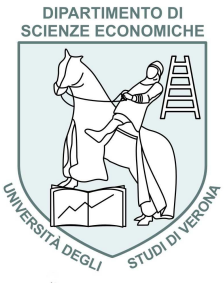

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The dynamics of pharmaceutical regulation and R&D investments*

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Abstract

The paper uses a real option approach to investigate the potential impact of performance-based risk-sharing agreements for the reimbursement of new drugs in comparison with standard cost-effectiveness thresholds. The results show that the exact definition of the risk-sharing agreement is key in determining its economic effects. In particular, despite the concerns expressed by some authors, the incentive for a firm to invest in R&D may be the same or even greater than under cost-effectiveness thresholds, if the agreement is sufficiently mild in defining the conditions under which the product is not (fully) reimbursed to the firm. In this case, patients would benefit from earlier access to innovations. The price for this is less value for money for the insurer at the time of adoption of the innovation.

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1 Introduction

Total pharmaceutical expenditure across OECD countries was estimated at over USD 700 billion in 2009, accounting for around 19% of total health expenditure. Between 2000 and 2009, average spending on pharmaceuticals rose by almost 50% in real terms (OECD, 2011). Although in several countries this is not the most rapidly growing component of health care expenditure, its regulation is receiving particular attention. Motivations for such pervasive regulation include market failures at several levels and the need to manage a complex trade-off between incentives to R&D investments for the industry, access to pharmaceuticals for patients, and value for money of public expenditure.

The identification of the ideal equilibrium is subject to some controversy. Opponents of strict regulation argue that it may adversely affect incentives to develop new and better products, and possibly cause crowding-out of price competition (Danzon and Chao, 2000). These concerns seem to be supported by growing evidence of a negative trend in productivity of the industry's R&D spending. In 2003, pharmaceutical companies invested more than US$ 33 billion in R&D worldwide compared to about US$ 13 billion just a decade before. However, the number of new molecular entities (NMEs) approved for market entry by the Food and Drug Administration (FDA) in the US declined from 53 in 1996 to only 26 in 2010 (PhRMA, 2011). DiMasi et al. (2003) report evidence of an increasing trend in the average R&D cost of new drugs. More recently, Pammolli et al. (2011) have shown that the R&D productivity of the pharmaceutical industry has been falling since 1990.

Although most of the research on pharmaceutical regulation has explored the welfare properties of alternative solutions focusing on the use of new drugs, some contributions have gone further, studying its impact on the industry's propensity to invest in R&D. Regulation of prices has received the greatest attention in this literature. The key trade-off is between static efficiency - making drugs accessible to all those who need them - and dynamic efficiency -

ensuring that a firms' profits are robust enough to sustain R&D investments. Filson (2012) investigates the welfare properties of pharmaceutical price regulation and concludes that consumers in the United States tend to be better-off with market prices: long-term losses in static efficiency due to regulation outweigh short-term gains in static efficiency. Danzon et al. (2012) show that with universal insurance, value-based prices can be second-best static and dynamic efficient within and across countries. Insurance is obviously crucial, because static efficiency depends on consumer prices. Lakdawalla and Sood (2009) show that public sector insurance can enhance welfare by mitigating the trade-off between static and dynamic efficiency. Garber et al. (2006) study the optimal coinsurance rate in a framework where patent-owning firms fix monopoly prices. We depart from this literature in both the regulatory policy we focus on and the methodology we adopt.

Our interest is not in price setting regulation, but in the rules that define under what conditions an insurer reimburses a new drug. In particular, we compare a well-established type of regulation based on a maximum threshold for the Incremental Cost-Effectiveness Ratio (ICER), with a performance-based *risk-sharing agreement*. Under the former, only technologies for which the increase in costs per unit of effectiveness gained falls below some predefined threshold are reimbursed. With performance-based *risk-sharing agreements* regulation operates at a later stage: the firm will not be (fully) paid by the insurer if the effectiveness of the product in use falls below a certain level. Risk-sharing agreements have recently gained increasing attention as means to mitigate the impact of uncertainty on the true effectiveness of new drugs, which is often still great at the time of approval. With these types of agreements regulator focus shifts from the stage at which the insurer decides whether to reimburse a new product, to the time when it is used by patients. Similar contracts are of potential interest to both public and private insurers. It is no surprise then that although the debate on this form of regulation has been mainly at the European level, interest is also growing in the U.S.

(Neumann et al., 2011).

Pita Barros (2011) studies the static efficiency properties of risk-sharing agreements. The author concludes that they are welfare improving only '*under a restrictive set of assumptions*' (Pita Barros, 2011, p. 467) and calls for further investigation of a number of issues including strategic reactions by the firm in price setting and the role of monitoring costs. The aims of our work are similar to those pursued by Jena and Philipson (2008) in their analysis of the static and dynamic efficiency implications of conditioning adoption to a cost-effectiveness threshold. They discuss the central role of the threshold in determining producers' surplus and hence the incentive to invest in innovation. A similar analysis still seems absent for risk-sharing agreements. In comparison with Jena and Philipson (2008) we limit attention to the supply side, but develop a fully dynamic, stochastic structure of the model.

Concerning methodology, some characteristics of the complex process of innovation and diffusion of pharmaceuticals do not seem to have been taken into full account so far in studying regulation. R&D investments are typically sunk costs on which the firm makes decisions under substantial uncertainty. Moreover, insurers' decisions on the reimbursement of new drugs will also be made under uncertainty, as evidence of the true effectiveness is typically scarce at the time of launch of innovations (Gelijns and Rosenberg, 1994) and effectiveness may differ from efficacy (Eichler et al., 2011). The real option approach provides a suitable tool to study optimal behaviour related to irreversible decisions made under uncertainty (Dixit and Pindyck, 1994). This approach has been previously adopted to study the value of pharmaceutical R&D projects (Pennings and Sereno, 2011; Shockley et al., 2002; Burman and Senn, 2003; Cassimon et al., 2004), but with no focus on the role of regulation.

To the best of our knowledge, this is the first dynamic model to investigate the implications of regulation of the adoption of new pharmaceuticals on different stages of a drug's life cycle, accounting for uncertainty related to: (i)

the success of the R&D investment (borne by the firm), (*ii*) the true effectiveness of the new drugs in clinical use (borne by the insurer). The timing with which patients gain access to innovations is a crucial policy objective and has been mentioned as one of the motivations for risk-sharing agreements. The adoption of a real option approach implies an explicit characterization of the time dimension in our analysis.

In comparison with cost-effectiveness thresholds, risk-sharing agreements reduce the risk faced by the payer during commercialization. This is obviously beneficial to the insurer. However, concerns have also been expressed that this may end up weakening the firm's incentive to undertake new development projects (Cook et al., 2008). Our analysis shows that it is not the replacement of cost-effectiveness thresholds with risk-sharing agreements *per se* to imply this, rather, the results depend on the specific terms of the agreement. In particular, a risk-sharing agreement may provide the same, or even a greater incentive to invest in R&D while allowing earlier patient access to the innovation. A necessary condition for this to be the case is that insurers agree to reimburse products whose value for money at the time of adoption is less than it would be if regulation were based on cost-effectiveness thresholds. Uncertainty plays a crucial role: the greater flexibility on the timing of commercialization allowed by risk-sharing agreements has a positive impact on the value of the industry's option to invest in R&D. However, this also implies that an increase in uncertainty tends to reduce the comparative advantage of risk-sharing agreements in allowing early access to innovations for patients.

The next section introduces the model, which is solved in Section 3 and Section 4 to determine the firm's optimal behaviour respectively under risk-sharing and cost-effectiveness thresholds. The following section compares the performance of the two regulatory schemes with respect to specific policy objectives. Section 6 discusses the policy implications of the results. Section 7 concludes.

2 The Model

In an infinite horizon continuous time framework, two separate stages of a new drug's life are studied:[1] (1) development of the new molecular entity and, (2) commercialization.

2.1 The industry

1. Development of the new molecular entity

At the initial stage, $t = t_0$, a pharmaceutical firm is faced with the decision whether to pay, in advance, the sunk cost I to start a R&D project of a new molecular entity, whose current effectiveness is μ_0. This level remains fixed until a development project is initiated. The effectiveness of the drug currently in use is denoted by $\underline{\mu}$.

If the development project is initiated, the effectiveness of the new drug evolves according to a stochastic process described as a Geometric Brownian Motion (GBM):

$$d\mu_t = \alpha\mu_t dt + \sigma_d \mu_t dw_t. \tag{1}$$

The above process shows a deterministic component (first term) and a stochastic component (second term). We assume that the drift α is positive, meaning that if the development project is undertaken it will enable improvement in the effectiveness of the innovation.[2] The realizations of dw_t are identically and independently distributed according to a normal distribution with mean zero and variance dt, and the volatility parameter σ_d is constant through time. Therefore, starting from an initial value μ_0, the random position of μ_t at time $t > 0$ has a lognormal distribution with mean $\ln \mu_0 + (\alpha - \frac{1}{2}\sigma_d^2)t$ and

[1] For a similar characterization of the process, see Pennings and Sereno (2011).

[2] For instance, this can be attained through dose ranging phase II studies. In principle, a positive relationship between α and I might be expected to exist. The optimal determination of I, for the case in which the firm is free to choose it, is beyond the scope of the present work.

variance $\sigma_d^2 t$ which increases as we look further into the future. Moreover, since the process has "no memory" (i.e. it is Markovian), at any point in time t, the observed μ_t is the best predictor of future effectiveness.[3] The development stage goes from t_0 to the time when the new drug is commercialized. That is, for $t \geq t_0$ the firm observes μ_t and, if allowed by the regulatory scheme in place, establishes the optimal timing, T, to bring the innovation to market. However, a number of events can bring the development process to a permanent halt.[4] We regulate these shocks by a Poisson process with intensity δ, so that for each period there is a probability δdt that a sudden jump occurs and the development process stops.[5]

2. Commercialization.

If the drug is to be sold on the international market, companies usually first apply for Food and Drug Administration (FDA) approval and then to national or super national authorities (e.g. the European Medicines Agency). For the drug industry approval is a prerequisite to one of the most crucial steps in the life of the new product: the listing process, i.e. the possibility of having the drug paid for through a public or private insurer. Approval from the FDA, or from corresponding national authorities, allows companies to sell the drug on the market at virtually any price. However, out-of-pocket expenditure for drug is rather limited and in any case it is unlikely to provide firms with sufficient returns on the investment. Hence, we concentrate on revenues to the firm from a third-payer. In our framework, the shift from development to commercialization is conditional on the success of the listing

[3]Assuming that the state variable follows a lognormal random walk is standard in real-option models (Dixit and Pindyck, 1994) and has been previously used in the health economics literature (Palmer and Smith, 2000; Levaggi et al., 2012).

[4]Examples include the impossibility of replicating results obtained on animals on humans or excessive toxicity of the molecular entity.

[5]We could alternatively assume that below a certain minimum level of effectiveness the firm abandons development. Taking this option to exit into account the analysis would be more complicated but the results would be identical because in both cases the drug never comes to commercialization.

process.

It may be useful to clarify some key terminology in what follows: we use the term *listing* for the procedure that defines whether a new drug will be reimbursed by an insurer.[6] Successful completion of the listing process implies *adoption* of the new drug. From the firm's perspective an *adoption* decision means the start of the *commercialization* stage. Finally, *de-listing* refers to the exclusion from reimbursement of a drug that had been previously adopted. Since we focus on sales paid for by and insurer, it also implies the end of commercialization.

If at T the drug is adopted, the firm's instantaneous pay-off through commercialization is:

$$\Pi_t = p - c \quad \text{for} \quad t \geq T, \tag{2}$$

where p is the unitary price and c the unitary production cost. Before commercialization ($t < T$) Π_t is always nil. The number of units sold - assumed constant in time - is normalized to one. The firm obtains Π_t for each period during commercialization. Since the focus of our paper is on the comparison between regulation based on standard cost-effectiveness thresholds *versus* risk-sharing agreements, the comparison assumes that the price, no matter how it is fixed, is the same under both regulatory schemes and it is kept constant in time. This is equivalent to assuming that the price is either exogenous (e.g. an external *reference price*)[7] or, if the two parties involved have some bargaining power, the regulation concerning listing does not affect the price setting strategy.[8]

[6] Note that for our analysis it is irrelevant whether regulator and insurer are the same institution or not.

[7] Several countries use the price previously fixed in other countries as an upper boundary for their internal price.

[8] One factor limiting the firm's power to fix prices is that insurers are not only interested in the cost-effectiveness implications of innovations but also in the expected budget impact. This may lead to situations where the price is determined by the size of the budget, which is often exogenous, and is not dependent on the effectiveness of the new drug.

Substantial uncertainty regarding new technologies coming to the market is a well known issue (Eichler et al., 2011). Hence, we assume that effectiveness is still stochastic after commercialization. Uncertainty is described by the following GBM process:

$$d\mu_t = \sigma_c \mu_t dw_t. \tag{3}$$

Unlike the process in eq. (1) this is a trendless process, reflecting the fact that adoption implies the end of the development stage, after which the product cannot be altered. The volatility component, σ_c, is also different in general, because the determinants of uncertainty change when moving from development to commercialization.[9]

2.2 The regulator

Within each regulatory scheme the regulator sets the relevant parameters before the firm makes any decision, and can commit to them. For the implementation of regulation, μ_t can be observed at any point in time, and it is also assumed to be verifiable.[10]

We mentioned in the Introduction a multiplicity of objectives that policy makers struggle to reconcile through regulation. The following list summarizes the main goals underlying the design of current policies and the ongoing debate:

1. Making effective products quickly available to patients;
2. Ensuring that innovations adopted are good value for money;
3. Providing incentives to R&D investment by the industry;

[9] See also Pennings and Sereno (2011) on this point.

[10] Consistent with the jargon from the literature on incomplete contracts, this implies that effectiveness can be verified by a third party, typically a court.

4. Reducing the risk that true effectiveness of the new drug in clinical use falls below the level reported at the time of adoption.

In what follows we will first characterize the firm's optimal decisions under risk-sharing agreements (Section 3) and regulation based on an ICER threshold (Section 4), and then compare performance of the two with respect to the attainment of these policy goals (Section 5).

3 Risk-sharing agreements

Regulation through risk-sharing (hereinafter, RS) agreements has recently come to be considered by regulators a means to mitigate the impact of uncertainty on the true effectiveness of new drugs. Such agreements can be classified into two categories (Adamski et al., 2010): performance-based and financial-based. In the former, prices depend on the evidence of effectiveness emerging during commercialization. In financial-based agreements it is total expenditure for the third payer that affects prices.

The type of regulation considered in the present section is consistent with performance-based RS. In order to stress the comparison between *ex-ante* and *ex-post* regulation, we assume that under RS no explicit condition is set for listing. However, if after adoption μ_t falls below a minimum threshold μ_l set by the regulator the new drug is de-listed, implying zero revenues for the firm in all subsequent periods.[11] Hence, μ_l is the policy parameter set by the regulator under RS. The type of RS agreement that we model is formally operating at the aggregate level: dependant on the value of μ_t after listing, either the entire eligible population is treated with the new drug (if $\mu_t \geq \mu_l$),

[11] Of course, this implies that adoption takes place only at levels of effectiveness such that $\mu_t > \mu_l$. Note that under some RS agreements the drop of effectiveness below μ_l does not imply de-listing (i.e. $p = 0$), but only a discount on p. The assumption that $p = 0$ for $\mu < \mu_l$ simplifies the analysis without changing the quality of the results. Agreements with this characteristic are sometime called *pay for performance*. In order to ease exposition, we ignore the difference between *risk-sharing* and *pay for performance* in what follows.

or no patient (if $\mu_t < \mu_l$).[12] Alternatively, agreements may operate at the individual level: only the cost of treatment for patients who have met specified clinical targets is (fully) paid to the firm. However, the economic implications are the same, since the scheme we model shares with those defined at the individual level the key economic characteristic that a more restrictive policy - due to an increase in the minimum level of effectiveness below which the treatment is not (or only partially) reimbursed - reduces the firm's expected profit. Therefore, given the boundary μ_l, a lower level of effectiveness at a given point in time during commercialization also implies lower profits in expected terms. The following proposition summarizes the link between regulatory policy and a firm's optimal behaviour:

Proposition 1 *A tightening of the RS regulatory policy through an increase in μ_l leads to a delay in adoption, a lower ICER at the time of adoption, and a weaker incentive to invest in R&D for the firm.*

The next two sub-sections and Appendix A describe the derivation of the results of Proposition 1.

3.1 Timing of listing

The problem the firm needs to solve is known as *optimal stopping* in the real option literature (Dixit and Pindyck, 1994). The solution is obtained by working backwards, starting from commercialization and subsequently moving to the development stage. Using an exogenously specified discount rate ρ, during commercialization, the value function for the firm is given by:

$$V^r(\mu_t) = E_t \left[\int_t^{T_l} \Pi_t e^{-\rho(s-t)} ds \right],$$

[12]The first risk sharing scheme prompted by a technology appraisal by the National Institute for Health and Care Excellence (NICE) in the UK, introduced in 2002 for the provision of beta interferons and glatiramer for multiple sclerosis was of this type. Companies agreed to lower drug prices if they failed to meet a £36,000/QALY threshold, with disease progression monitored in a minimum of 5,000 patients over a 10-year period.

where $T_l = \inf(t \geq 0 : \mu_t \leq \mu_l)$ be the stochastic de-listing time, i.e. the first time that μ_t hits the lower level μ_l, $E_t(\cdot)$ is the expectation taken with respect to eq. (3).

The general solution for $V^r(\mu_t)$ is obtained by verifying that the expected change of $V^r(\mu_t)$ satisfies a second-order linear differential equation under some suitable boundary conditions at T_l (see Appendix A). The solution is:

$$V^r(\mu_t) = C_2^r \mu_t^\theta + \frac{p-c}{\rho}, \tag{4}$$

where:

$$C_2^r = -\mu_l^{-\theta}\left(\frac{p-c}{\rho}\right) < 0 \tag{5}$$

and

$$\theta = \frac{1}{2} - \sqrt{\frac{1}{4} + \frac{2\rho}{\sigma_c^2}} < 0. \tag{6}$$

The interpretation is straightforward: the value is the present value of profits (second term in eq. 4), net of the cost associated with the possibility that the threshold value μ_l is hit (first term in eq. 4).
Before commercialization, the firm observes the evolution of μ_t according to the stochastic process in eq. (1), and can decide the time T^r when the product is taken to the market. Intuitively, the higher μ_t at the time of adoption, the lower the probability that the de-listing threshold is hit within a certain period, the higher the expected profits. This is the return for the firm when deciding to postpone commercialization to develop the new drug further.

Then, at each time $t \geq t_0$ the firm's problem is one of choosing the commercialization time T^r that maximizes the following value function:

$$F^r(\mu_t) = E_t\left\{e^{-\rho(T^r - t)} V^r(\mu^{*r})\right\}, \tag{7}$$

where $V^r(\mu^{*r})$, given by eq. (4), indicates the present value of profits resulting

from commercializing the drug at the trigger μ^{*r}, and T^r is the random commercialization time defined as $T^r = \inf(t \geq 0 : \mu_t \geq \mu^{*r})$. The solution to $F^r(\mu_t)$ as well as the optimal commercialization threshold μ^{*r} can be obtained by verifying that the expected change of $F^r(\mu_t)$ satisfies a second-order linear differential equation under some suitable boundary conditions at T^r (see Appendix A). The general solution of eq. (7) is given by:

$$F^r(\mu_t) = B_1^r \mu_t^{\beta}, \tag{8}$$

where:

$$B_1^r = \mu_l^{-\beta} \left(\frac{\beta}{\beta - \theta}\right)^{\frac{\theta-\beta}{\theta}} \left(\frac{\theta(c-p)}{\rho\beta}\right) > 0 \tag{9}$$

and

$$\beta = \frac{1}{2} - \frac{\alpha}{\sigma^2} + \sqrt{\left(\frac{1}{2} - \frac{\alpha}{\sigma^2}\right)^2 + \frac{2(\rho+\delta)}{\sigma^2}} > 1. \tag{10}$$

The optimal threshold is:

$$\mu^{*r} = \mu_l \left(\frac{\beta}{\beta - \theta}\right)^{\frac{1}{\theta}}. \tag{11}$$

Eq. (11) defines the value of the stochastic effectiveness that should trigger the decision by the firm to commercialize the new drug. Below that value, it is optimal to carry development on. It is worth noting that the optimal threshold and hence the optimal timing is independent of the price p. Moreover, since $\left(\frac{\beta}{\beta-\theta}\right)^{\frac{1}{\theta}} > 1$, the value of effectiveness that will induce the firm to take the product to market is linearly increasing in the de-listing threshold μ_l. Therefore, the expected time to adoption is increasing in μ_l (first statement of Proposition 1).

We formally define the ICER as,

$$\frac{p}{\mu_t - \underline{\mu}}, \tag{12}$$

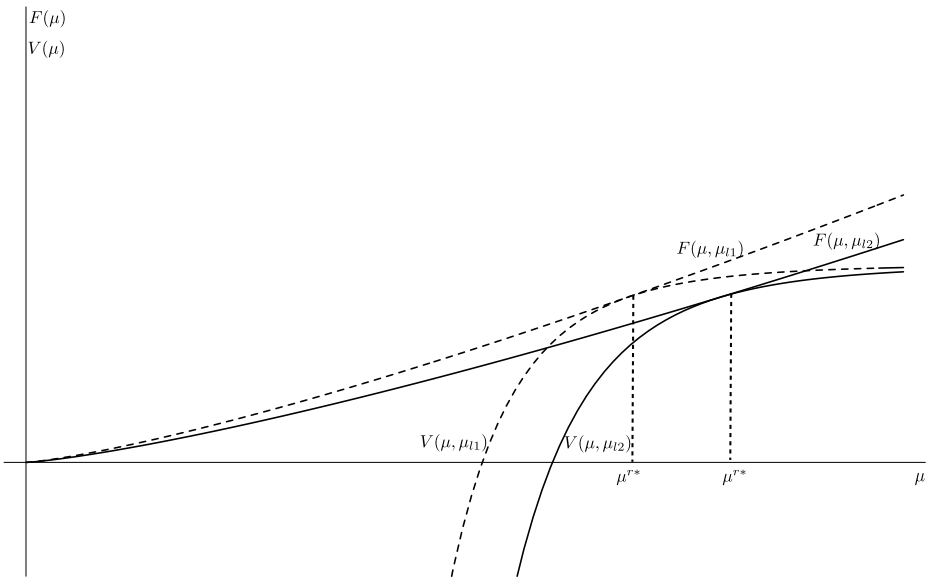

Figure 1: Value functions under RS

where, for the sake of simplicity, the price of the existing alternative has been normalized to zero. Given the fixed price, an increase in μ_l implies a lower ICER at the time of adoption ($\mu_t = \mu^{*r}$) due to the increase in the optimal threshold μ^{*r} (second statement of Proposition 1).
Summarizing, from eq. (4) and eq. (8), the value function for the firm can be written in compact notation as:

$$F^r(\mu_t) = \begin{cases} B_1^r \mu_t^\beta & \text{for } \mu_t < \mu^{*r} \\ C_2^r \mu_t^\theta + \frac{p-c}{\rho} & \text{for } \mu_t \geq \mu^{*r} \end{cases}. \tag{13}$$

Eq. (13) shows that the value of the development project for the firm can be interpreted as the value of the option to commercialize the innovation. That option will be exercised if μ_t reaches the optimal threshold μ^{*r}. After this stage, the value is the discounted cash-flow of the drug's sales, net of the loss related to the possibility of de-listing.

Figure 1 provides a graphic illustration of the solution to the optimal stopping problem for two different values of the de-listing threshold ($\mu_{l1} < \mu_{l2}$). For $\mu_t < \mu^{*r}$ the value of waiting exceeds the value of taking the drug to market, so that $F^r(\mu_t)$ is the relevant value function. This equals $V^r(\mu_t)$ in μ^{*r}, where the two curves are tangent (See Appendix A). For values of μ_t greater than the optimal threshold $V^r(\mu_t)$ becomes the relevant function.
The role of μ_l in determining the timing of investment is consistent with eq. (11): a higher value (μ_{l2}) increases the threshold μ^{*r}, implying a delay in the expected time of listing.

3.2 Project value

Since the sunk cost I needs to be paid before starting the development process, the project is viable only if $F^r(\mu_0) - I \geq 0$. In other words, at the starting point (t_0, μ_0) the firm decides whether to buy the option to develop the new chemical entity by paying the sunk cost I. Since we are assuming that there can be no development without investment, μ_0 is kept fixed and our time horizon starts when the investment, if any, takes place.

From eq. (13), a greater value of B_1^r can then be interpreted as a stronger incentive for the industry to invest in development projects. For given values of p and c, B_1^r (eq. 9) depends on the structure of uncertainty (through β and θ) as well as on the regulatory parameter μ_l. Since β is positive and the second and third term in eq. (9) are also positive, an increase in μ_l weakens the incentive to invest in R&D by reducing B_1^r (last part of Proposition 1). In Fig. 1, $F^r(\mu_t; \mu_{l2})$ lies below $F^r(\mu_t; \mu_{l1})$ for any $\mu_t < \mu^{*r}$.

4 Cost-effectiveness thresholds

An increasing number of health care systems condition the decision to reimburse new drugs to an assessment of their cost-effectiveness. We define regulation based on an ICER threshold (IT) as a listing process based on

the comparison of the new drug's ICER with a threshold λ that is meant to reflect society's willingness to pay for a unit increase in effectiveness.

The condition for adoption is then:

$$\frac{p}{\mu_t - \underline{\mu}} \leq \lambda, \tag{14}$$

Since, under our assumptions, p is independent of μ_t, it is optimal for the firm to move to commercialization as soon as the above condition is satisfied,[13] which happens when μ_t equals

$$\hat{\mu} = \underline{\mu} + \frac{p}{\lambda}. \tag{15}$$

Compared to RS, this implies an anticipation of the effects of regulation from the commercialization stage to the listing stage. In this case, the firm is not allowed to optimally choose the timing of access to the market. However, IT is less binding during commercialization. In order to emphasize this difference, we assume that under IT the new drug can only be de-listed if its effectiveness falls below that of the existing alternative (i.e. $\mu_t < \underline{\mu}$). We follow Jena and Philipson (2008) in interpreting λ as the relevant parameter for regulation based on cost-effectiveness thresholds. The following proposition summarizes the link between regulatory policy and the firm's optimal decisions:

Proposition 2 *A tightening of the IT regulatory policy through a reduction in λ leads to a delay in adoption, a lower ICER at the time of listing, and a weaker incentive for the firm to invest in R&D.*

The next two sub-sections and Appendix B provide a detailed description of the results of Proposition 2.

[13] A natural extension to our model would be to let the firm ask for (and obtain) listing at any level of μ_t provided that it also fixes a sufficiently low price. This would turn the IT scheme into a '*value-based*' pricing scheme. However, this would complicate the comparison with RS agreements, for which a simultaneous characterization of the optimal pricing and entry policy would be needed. Nonetheless, the extension of our analysis to value-based prices is a natural one.

4.1 Timing of listing

As before, we solve the firm's problem by working backwards. Conditional on the decision to invest in the development project, entry to the market depends only on the evolution of the stochastic process of eq. (1). The firm faces no optimal stopping problem in this case, the commercialization threshold $\hat{\mu}$ being exogenous. The relationship between the decision by the regulator on λ and the timing of adoption is clear: the lower λ, the higher $\hat{\mu}$, the longer the expected time to adoption. This proves the first and second statement of Proposition 2.

4.2 Project value

During commercialization, the only difference between IT and RS is the de-listing threshold. Hence, the corresponding value function is obtained by simply replacing μ_l with $\underline{\mu}$ in eq. (5). This leads to:

$$V^t(\mu_t) = C_2^t \mu_t^\theta + \frac{p-c}{\rho}, \tag{16}$$

with,

$$C_2^t = -\underline{\mu}^{-\theta}\left(\frac{p-c}{\rho}\right) < 0\ . \tag{17}$$

Before commercialization, the firm observes the evolution of μ_t according to eq. (1), and decides to go through listing when $\hat{\mu}$ is hit for the first time. Then, for each time $t \geq t_0$ the firm's value is simply:

$$F^t(\mu_t) = E_t\left\{e^{-\rho(T^t-t)}V^t(\hat{\mu})\right\}, \tag{18}$$

where $V^t(\hat{\mu})$ is given by eq. (16) and T^t is the random listing time defined as $T^t = \inf\left(t \geq 0 : \mu_t \geq \hat{\mu}\right)$. As for RS, the shape of the value function before

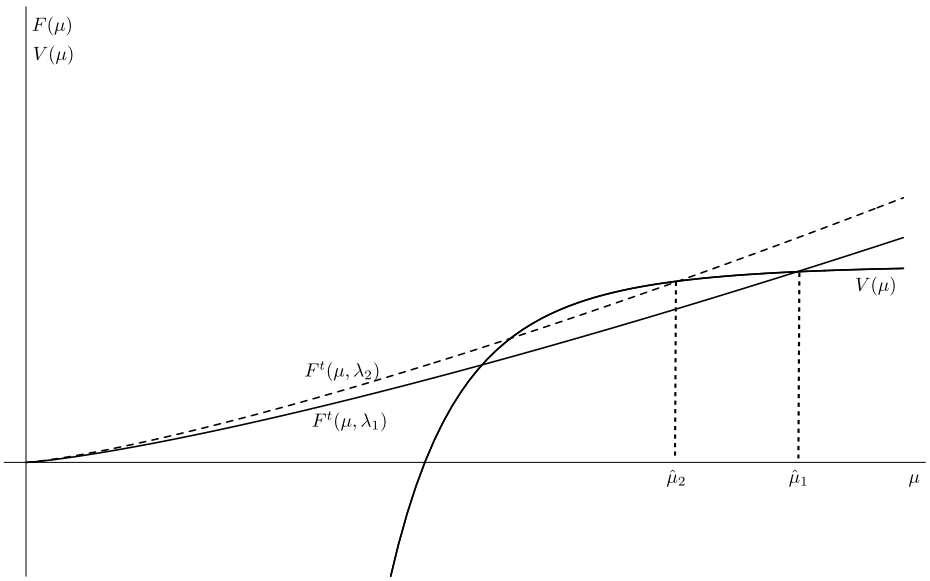

Figure 2: Value functions under IT

commercialization, $F^t(\mu_t)$, is given by (see Appendix B):

$$F^t(\mu_t) = B_1^t \mu_t^\beta, \tag{19}$$

where, in this case:

$$B_1^t = \left(\frac{p-c}{\rho}\right) \hat{\mu}^{-\beta} \left[1 - \left(\frac{\hat{\mu}}{\underline{\mu}}\right)^\theta\right]. \tag{20}$$

Summarizing, for any $t \geq t_0$, the firm's value function can be written as:

$$F^t(\mu_t) = \begin{cases} B_1^t \mu_t^\beta & \text{for } \mu_t < \hat{\mu} \\ C_2^t \mu_t^\theta + \frac{p-c}{\rho} & \text{for } \mu_t \geq \hat{\mu} \end{cases} \tag{21}$$

Figure 2 shows eq. 21 for two different values of the maximum ICER threshold ($\lambda_1 < \lambda_2$), which is the relevant regulatory parameter under IT.

For a given price p, the thresholds λ_1 and λ_2 can be converted into minimum effectiveness requirements $\hat{\mu}_1$ and $\hat{\mu}_2$ ($\hat{\mu}_1 > \hat{\mu}_2$). Unlike in Fig. 1, there is no tangency between $F^t(\mu_t)$ and $V^t(\mu_t)$ at $\hat{\mu}$, which separates development from commercialization. This is due to the firm's lack of flexibility in choosing the optimal commercialization time, implied by the fact that IT regulation enters exactly at $\hat{\mu}$, and it has a negative impact on the value of the option to invest in the development project (see Appendix B for more details).

As under RS, the regulatory parameter plays a crucial role, together with the structure of uncertainty, in determining the value of the option to invest in the development project as captured by B_1^t. A more restrictive regulation (lower λ and higher $\hat{\mu}$) reduces B_1^t, thus making the investment less appealing to the firm for any given values of μ_0 and I. As proved in Appendix B, the derivative of B_1^t with respect to λ is positive whenever the IT regulation is binding. This proves the last part of Proposition 2.

In Figure 2, $V^t(\mu_t)$ is independent of whether λ_1 or λ_2 is the relevant ICER threshold, as this has no impact during commercialization. However, λ_1 implies that adoption will occur when effectiveness is higher ($\mu_t = \hat{\mu}_1 > \hat{\mu}_2$), thus shifting $F^t(\mu_t)$ downward and to the right in the region that is relevant for the decision whether to undertake the development project.

5 Comparison

According to our definition of RS and IT, a single parameter - μ_l for RS and λ for IT - defines how tight the regulation policy is, under each scheme. Comparatively high values of μ_l and low values of λ indicate tighter regulation under the respective schemes. One interesting difference between the two is that IT works at the listing stage, whereas RS only impacts after adoption. In order to ensure consistency with these characteristics, we introduce the following restrictions:

R1 *RS agreements imply de-listing at effectiveness levels which are higher*

than that of the drug currently in use.

Restriction 1 simply implies:

$$\mu_l > \underline{\mu}. \tag{22}$$

R2 *The cost-effectiveness threshold is a binding constraint for the firm.*

Restriction 2 requires that $\hat{\mu}$ exceeds the threshold the firm would choose if it were free to do so. This corresponds to the adoption threshold under RS μ^{*r}, for the case $\mu_l = \underline{\mu}$. Hence, Restriction 2 becomes $\hat{\mu} \geq \underline{\mu}\left(\frac{\beta}{(\beta-\theta)}\right)^{\frac{1}{\theta}}$, or:

$$\lambda \leq \hat{\lambda} \equiv \frac{p}{\underline{\mu}}\left[\left(\frac{\beta}{\beta-\theta}\right)^{1/\theta} - 1\right]^{-1}. \tag{23}$$

In this section, we study the relationship between the two policy parameters (μ_l, λ) and the achievement of the four policy goals described in Section 2.2. Having solved the model in Sections 3 and 4, these can now be linked to the specific parameters of the model:

1. *Making effective products quickly available to patients.* The *timing* of adoption is related to the adoption thresholds, μ^{*r} and $\hat{\mu}$. The higher the adoption threshold, the longer the expected time to adoption.[14]

[14]Following the Markov property of μ_t the random variables T^r and T^t are independent. Then, providing that $\left(\alpha - \frac{1}{2}\sigma_d^2\right) > 0$, the firm's average time to reach either μ^{*r} or $\hat{\mu}$ is given by (Cox and Miller, 1965, p.221-222):

$$E(T^r) = \left(\alpha - \frac{1}{2}\sigma_d^2\right)^{-1} \log\left(\frac{\mu^{*r}}{\mu_0}\right) \text{ and } E(T^t) = \left(\alpha - \frac{1}{2}\sigma_d^2\right)^{-1} \log\left(\frac{\hat{\mu}}{\mu_0}\right)$$

respectively.

2. *Ensuring that innovations adopted are good value for money.* This objective can be measured by the incremental cost-effectiveness ratio. This ratio is $\frac{p}{\mu^{*r}-\underline{\mu}}$ for RS and, by definition, λ for IT.

3. *Providing incentives to R&D investment by the industry.* The incentive will be greater the larger the value of the opportunity to invest in the development project. For a given value of μ_0, the firm is more likely to invest in development the larger the value of B_1^i, $i = r, t$.

4. *Reducing the risk that true effectiveness of the new drug in clinical use falls below the level reported at the time of adoption.* This can be measured by the minimum level of effectiveness for which the price of the new drug is reimbursed. This is, μ_l and $\underline{\mu}$ respectively under RS and IT.

The comparison is made for a given level of price, which is assumed to be the same under both types of regulation. The following proposition summarizes the results of the comparison that will be discussed in the remaining part of this section:

Proposition 3 *For a given level of λ, the comparative performance of IT versus RS with respect to the policy goals depends on the value of μ_l, as illustrated in Table 1, where a $>$ ($<$) sign denotes a better (worse) performance.*

The proposition defines μ_l in terms of λ. Of course, the opposite could be done with no impact on the results. As to the first objective, different values of the policy parameters μ_l and λ imply different adoption thresholds. Note that under our assumptions the trade-off between *timing* and *value for money* cannot be mitigated,[15] because an earlier adoption under RS requires a lower value of μ^{*r}, which implies a worse ICER. This explains why whenever a scheme is superior in one dimension it is dominated in the other

[15] In particular, the assumption of a fixed price plays a role here.

Region Range	**A** $\mu_l \leq \tilde{\mu}$	**B** $\tilde{\mu} < \mu_l \leq \check{\mu}$	**C** $\mu_l > \check{\mu}$
Timing	$RS > IT$	$RS \geq IT$	$IT > RS$
Value for money	$IT > RS$	$IT \geq RS$	$RS > IT$
Incentive to investment	$RS \geq IT$	$IT > RS$	$IT > RS$
Risk after listing	$RS > IT$	$RS > IT$	$RS > IT$

Table 1: Policy goals and regulation performance: RS vs. IT

(comparison of rows 1 and 2 of Table 1). Moreover, RS is always superior to IT in terms of *risk after listing*, due to its more aggressive de-listing policy (Restriction 1). Therefore, information on the comparative performance along the four dimensions can be completed by analytically studying only two of them: *timing*, through the adoption thresholds (μ^{*r} and $\hat{\mu}$), and *incentive to investment* through the value of the opportunity to invest in the development project (B_1^r and B_1^t).

By equating B_1^r (eq. 9) to B_1^t (eq. 20), we get the combinations of μ_l and λ such that the incentive to investment is the same under the two schemes:

$$\mu_l = \tilde{\mu}_l \equiv \left\{ \frac{\beta}{-\theta} \left(\frac{\beta}{\beta - \theta} \right)^{\frac{\beta-\theta}{\theta}} \left(\underline{\mu} + \frac{p}{\lambda} \right)^{-\beta} \left[1 - \left(1 + \frac{p}{\lambda \underline{\mu}} \right)^{\theta} \right] \right\}^{-\frac{1}{\beta}}. \quad (24)$$

Therefore, for any given value of λ, the value of the investment opportunity will be greater (smaller) under RS than under IT if:

$$\mu_l < \ (>) \ \tilde{\mu}_l.$$

Similarly, by equating μ^{*r} (eq. 11) to $\hat{\mu}$ (eq. 15), the condition under which the adoption thresholds are the same is:

$$\mu_l = \breve{\mu}_l \equiv \left(\underline{\mu} + \frac{p}{\lambda}\right)\left(\frac{\beta}{\beta-\theta}\right)^{-\frac{1}{\theta}}. \tag{25}$$

As a result, adoption will occur earlier (later) under RS than under IT if:

$$\mu_l < \ (>) \ \breve{\mu}_l.$$

Finally, a full characterization of the trade-off among policy goals requires a comparison of $\tilde{\mu}_l$ with $\breve{\mu}_l$. For $\tilde{\mu}$ to be smaller than $\breve{\mu}$ the expression in eq. (24) must be smaller than that in eq. (25). By straightforward algebraic manipulation the inequality boils down to,

$$\lambda \leq \frac{p}{\underline{\mu}}\left[\left(\frac{\beta}{\beta-\theta}\right)^{\frac{1}{\theta}} - 1\right]^{-1}. \tag{26}$$

This is exactly eq. (23), meaning that as long as Restriction 2 holds, $\tilde{\mu}$ is smaller than $\breve{\mu}$. For $\lambda = \hat{\lambda}$ the two expressions are equal. It is also easily verifiable that $\tilde{\mu}(\hat{\lambda}) = \breve{\mu}(\hat{\lambda}) = \underline{\mu}$. This is due to the fact that if the de-listing threshold is the same ($\mu_l = \underline{\mu}$) and λ is set so that the listing threshold is also the same ($\lambda = \hat{\lambda}$), the two schemes are perfectly equivalent. Figure 3 provides a graphic illustration.

Areas A, B and C correspond to columns in Table 1. For a given value of λ, with comparatively low values of μ_l (region A), RS ensures earlier adoption and a stronger incentive to invest in R&D than IT. The latter, however, provides better value for money. For intermediate values of μ_l ($\tilde{\mu}_l < \mu_l \leq \breve{\mu}_l$) IT becomes preferred in terms of incentive to invest, with no change in the other dimensions (region B). Finally, further increases in μ_l ($\mu_l > \breve{\mu}_l$) may

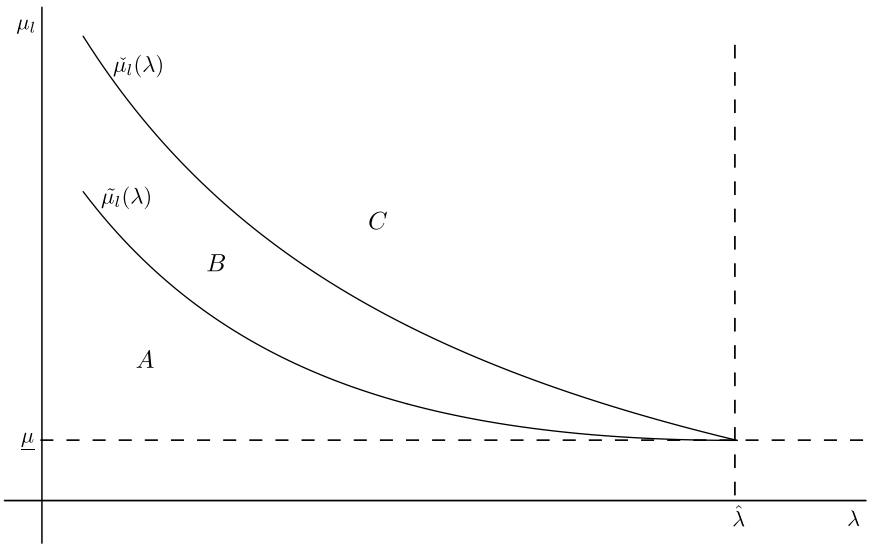

Figure 3: Combinations of λ and μ_l defining areas A, B and C (see Table 1).

lead to a situation where adoption occurs earlier under IT (region C).
Proposition 3 and the above discussion lead to some relevant policy implications:

Corollary 1 *A risk-sharing agreement providing at least as powerful incentive towards R&D investment as regulation based on an ICER threshold entails a shorter expected time to adoption and a higher ICER at the time of adoption.*

Corollary 2 *A risk-sharing agreement leading to adoption at the same level of ICER (and at the same expected time) as under regulation based on an ICER threshold provides a weaker incentive to invest in R&D.*

These results will be further discussed in Section 6.

We conclude this section, with some comparative statics on the role of uncertainty as a factor influencing the relative convenience of the two schemes

under comparison. In particular, we focus on the relative size of the uncertainty of commercialization (σ_c) with respect to development (σ_d). Therefore, we can rewrite σ_c as $\phi\sigma_d$ and study the impact of changes in $\phi > 0$. As in the previous part of this section, the formal analysis can be restricted to the impact on *timing* and *incentive to investment*.

Let us start from the analysis of *timing*. Working through straightforward algebraic manipulations it is easy to show that $\tilde{\mu}_l \to \check{\mu}_l$ as $\phi \to \infty$ and that $\frac{\partial \tilde{\mu}_l}{\partial \phi} < 0$ (See Appendix C). This implies a downward shift of the line separating areas B and C, and leads to the conclusion that an increase in uncertainty during commercialization widens area C in Fig. 3 to the detriment of areas A and B. In other words, looking at Table 1, an increase in uncertainty during commercialization shrinks the range of values of μ_l for which adoption occurs earlier under RS (and IT provides better value for money).

The outcome is consistent with a typical result from the real options literature: an increase in uncertainty leads to a delay in investment whenever there is flexibility on the timing. Intuitively, in our case the widening of Area C results from the combination of two effects: there is no impact of an increase in uncertainty under IT, due to the lack of flexibility, whereas the commercialization threshold increases under RS ($\frac{\partial \mu^{*r}}{\partial \phi} > 0$).

Moving to an analysis of the impact on the incentive to invest of a relative increase in uncertainty during commercialization, it is clear from eq. (20) that $\frac{\partial B_1^t}{\partial \phi} < 0$. In this case, the only implication of an increase in ϕ is a larger probability of hitting the de-listing boundary during commercialization, which implies less value of the investment opportunity for the firm. On the contrary, there is ambiguity regarding the sign of $\frac{\partial B_1^r}{\partial \phi}$. This makes it impossible to predict the effect of uncertainty on $\tilde{\mu}_l$ and then the direction in which the line separating areas A and B in Fig. 3 moves due to an increase in ϕ.

This result is also consistent with the dynamic structure of our stochastic model. For any given threshold μ^{*r}, more uncertainty during commercial-

ization means less value of the investment opportunity due to the increased probability of de-listing (i.e. $\frac{\partial B_1^r}{\partial \phi} < 0$). However, under RS, the adoption threshold is no longer exogenous. It has been shown above, that $\frac{\partial \mu^{*r}}{\partial \phi} > 0$. Hence, the opportunity for the firm to increase the adoption threshold as a reaction to the increased probability of de-listing could lead to an overall positive effect (i.e. $\frac{\partial B_1^r}{\partial \phi} > 0$).

6 Policy implications

Propositions 1 and 2 show that tighter regulation, no matter whether based on IT or RS, leads to a delay in the adoption of innovations and a weaker incentive for the industry to invest in R&D. Empirical evidence for these theoretically unsurprising results has been previously found (Danzon and Epstein, 2008; Golec et al., 2010; Vernon, 2005; Danzon et al., 2005; Kyle, 2007). Under either regulatory scheme, an efficient choice by the regulator must weight these undesired effects against the necessity of managing resource scarcity.

A more interesting question that we address is which scheme performs better: well-established ICER thresholds or emerging RS agreements. In discussing the latter, some authors have focused on the commercialization stage and noted that these agreements are, rather, forms of *risk-shifting*, as the price can only be adjusted downward (Towse and Garrison, 2010). They have also been interpreted as warranties provided by the firm on the true effectiveness of the new product (Cook et al., 2008). Cook et al. conclude that RS may reduce the attractiveness for the firm to invest in the development of new products, and lead to under-supply of innovation for consumers. By focusing on commercialization, these contributions do not explicitly consider the impact that RS may have on the previous stages of the process. In particular, in our framework, this implies the assumptions that cost-effectiveness at the

time of adoption is the same under IT and RS. Referring to Figure 3, this is true along the line separating region B from region C, i.e. for $\mu_l = \check{\mu}$. Since both in region B and C the incentive to invest is weaker under RS (see Table 1) the results from the literature are confirmed by our analysis for this portion of the plane (see Corollary 2). However, there is also one region (A) where the incentive to invest is greater under RS. In this case, the negative impact on the firm's value of RS at the commercialization stage is more than offset by the greater flexibility for the firm on the timing of entry, which increases the value to the firm of the option to invest in R&D.

A necessary condition for the incentive to invest to be at least as powerful under RS as under IT is that the ICER at time of listing is strictly greater (Corollary 1). In other words, regulators willing to reduce risk after-listing while maintaining a sufficiently powerful incentive to invest in R&D must be ready to concede something in terms of 'value for money'. This result is consistent with those obtained by Pita Barros (2011), in a different setting.[16] Ensuring earlier access to innovations for patients was among the original objectives of RS agreements. Our analysis also shows that they have the potential to achieve this (regions A and B), unless the RS policy is too stringent. Although evidence on the impact of RS on timing is still scarce, the first analyses seem to suggest that a shortening of time to market is actually taking place.[17] Overall, Table 1 (last row) shows that RS unambiguously helps regulators to bridge the efficacy-effectiveness gap (Eichler et al., 2011). This is due to the *shifting* of risk during commercialization. Concerning the other policy goals, our analysis shows that it is not the introduction of a RS agree-

[16]Pita Barros shows that under some conditions the introduction of a RS agreement can make the firm better off and be generally welfare enhancing. In his model, the effectiveness of the new treatment is fixed, whereas the RS agreement leads the firm to increase the price. In our case, prices are fixed and the endogenous effectiveness at the time of adoption is lower under a RS agreement such that the value of the investment project to the firm is at least as large as under IT. However, the impact on the ICER is the same - an increase - in both situations.

[17]For example, Russo et al. (2010) estimate a reduction of 265 days in time to market for drugs for which a RS agreement is in operation.

ment *per se* to determine the trade-off among them, but rather the specific design of the contract. This raises a new issue concerning the implementation of these agreements, in addition to those discussed elsewhere.[18] Have regulators sufficient information to negotiate such agreements consistent with their objective function and the related balance among policy goals? It may be argued that our analysis also shows this to be an issue for IT, at the stage of defining the value of λ, as was also proved by Jena and Philipson (2008) and Golec et al. (2010). Assigning a specific value to the ICER threshold that should reflect the societal willingness to pay for an increase in effectiveness is no easy task, as witnessed by the worldwide attention paid to those few cases where this has been done (e.g. the £20,000/QALY[19] threshold adopted by NICE in the UK). However, this parameter has two characteristics that make it comparatively easy to determine: it is a relative measure and it is not specific to a technology - as long as the denominator is a measure of utility like QALY. Since RS agreements are formally based on the definition of clinical thresholds that trigger the price cut, understanding the economic implications of these contractual terms may be even more difficult. Regulators should seriously consider an exploration of the cost-effectiveness implications of such effectiveness thresholds.

7 Conclusion

Regulators are struggling to curb the pressure of pharmaceutical innovation on health care expenditure, while the industry has to cope with a slower pace of innovation than in the past. Concerns have been expressed that tightening of regulation may undermine the incentive for the industry to invest in R&D, and potentially exclude consumers from the benefits of further innovation.

[18] See for example De Pouvourville (2006), Neumann et al. (2011) and Pita Barros (2011).
[19] Quality-Adjusted Life Years.

Recently, the interest in risk-sharing as a regulatory policy has been growing. However, some authors have referred to the *shifting* of risk from the insurer to the firm during commercialization, typically involved in these agreements, as a mechanism with a potentially negative impact on the incentive for the firm to invest in R&D.

We compare a well established type of regulation based on a maximum threshold for the ICER, above which the innovation is not adopted, with a risk-sharing agreement implying milder regulation at the listing stage, but with the condition that the product will be paid for by the insurer only if its actual effectiveness remains sufficiently high. The comparison considers the whole product life cycle and attention is paid to the impact on four specific policy goals: making effective products quickly available to patients; ensuring that innovations adopted are good value for money; providing incentives to R&D investment by the industry; reducing the risk that true effectiveness of the new drug in clinical use falls below the level reported at the time of adoption.

By their own nature, RS agreements reduce the risk faced by the payer during commercialization. Concerning the other policy objectives, our analysis shows that either scheme can do better, depending on the parameters that define how tight regulation is under the two schemes. Replacing IT with RS weakens the incentive to invest in R&D if the new drug is required to have the same cost-effectiveness properties at the time of adoption. Lacking this requirement, investment in R&D can be even greater under RS, with adoption of the new drug occurring earlier. In our framework, the greater flexibility on the timing of commercialization enjoyed by the firm under RS is crucial for this result, because it increases the value of the option to invest in innovation. To achieve this, insurers must be ready to concede something in terms of value for money at the time of adoption. This should warrant a shift in attention from the choice of signing a RS agreement or not, to the content of the agreement itself.

The paper contributes to the existing literature by exploring the full dynamics of the process, from development to commercialization, allowing for uncertainty at both stages. In so doing, it also comes with limitations, which may suggest lines for future research. For example, the assumption of a fixed price on which the comparison between the two regulatory schemes is based, makes the model more realistic for systems where the scope for price negotiation is limited (e.g., through the use of external reference prices). Moreover, extensions to a multi-country setting might improve the understanding of decisions made by firms often operating in a global context, and possibly of strategic interactions among regulators.

Appendix A

The Bellman equation for the commercialization stage is,

$$\rho V^r(\mu_t) = p - c + lim_{dt\to 0}\frac{1}{dt}E[dV^r(\mu)]. \tag{27}$$

Using the stochastic process in eq. (3) and Ito's Lemma, this leads to the following partial differential equation:

$$\frac{1}{2}\sigma_c^2\mu_t^2 V^r_{\mu\mu}(\mu_t) - \rho V^r(\mu_t) + (p-c) = 0. \tag{28}$$

The general solution to this equation can be written as (Dixit and Pindyck, 1994):

$$V^r(\mu_t) = C_1^r\mu_t^{\theta_1} + C_2^r\mu_t^{\theta_2} + \frac{p-c}{\rho}, \tag{29}$$

where $\theta_1 > 1$ and $\theta_2 < 0$ are the roots of the auxiliary equation:

$$\frac{1}{2}\sigma_c^2\theta(\theta-1) - \rho = 0.$$

Two boundary conditions are needed to solve for the value of the constants C_1^r and C_2^r. Given that after commercialization a fixed finite price per unit is paid to the firm, the value must be bounded upward, even for very large values of μ_t. This would not be the case if the constant C_1^r assumed any positive value. Hence, the first constant must be set equal to zero. The second boundary condition comes

from the de-listing condition, which implies $V^r(\mu_l) = 0$. Solving for C_2^r yields:

$$C_2^r = -\mu_l^{-\theta}\left(\frac{p-c}{\rho}\right) < 0.$$

In order to keep notation as simple as possible, θ_2 is replaced by θ both in the main text and in the remaining part of the Appendix.
Let us now consider development. Since during this stage the investment opportunity yields no cash flow, the Bellman equation is simply:

$$\rho F^r(\mu_t) = lim_{dt\to 0}\frac{1}{dt}E[dF^r(\mu_t)], \tag{30}$$

Using the stochastic process in eq. (1) and applying Ito's Lemma, taking into account that for each time interval dt there is a probability δdt that μ_t falls to zero, we obtain:

$$E[dF^r(\mu_t)] = (1-\delta dt)\left(\frac{1}{2}\sigma_d^2\mu_t^2 F_{\mu\mu}^r(\mu_t) + \alpha\mu_t F_\mu^r(\mu_t)\right) + (\delta dt)\left(-F^r(\mu_t)\right). \tag{31}$$

Substituting this into eq. (30) leads to the following second order differential equation:

$$\frac{1}{2}\sigma_d^2\mu_t^2 F_{\mu\mu}^r(\mu_t) + \alpha\mu_t F_\mu^r(\mu_t) - (\rho+\delta)F^r(\mu_t) = 0. \tag{32}$$

The general solution is:

$$F^r(\mu_t) = B_1^r\mu_t^{\beta_1} + B_2^r\mu_t^{\beta_2}, \tag{33}$$

where, $\beta_1 > 1$ and $\beta_2 < 0$ are the roots of the auxiliary equation $\frac{1}{2}\sigma_d^2\beta(\beta-1) + \alpha\beta - (\rho+\delta) = 0$. The value of the constants B_1^r and B_2^r are obtained by imposing appropriate restrictions. In particular, for values of μ_t that tend to zero, the term $B_2^r\mu_t^{\beta_2}$ would make the value jump to infinity. Of course, this is inconsistent with our problem, given that the firm cannot disinvest (i.e. it is not worthwhile to disinvest) after having spent in R&D. Therefore, setting $B_2^r = 0$ and, to simplify the notation, $\beta_1 = \beta$, the value of the firm reduces to $F^r(\mu_t) = B_1^r\mu_t^\beta$ as in the text.
The values of μ^{*r} and B_1^r are simultaneously determined by imposing *value matching* and *smooth pasting* conditions, which ensure respectively that the value function is continuous and differentiable in μ^{*r}:

$$F^r(\mu^{*r}) = V^r(\mu^{*r})$$

$$\frac{\partial F^r(\mu^{*r})}{\partial\mu} = \frac{\partial V^r(\mu^{*r})}{\partial\mu}.$$

From the smooth pasting condition we obtain:

$$B_1^r = \mu_l^{-\beta} \left(\frac{\beta}{\beta - \theta} \right)^{\frac{\theta-\beta}{\theta}} \left(\frac{\theta(c-p)}{\rho\beta} \right) > 0.$$

Then, substituting B_1^r into the value matching condition yields the threshold:

$$\mu^{*r} = \mu_l \left(\frac{\beta}{\beta - \theta} \right)^{\frac{1}{\theta}} > \mu_l.$$

Appendix B

For the case of a cost-effectiveness threshold, the model is over-simplified. Having defined the value function during commercialization (eq. 16 and 17), the only variable to be determined is the constant B_1^t for the value of the firm during development. In this case, the firm cannot optimally choose the listing threshold, which is exogenously set through the policy parameter λ. Hence, the *smooth pasting* condition that we imposed under RS to determine μ^{*r} no longer holds. It is simply required that the firm's value function is continuous (*value matching*) over the whole domain, and in particular in $\hat{\mu}$. The value matching implies:

$$F^t(\hat{\mu}) = V^t(\hat{\mu}) \quad \Longrightarrow \quad B_1^t \hat{\mu}^\beta = C_2^t \hat{\mu}^{\theta_2} + \frac{p-c}{\rho}, \tag{34}$$

where $\hat{\mu} = \underline{\mu} + \frac{p}{\lambda}$. From eqs. (34) and (17), we get:

$$B_1^t = \left(\frac{p-c}{\rho} \right) \hat{\mu}^{-\beta} \left[1 - \left(\frac{\hat{\mu}}{\underline{\mu}} \right)^{\theta} \right].$$

It can be shown through straightforward algebraic manipulation that the derivative of B_1^t with respect to λ is positive if the following condition is satisfied:

$$\lambda \leq \frac{p}{\underline{\mu}} \left[\left(\frac{\beta}{\beta - \theta} \right)^{1/\theta} - 1 \right]^{-1}.$$

It can be seen that this is equivalent to requiring that $\hat{\mu}$ is greater than $\mu_l(\underline{\mu})$, i.e. the right hand side of eq. 11 when the de-listing threshold is $\underline{\mu}$, as in the case of IT. In other words, this condition simply requires that the exogenous threshold $\hat{\mu}$ is greater than the endogenous one, for $\mu_l = \underline{\mu}$, i.e. that the constraint set by the definition of λ is binding (see also eq. 23).

Appendix C

First, from eq. (24) we are able to show that:

$$\tilde{\mu}_l^{-\beta} = \check{\mu}_l^{-\beta} \left(\frac{\beta - \theta}{-\theta} \right) \left[1 - \left(1 + \frac{p}{\lambda \underline{\mu}} \right)^{\theta} \right],$$

or

$$\left(\frac{\check{\mu}_l}{\tilde{\mu}_l} \right)^{\beta} = \left(\frac{\beta - \theta}{-\theta} \right) \left[1 - \left(1 + \frac{p}{\lambda \underline{\mu}} \right)^{\theta} \right] > 1,$$

i.e. $\check{\mu}_l$ always lies above $\tilde{\mu}_l$. In addition, recalling that $\frac{\partial \theta}{\partial \phi} > 0$, it is easy to show that $\lim_{\phi \to \infty} \left(\frac{\check{\mu}_l}{\tilde{\mu}_l} \right)^{\beta} = 1$. Second, taking the derivative of eq. (25) with respect to ϕ, we obtain:

$$sign \left[\frac{\partial \check{\mu}_l}{\partial \phi} \right] = sign \left[\ln \left(\frac{\beta}{\beta - \theta} \right) - \frac{\theta}{\beta - \theta} \right].$$

For $\phi \to 0$ the first term on the right hand side goes to $-\infty$, and the second term to -1, implying that for sufficiently small values of ϕ the sign of $\frac{\partial \check{\mu}_l}{\partial \phi}$ is negative. For $\phi \to \infty$, both terms tend to zero. However, it can be shown that the derivative of $\ln \left(\frac{\beta}{\beta - \theta} \right)$ is always positive and greater than that of $\frac{\theta}{\beta - \theta}$, implying that the former tends to zero lying below the latter. It follows that $\frac{\partial \check{\mu}_l}{\partial \phi} < 0$.

References

J. Adamski, B. Godman, G. Ofierska-Sujkowska, B. Osinska, H. Herholz, K. Wendykowska, O. Laius, S. Jan, C. Sermet, C. Zara, M. Kalaba, R. Gustafsson, K. Garuoliene, A. Haycox, S. Garattini, and L. Gustafsson. 2010. Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for european payers. *BMC Health Services Research*, 10(1):153.

C. Burman and S. Senn. 2003. Examples of option values in drug development. *Pharmaceutical Statistics*, 2(2):113–125.

D. Cassimon, P. J. Engelen, L. Thomassen, and M. Van Wouwe. 2004. The valuation of a NDA using a 6-fold compound option. *Research Policy*, 33(1): 41–51.

J. Cook, J. Vernon, and R. Mannin. 2008. Pharmaceutical risk-sharing agreements. *Pharmacoeconomics*, 26:551–6.

P. M. Danzon and L.-W. Chao. 2000. Does regulation drive out competition in pharmaceutical markets? *Journal of Law and Economics*, 43(2):311–57.

P. M. Danzon and A. J. Epstein. 2008. Effects of regulation on drug launch and pricing in interdependent markets. NBER Working Papers 14041, National Bureau of Economic Research, Inc.

P. M. Danzon, Y. R. Wang, and L. Wang. 2005. The impact of price regulation on the launch delay of new drugs-evidence from twenty-five major markets in the 1990s. *Health Economics*, 14(3):269–292.

P. M. Danzon, A. K. Towse, and J. Mestre-Ferrandiz. 2012. Value-based differential pricing: Efficient prices for drugs in a global context. NBER Working Papers 18593, National Bureau of Economic Research, Inc.

G. De Pouvourville. 2006. Risk-sharing agreements for innovative drugs. *The European Journal of Health Economics*, 7:155–157.

J. A. DiMasi, R. W. Hansen, and H. G. Grabowski. 2003. The price of innovation: new estimates of drug development costs. *Journal of Health Economics*, 22(2): 151–185.

A. Dixit and R. Pindyck, 1994. *Investment Under Uncertainty*. Princeton University Press, Princeton.

H.-G. Eichler, E. Abadie, A. Breckenridge, B. Flamion, L. L. Gustafsson, H. Leufkens, M. Rowland, C. K. Schneider, and B. Bloechl-Daum. 2011. Bridging the efficacy-effectiveness gap: a regulator's perspective on addressing variability of drug response. *Nat Rev Drug Discov*, 10(7):495–506.

D. Filson. 2012. A Markov-perfect equilibrium model of the impacts of price controls on the performance of the pharmaceutical industry. *RAND Journal of Economics*, 43(1):110–138.

A. M. Garber, C. Jones, and P. Romer. 2006. Insurance and incentives for medical innovation. *Forum for Health Economics & Policy*, biomedical research:4.

A. Gelijns and N. Rosenberg. 1994. The dynamics of technological change in medicine. *Health Affairs*, 13(3):28–46.

J. Golec, S. Hegde, and J. A. Vernon. 2010. Pharmaceutical R&D spending and threats of price regulation. *Journal of Financial and Quantitative Analysis*, 45 (01):239–264.

A. B. Jena and T. Philipson. 2008. Cost-effectiveness analysis and innovation. *Journal of Health Economics*, 27(5):1224–1236.

M. K. Kyle. 2007. Pharmaceutical price controls and entry strategies. *The Review of Economics and Statistics*, 89(1):88–99.

D. Lakdawalla and N. Sood. 2009. Innovation and the welfare effects of public drug insurance. *Journal of Public Economics*, 93(3-4):541–548.

R. Levaggi, M. Moretto, and P. Pertile. 2012. Static and dynamic efficiency of irreversible health care investments under alternative payment rules. *Journal of Health Economics*, 31(1):169 – 179.

P. J. Neumann, J. D. Chambers, F. Simon, and L. M. Meckley. 2011. Risk-Sharing Arrangements That Link Payment For Drugs To Health Outcomes Are Proving Hard To Implement. *Health Affairs*, 30(12):2329–2337.

OECD. 2011. Health at a glance 2011: OECD indicators. Technical report, OECD.

S. Palmer and P. C. Smith. 2000. Incorporating option values into the economic evaluation of health care technologies. *Journal of Health Economics*, 19:755–766.

F. Pammolli, L. Magazzini, and M. Riccaboni. 2011. The productivity crisis in pharmaceutical R&D. *Nat Rev Drug Discov*, 10(6):428–438.

E. Pennings and L. Sereno. 2011. Evaluating pharmaceutical R&D under technical and economic uncertainty. *European Journal of Operational Research*, 212(2): 374–385.

PhRMA. 2011. Annual report 2011. Technical report, PhRMA.

P. Pita Barros. 2011. The simple economics of risk sharing agreements between the NHS and the pharmaceutical industry. *Health Economics*, 20(4):461–470.

P. Russo, F. S. Mennini, P. D. Siviero, and G. Rasi. 2010. Time to market and patient access to new oncology products in Italy: a multistep pathway from European context to regional health care providers. *Annals of Oncology*, 21 (10):2081–2087.

R. L. Shockley, S. Curtis, J. Jafari, and K. Tibbs. 2002. The option value of an early-stage biotechnology investment. *Journal of Applied Corporate Finance*, 15 (2):44–55.

A. Towse and L. Garrison. 2010. Can't get no satisfaction? Will pay for performance help? Toward an economic framework for understanding performance-based risk sharing agreements for innovative medical products. *Pharmacoeconomics*, 28:93–102.

J. A. Vernon. 2005. Examining the link between price regulation and pharmaceutical R&D investment. *Health Economics*, 14(1):1–16.