
| <i>no RP</i>    | 18.92   | 32.76   | 28.52   |
| <i>RP seq 1</i> | –       | 34.65   | 28.9    |
| <i>RP seq 2</i> | 17.76   | 31.10   | 26.04   |

Notice that prices are higher under sequence 1, due to the disappearance of the first innovation.

Delays are more difficult to interpret as in the model we ignore the intrinsic randomness of innovation. In the data we have a delay of 9 years for the vertical innovation, and 2 and 6 years for an horizontal innovation, so an average of 3 years. In our model  $\hat{\tau}_2 < \hat{\tau}_1$  which is not the case in the data. This may be due to randomness and/or to external effects such as the deflationary trend. We set  $\gamma = 0.5$  and we do not calibrate the costs parameters  $c$  and  $C$  but rather check that predicted innovation delays are consistent with observed patterns. For various value of  $\alpha$  we adjust these costs to generate various scenarios. All our results have pointed to the same conclusions.

We present below the predicted trajectories for various scenarios. We also computed the discounted consumers' surplus (the term  $h$  or  $H$  in the surplus) and the discounted expenses (the term  $e$  or  $E$ ). More precisely we computed the change in the benefits for consumers and in expenses compared to a situation with no innovation at all.

We summarize the results below

|                |                           |                |                           |        |          |
|----------------|---------------------------|----------------|---------------------------|--------|----------|
| $\alpha = 0.2$ | $\tau_1$ or $\varsigma_1$ | $t_2$ or $T_2$ | $\tau_2$ or $\varsigma_2$ | health | expenses |
| <i>no RP</i>   | 4.8                       | 11.4           | 0.73                      | 20.11  | 6.13     |
| <i>RP</i>      | 4.96                      | 11.5           | 0.93                      | 20.02  | 4.71     |
| <i>no RP</i>   | 7.14                      | 9.64           | 1.13                      | 21.31  | 6.73     |
| <i>RP</i>      | <i>NO</i>                 | 9.52           | 1.1                       | 21.28  | 7.61     |
| $\alpha = 0.4$ | $\tau_1$ or $\varsigma_1$ | $t_2$ or $T_2$ | $\tau_2$ or $\varsigma_2$ | health | expenses |
| <i>no RP</i>   | 5.1                       | 10.76          | 0.93                      | 39.49  | 5.58     |
| <i>RP</i>      | 5.65                      | 10.9           | 1.36                      | 39.1   | 3.06     |
| <i>no RP</i>   | 7.06                      | 10.3           | 1.78                      | 39.54  | 5.82     |
| <i>RP</i>      | <i>NO</i>                 | 10.06          | 1.86                      | 39.26  | 7.03     |

| $\alpha = 0.6$ | $\tau_1$ or $\varsigma_1$ | $t_2$ or $T_2$ | $\tau_2$ or $\varsigma_2$ | health | expenses |
|----------------|---------------------------|----------------|---------------------------|--------|----------|
| <i>no RP</i>   | 4.82                      | 9.91           | 0.65                      | 79.83  | 4.98     |
| <i>RP</i>      | 6.01                      | 10.02          | 1.32                      | 78.57  | 1.88     |
| <i>no RP</i>   | 5.88                      | 9.86           | 1.22                      | 79.11  | 5.09     |
| <i>RP</i>      | <i>NO</i>                 | 9.49           | 1.52                      | 78.12  | 6.39     |

From the simulation we conclude that

1. The *RP* system tend to delay innovations. The only case where this not the case is when the level 1 innovation disappears and the pioneer arrives sooner.
2. In all cases, the *RP* system has a negative impact on health surplus
3. The system reduces expenses when the trajectory of innovation is not affected due to lower prices and less innovations.
4. But it raises expenses when some innovation is discouraged.

The global welfare effect will depend on the weight put on expenses relative to health. In any case it is negative when the trajectory changes.

## 7 Conclusions and extensions

The model allows to emphasize the interaction between the pricing policy constrained by various forms of regulation and the effort of innovation by pharmaceutical laboratories. We have identified antagonist effects of the regulation by means of the *RP* regulation: a decrease in price due to the production of followers reduces the incentives to create pioneer drugs; inversely, the introduction of followers is delayed, which gives positive incentives to launch pioneers. Consequently, the net effect of the uniform pricing rule within a class is ambiguous. However, it remains possible to obtain explicit solutions through numerical simulations.

Simulations show that the dynamic impact on the health of the population is negative due to less innovation, while the impact on expenses is ambiguous. What appears is that by favouring pioneer innovations at the expense of cost reducing innovations, the regulation may generate a medium/long run increase in expenses, despite potential short-run benefits.

In the model developed so far, we have introduced several drastic hypothesis in order to obtain a first analytical friendly framework. The next step will be to test how robust the results are when these simplifications are relaxed. Here are some examples.

i) The patient is fully reimbursed for all health expenses. This seems relevant for most European countries where demand shows little sensitivity to price for many treatments. The coverage may come from the social security system, or from private insurance contracts. It will have to (and can) be relaxed latter on.

ii) Prices are negotiated in our model, which is natural with 100% coverage. In many countries prices can freely be set above reimbursed levels. We should extend the model to allow for competitive pricing by the firms.

iii) We have adopted a deterministic innovation model according to which the laboratory chooses the time devoted to develop the new product. The extended version of the model should allow for random innovation technologies. In particular, we can use a random innovation process based on the Poisson law determining the instantaneous probability of discovery.

iv) The last point implies that the model does not allow for the coexistence on the market of drugs known for their large efficiency along with less efficient and less costly medications.<sup>21</sup>

v) We have ignored the potential moral hazard issues that may emerge during the course of the relationship between patients and doctors<sup>22</sup>. Doctors, after examination of the patients, could use their private information in a selfish manner.<sup>23</sup>

vi) We have ruled out pharmaceutical groups that produce several drugs and would internalize the effect of a new drug on the profitability of their portfolio. At the level of details that corresponds to the concept of therapeutic equivalence, this seems a reasonable assumption as groups tend to have only one molecule in a would-be class.

vii) The regulator maximizes the consumers' surplus net of the social cost of health expenditures. Moreover, the regulator is myopic, meaning that he only takes into account the current surplus and ignores the impact

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<sup>21</sup>This assumption is consistent with the model if the ranking between drugs is not uniform for all patients. Alternatively one could introduce marketing strategies.

<sup>22</sup>The so-called induced demand.

<sup>23</sup>Relaxing these assumptions may also allow to leave some room for advertising. The marketing strategies of pharmaceutical groups include both an informative dimension and a persuasive one (see for instance Hurwitz and Caves [1988]).



of the current prices on future prices and the innovation process. These assumptions allow to isolate the negotiation of prices from the innovation process <sup>24</sup>.

vii) Each innovation is supposed to be protected by an unchallenged patent of infinite duration. The model can be extended to fix the patent duration and to handle the problem of generic products.

## References

- [1] Anderson S, de Palma A and Thisse J, 1992, *Discrete Choice Theory of Product Differentiation*, MIT Press.
- [2] Bardey D and Lesur R, 2006, "Supply Induced Demand, [Ex post](#) Moral Hazard and Optimal Health Insurance Contract", [Annals of Economics and Statistics](#), forthcoming.
- [3] Blomqvist A., 1997, "Optimal non-linear health insurance", [Journal of Health Economics](#), 16, p303-321.
- [4] Cabrales A, 2003, "Pharmaceutical Generics, Vertical Product Differentiation, and Public Policy", Working Paper Pompeu Fabra.
- [5] Castello A-M, 2003, "Impact of the reference Price System on the Pharmaceutical Market: a Theoretical Approach", Working Paper Pompeu Fabra.
- [6] Caves R, Whinston M and Hurwitz M, 1991, "Patent Expiration, Entry, and Competition in the US Pharmaceutical Industry", [Brooking Papers on Economic Activity: Microeconomics](#), p1-66.
- [7] Danzon P and Chao L, 2000, "Does Regulation Drive Out Competition in Pharmaceutical Markets", [Journal of Law and Economics](#), 43, p311-357.
- [8] Danzon P and Liu H, 1996, "Reference Pricing and Physician Drug Budgets: The German Experience in Controlling Pharmaceutical Expenditures, Working Paper Wharton School.

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<sup>24</sup>In other words, we have assumed that innovations arise at a pace that is slow enough not to interfere with price negotiations.

- [9] Danzon P and Ketchman, 2003, "Reference Pricing of Pharmaceuticals for Medicare: Evidence from Germany, the Netherlands and New Zealand", NBER Working Paper.
- [10] Danzon P and Pauly M, 2002, "Health Insurance and the Growth in Pharmaceutical Expenditures", [Journal of Law and Economics](#), vol XLV, p587-613.
- [11] Eggleston K, 2000, "Risk Selection and Optimal Payment Systems for Medical Services", [Journal of Risk and Insurance](#), 67(2), p173-196.
- [12] Frank R and Salkever S, 1992, "Pricing, Patent Loss and the Market for Pharmaceuticals", [Southern Economic Journal](#), 59, p165-179.
- [13] Frank R and Salkever S, 1997, "Generic Entry and the Market for Pharmaceuticals", [Journal of Economic and Management Strategy](#), 6, p75-90.
- [14] Gal-Or E, 1997, "Exclusionary Equilibria in Health Care Markets", [Journal of Economic and Management Strategy](#), p5-43.
- [15] Gal-Or E, 1999, "Mergers and Exclusionary Practices in Health Care Markets", [Journal of Economic and Management Strategy](#), p 315-350.
- [16] Grabowski H, 1980, Drug Regulation and Innovation.
- [17] Hurwitz M and Caves R, 1988, "Persuasion or Information? Promotion and the Shares of Brand-Name and Generic Pharmaceuticals", [Journal of Law and Economics](#), 31, p299-320.
- [18] Laffont J-J and Tirole J, 1993, A Theory of Incentives in Procurement and Regulation, MIT Press.
- [19] Lopez-Casnovas G and Puig-Junoy J, 2000, "Review of the literature on reference pricing", [Health Policy](#), 54, p87-123.
- [20] Ma A. and McGuire T, 1997, "Optimal Health Insurance and Provider Payment", [American Economic Review](#), 87, No. 4.
- [21] Manning R and Marquis S, 1996, "Health Insurance: The Trade-off between Risk Pooling and Moral Hazard", [Journal of Health Economics](#), 15, p609-640.

- [22] Mestre-Ferrandiz J, 1999, "The Impact of Generic Goods in the Pharmaceutical Industry", [Health Economics](#), 8, p599-612.
- [23] Pauly M, 1968, "The Economics of Moral Hazard: Comment", [American Economic Review](#), 58, pp.531-537.
- [24] Rice D, 1993, "Demand Curves, Economists and Deserts Islands: a response to Feldman and Dowd", [Journal of Health Economics](#), 12, pp.201-204.
- [25] Rizzo J and Zeckhauser R, 2005, "Generic Scrip Share and the Price of Brand-Name Drugs: the Role of Consumer Choice", NBER Working Paper.
- [26] Scherer F, 1993, "Pricing, Profits and Technological Progress in the Pharmaceutical Industry", [Journal of Economic Perspectives](#), 7(3), p97-115.
- [27] Schmalensee R, 1982, "Product Differentiation Advantages of Pioneering Brands, 72, [American Economic Review](#), p349-365.
- [28] Weisbrod B, 1991, "The Health Care Quadrilemma: An Essay on Technological Change, Insurance, Quality of care, and Cost Containment", [Journal of economic Literature](#), 29, p 523-552.
- [29] Zeckhauser R, 1970, "Medical Insurance: A Case Study of the Tradeoff Between Risk Spreading and Appropriate Incentives", [Journal of Economic Theory](#), 2, 10-26.
- [30] Zweifel P and Crivelli L, 1996, "Price Regulation: Lessons from Germany, 9, [Journal of Regulatory Economics](#).

## 8 Appendix

### 8.1 Proof of Lemma 1

**Proof.** The slope of the function  $\Phi$  is:

$$\Phi'(\Delta) = \Phi(\Delta) \left( \gamma - \frac{r}{1 - e^{-r\Delta}} \right).$$

$\Phi$  is quasi-convex with a minimum

$$\underline{\Phi} = \frac{c\gamma \left(\frac{\gamma-r}{\gamma}\right)^{-\frac{\gamma-r}{r}}}{r} \text{ at } \underline{\Delta} = -\frac{\ln(1 - \frac{r}{\gamma})}{r} > 0$$

By assumption 3, we have

$$\underline{\Phi} > \frac{\hat{p}_1^2}{2r} e^{(\gamma-r)\underline{\Delta}}.$$

As the function decreases on  $(0, \underline{\Phi})$ ,  $\Phi(\Delta) > \frac{\hat{p}_1^2}{2r} e^{(\gamma-r)\bar{t}_2}$  for all  $\Delta \leq \bar{t}_2 < \underline{\Delta}$ . Thus the equilibrium exists if  $\frac{\hat{p}_1^2}{2r} e^{(\gamma-r)\bar{t}_2} \leq \underline{\Phi}$ . This closes the proof. ■

## 8.2 Proof of Proposition 1

**Proof.** An equilibrium exists for all values of  $\bar{t}$  if  $\bar{t}_2 < \hat{t}_2$ .

$$\begin{aligned} \chi'(p) &= \frac{1}{2r} \left( 2 - \left( \frac{(1-\alpha) \left[ p + \frac{\theta}{3(1+\lambda)} \right]}{c2r} \right)^{\frac{r}{\gamma-r}} \right) \\ &\quad - \frac{p}{2r} \left( \frac{r}{\gamma-r} \left( \frac{1-\alpha}{c2r} \right)^{\frac{r}{\gamma-r}} \left( p + \frac{\theta}{3(1+\lambda)} \right)^{\frac{r}{\gamma-r}-1} \right) \end{aligned}$$

$$2r\chi'(p) = 2 - \left( 1 + \frac{p}{p + \frac{\theta}{3(1+\lambda)}} \left( \frac{r}{\gamma-r} \right) \right) \left( \frac{(1-\alpha) \left[ p + \frac{\theta}{3(1+\lambda)} \right]}{c2r} \right)^{\frac{r}{\gamma-r}}$$

$\chi(p)$  is concave. For  $c$  large it is increasing in the relevant range. By assumption 3

$$\begin{aligned} 2r\chi'(p) &> 2 - \left( 1 + \frac{p}{p + \frac{\theta}{3(1+\lambda)}} \left( \frac{r}{\gamma-r} \right) \right) \\ &> 1 - \frac{p}{p + \frac{\theta}{3(1+\lambda)}} \left( \frac{r}{\gamma-r} \right) > \frac{p \left( \frac{\gamma-2r}{\gamma-r} \right) + \frac{\theta}{3(1+\lambda)}}{p + \frac{\theta}{3(1+\lambda)}} \end{aligned}$$

This is positive for  $\gamma > 2r$  for any price.

When  $\chi$  is increasing the results follows from  $\bar{p}_2^1 > \hat{p}_2^1$ . ■

Figure 1:

Figure 2: