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Risk-Sharing Agreements in Pharmaceutical Markets*

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ABSTRACT

In this article, we model the relationship between a health authority and a pharmaceutical firm when the real efficacy of the drug manufactured by the firm is uncertain. The *ex-ante* information on the efficacy of the new drug is provided by the outcomes of a clinical trial. We focus on two types of contracts. On the one hand, the health authority can set a unit price regardless of the *ex-post* real effectiveness of the drug (traditional contract, i.e. no risk sharing). Alternatively, the health authority can make the payments contingent upon the observed *ex-post* effectiveness (risk-sharing contract). The optimal contract depends on the trade-off between the monitoring costs, the marginal production cost and the health cost derived from treatment failure. When the efficacy of the drug in the clinical trial is relatively high, a traditional contract is optimal for relatively low marginal costs. When the efficacy in the clinical trial is relatively low, the health authority always prefers to condition the payments upon the effectiveness outcomes.

Keywords: Risk-Sharing, Clinical Trials, Efficacy, Cost-Effectiveness Ratio.

Los acuerdos de riesgo compartido en mercados farmacéuticos

RESUMEN

En este artículo, se modela la relación entre una autoridad sanitaria y una empresa farmacéutica cuando la eficacia del medicamento producido por la empresa es incierta. La información *ex-ante* sobre la eficacia viene dada por los resultados de un ensayo clínico. Se analizan dos tipos de contratos. Por una parte, las autoridades sanitarias pueden fijar un precio unitario independientemente de la efectividad real *ex-post* del medicamento (no riesgo compartido). Alternativamente, la autoridad sanitaria puede condicionar el precio a la efectividad *ex-post* observada (contrato de riesgo compartido). El contrato óptimo depende de la relación entre los costes de monitorización, los costes marginales de producción y el coste sanitario derivado del fallo del tratamiento. Cuando la eficacia del medicamento en el ensayo clínico es relativamente alta, un contrato de no riesgo compartido es óptimo para valores relativamente bajos del coste marginal. Cuando la eficacia en el ensayo clínico es relativamente baja, la autoridad sanitaria siempre prefiere condicionar los pagos a los resultados de efectividad.

Palabras Clave: Riesgo compartido, eficacia, ratio coste-efectividad.

JEL Classification: I11, I18

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1. INTRODUCTION

Drugs are products subject to many regulatory regimes that affect major issues such as their production, registration, price, reimbursement, distribution and prescription. Many of the administrative actions related to drug regulation take place in a context of uncertainty, which may have important implications in medical practice. Some of these implications refer to effectiveness and safety, which also have economic consequences. Furthermore, after the initial regulation that authorises the marketing of a new drug, even though no uncertainty is assumed on medical grounds, the sales of the drug may increase the total pharmaceutical budget and create some financial difficulties to health authorities. That is, some uncertainties have straightforward consequences on health budgets while others affect them in a less direct way.

On other occasions, besides uncertainty, there may be asymmetries of information during the regulatory process between payers and drug manufacturers. There are many examples of information asymmetries: design and result presentations of the clinical trials, the sales force devoted to the new drug, sales expectations, rate of substitution of other drugs, and the growth of the prevalence rate of the disease, etc. The existence of asymmetries of information may delay the regulation process, affect total sales, and has implications for the strategic behaviour of both parties.

Payers (health authorities) have dealt with the problems derived from uncertainty and asymmetries of information in different ways. They have attempted to fix low prices for new drugs (to reduce the risk of having an uncontrolled budget). They have also established some constraints that guarantee efficiency before adopting a decision on reimbursement (for instance, accepting only those drugs with a cost-effectiveness ratio below a given threshold). In some jurisdictions, health authorities have bargained upon price rebates (once the drug has been traded and proved in current medical practice), or have reviewed the original price after experiencing the prescription success of the new drug (checking by experience a set of features such as effectiveness, safety, substitution of other drugs or medical procedures, and total sales-purchases forecast, etc.). Even, health authorities have required donations to health R+D national funds when total sales surpass a given ceiling.

During the last twenty years, one emerging way of coping with uncertainty has been channelled through the signing of risk-sharing contracts between pharmaceutical firms and public administrations. The main feature of these contracts is that health authorities pay for performance, that is, payments are contingent on health outcomes as described by Towse and Garrison (2010). There are some experiences as in New Zealand, where Pfizer and PHARMAC (Pharmaceutical Management Agency) signed a price-volume agreement for atorvastatin (Begg et al., 2003); in Australia, a similar agreement was

established for etenarcept, a drug for the treatment of rheumatoid arthritis (Lu et al., 2004). In the United Kingdom, the outcomes-guarantee agreement between Pfizer and the NHS for the treatment of hyperlipaemia (Chapman et al., 2003) deserves to be mentioned as it yielded beneficial results for both purchasers and drug firms (Chapman et al., 2004). However, the most cited contract took also place in the United Kingdom and dealt with the treatment of multiple sclerosis (Department of Health, 2005). That contract involved a detailed monitoring of a cohort of patients to confirm the cost-effectiveness of the treatment. This is a very important agreement as it established a link between the idea of paying for performance (i.e. under uncertainty conditions) and the results of the economic evaluation of health technologies. The agreement ensured that the treatment was cost-effective for the NHS, by fixing a threshold cost per QALY of £36,000. In some countries (Sweden, The Netherlands, and some jurisdictions of the UK) where economic evaluation reports are available previously to the adoption of decisions on price and reimbursement for new drugs, it is easier to use risk-sharing contracts for drugs whose efficiency ratio is above a given threshold (Oliva et al., 2008). In Spain, the first risk-sharing contract was signed in 2010 between the Hospital Virgen de las Nieves at Granada and the pharmaceutical firm GSK for Volibris (Ambrisentan DCI), a drug to treat lung hypertension. The effects of this agreement have not yet been assessed (Navarro et al., 2011). More recently, in 2013, the Catalan government and UCB Pharma have signed a new agreement involving an anti-TNF drug for the treatment of rheumatoid arthritis (Redacción Médica, 2013).

As Mzarek (2002) and Sudlow (2003) remarked, the application of risk-sharing contracts is not a simple task as it requires a narrow monitoring of health outcomes and of many other subtleties (eligibility criteria of recruited patients, dose regimes, duration of treatments, co-morbidities, and so on). After some years of new experiences, Neumann et al., (2011) also pointed these difficulties out for the implementation of these contracts as well as Adamski et al., (2010) and Garattini and Casadei (2011), who suggested some recommendations for their application too. The budgetary and sales results of these contracts do not always turn out to be as initially expected for the concerned parties and some contracts have raised controversy and created legal problems; this was the case of the aforementioned multiple sclerosis agreement.

These experiences reflect a change of paradigm in the regulation of drugs, as Pouvourville (2006) highlighted. However, some authors (Duerden at al., 2004) consider these initiatives mainly as a way of controlling costs and are not deemed very useful for dealing with uncertainty and information asymmetries.

Payments for performance agreements may be conceptualized in different ways. According to Puig-Junoy and Meneu (2005), any contract linking revenues of the pharmaceutical firm to any agreed target of volume, utilization, or

results can be considered to belong to this class. Hence, risk-sharing contracts may be based on price-volume targets (e.g., if a fixed sales ceiling is reached, prices will be lowered for the next period), or on reimbursement-effectiveness conditions (e.g., if a given effectiveness rate is not reached, manufacturers will return the money) and even on the efficiency of the utilisation of the drug (e.g. fixing a cost-utility ratio over which the price of the drug will be lowered). More recently, Espín et al., (2011) have also provided another classification of these agreements and described their features and possibilities of application. Other texts as the one by Badía and Prior (2010) have promoted their utilization in Spain.

From a theoretical perspective, some articles have modelled the financial risk-sharing schemes. Zaric and O'Brien (2005) presented a model based on the total budget impact of marketing a new drug. Another model by Lilico (2003) showed that in presence of risk-averse payers, risk-sharing contracts could increase both profits for firms and health benefits for patients. Pita (2011) conceptualized the relationship between health authorities and drug firms in a highly stylised model and characterized the conditions under which risk-sharing agreements were advantageous for the parties involved. In his paper, prices were assumed to be set by the firm although in many countries prices are rather set through a negotiation process or the health authorities make a take-it-or-leave-it offer to the companies, if no agreement is reached. Zaric and Xie (2009) used a dynamic approach to compare two types of risk-sharing agreements. In one model, the payer assumed the total cost in the first period but stops financing the drug in the second period if the first period net benefit is negative. In the second model, the firm offered a rebate in each period when the net benefit for the health authority is negative. They concluded that the parties involved did not unambiguously prefer a particular contract. Antoñanzas et al., (2011) developed a theoretical model where the health authorities and the pharmaceutical firm bargain upon the conditions of the agreement. The model characterized the risk-sharing contracts that health authorities could design when they faced a regulatory decision on drug pricing and reimbursement in a context of uncertainty. They found that the optimal contract depended on the monitoring costs, the marginal production costs and the benefits derived from treatment.

In summary, theoretical literature on risk-sharing contracts is still rather scarce and no other references, beside the ones aforementioned, have been found.

In this paper, we extend the literature on risk-sharing agreements. Following Antoñanzas et al., (2011) we develop a different stylized theoretical model that captures some of the relevant aspects that arise in the relationship between a pharmaceutical firm and the health authority. In this model, there is no negotiation process about the conditions of the agreement (i.e. about prices and reim-

bursement). The pharmaceutical firm sells a drug whose efficacy has been proved in a clinical trial. Given the uncertainty of the real effectiveness of the drug, the health authority designs the economic incentives to balance the health outcomes (cured patients) and the health budget. In particular, the health authority offers a contract with the pricing and reimbursement conditions to the pharmaceutical firm.

In particular, we focus on two types of contracts. On the one hand, we consider that the payments to the firm do not depend on the health outcomes, and the health authority sets a unit price regardless of the health outcomes. Alternatively, the health authority can make the payments contingent upon the observed ex-post effectiveness. For both types of contracts, the health authority must monitor the sales of the firm. When the payments to the firm are contingent upon the ex-post effectiveness, the health authority must also monitor the health outcomes. We find that the optimal contract will depend on the trade-off between the monitoring costs, the marginal production cost and the health cost derived from treatment failure. We also analyse the determination of the optimal contract when the decision by the health authority is based on the cost-effectiveness ratio. In this case, we show that the health authority always offers a risk-sharing contract. Our model goes beyond other theoretical references because it emphasizes the differences between the efficacy results obtained from a clinical trial and the final effectiveness in real world, allowing the firm to maximize its profits depending on the selection of the target population and applying, as in other models, payments contingent on such effectiveness. This model assumes that prices are fixed by health authorities and it characterizes the relationship between the variables at stake (monitoring costs, health costs, production costs and the design of the clinical trial) for a risk-sharing contract to be chosen.

The paper is structured as follows. We describe the model in section 2. In section 3, we characterize the optimal contract. In section 4, we obtain the optimal contract when the decision is taken based on the cost-effectiveness ratio. Finally, we present the conclusions in section 5.

2. THE MODEL

Consider a population of size one of patients with a specific disease. Patients are indexed with a parameter θ that represents their personal characteristics such as age, co-morbidities, or even some analytical parameter (cholesterol level, blood pressure, biomarker, etc.). We assume that θ is distributed uniformly within the interval [0, 1]. A pharmaceutical firm has developed a new drug whose therapeutic value has been previously proved in a clinical trial.

A clinical trial is defined by $\{\theta_t, q(\theta_t)\}$ where $\theta_t \in (0,1)$ represents the characteristics of the patients above which the new drug is tested and $q(\theta_t) \in (0,1]$ is the probability that the drug is effective (that is to say, the drug cures, meaning in this setting that it restores completely the quality of life previous to the disease). In other words, patients with $\theta \geq \theta_t$ participate in the clinical trial, and they are cured with probability $q(\theta_t)$. For the sake of simplicity, we will assume that the probability that the drug cures in the clinical trial is one: $q(\theta_t) = 1$. [1]

For patients with $\theta < \theta_t$, the clinical trial does not provide any information about the drug efficacy. In real clinical practice, the drug can be administered to patients with $\theta < \theta_t$ but its effectiveness is uncertain. We assume that $\Pr(cure \mid \theta < \theta_t) = \frac{\theta}{\theta_t}$. Thus, the drug cures with a low probability if it is administered to a patient whose personal characteristics differ much from θ_t. Both the health authority and the pharmaceutical firm know this probability of cure and the results of the clinical trial (the parameter θ_t and the probability $q(\theta_t)$.

The benefit a cured patient obtains is 1. If the drug does not cure, the patient's benefit is $1-s$, where the health cost derived from being sick is $s \in (0,1]$. For the sake of simplicity, the benefit of non-treated patients is also assumed to be $1-s$. We are implicitly assuming that the treatment does not have additional negative affects for the patient when it fails.

We consider a two-stage game. Given a clinical trial $\{\theta_t, q(\theta_t)\}$, the health authority (hereinafter, the principal) firstly decides the type of contract offered to the firm: either a contract with a reimbursement that does not depend on the observed effectiveness of the drug or, by the contrary, a contract where the reimbursement is contingent upon the effectiveness (a risk-sharing contract). In the first case, the contract specifies a price per treated patient, regardless of whether the patient is cured or not. In the second case, the principal offers a contract that specifies a price per cured patient. Then, secondly, the pharmaceu-

[1] In the real world, $q(\theta_t)$ is lower than one. It also depends on θ_t, the type of patients that participate in the clinical trial. The assumption we make simplifies the analysis and does not change qualitatively the results.

tical company (the agent) decides on the acceptance of the contract. If it accepts the contract, it selects the threshold of the type of patient $\theta \in [0,1]$ above which the drug will be prescribed. We will characterize the conditions for the existence of a Nash equilibrium.

In our setting, the firm chooses the patients to be treated. In the real world, the sales of the pharmaceutical firm are determined by the doctors' prescribing behaviour, which frequently is influenced by the firm's marketing effort (as Angell (2004) points out, marketing expenses in pharmaceutical firms are higher than R&D, neighbouring 30 % of sales). As the model does not pursue to characterize such a marketing relationship, we assume that indirectly the firm makes the decision on sales and doctors prescribe the drug as if the firm did such activity. Ideally, we should have added an additional stage to the game in which the firm decided the marketing effort, and then the prescribers, influenced by the marketing activities, decided the patients to be treated. However, we have simplified the process, assuming implicitly that the marketing effort is fully effective, and doctors prescribe as intended by the firm. Regarding price setting, we have given all the bargaining power to the health authorities, and in fact, we have considered that the contract is designed by them. In real world, a bargaining process usually takes place, and neither the health authorities nor the firm sets unilaterally the prices.

Since the incentives that the health authority offers to the company are conditioned to the number of treated and cured patients, it is necessary that the principal observe both variables ex-post. Therefore, it will be assumed that the principal can credibly commit to monitor ex-post the number of treated and cured patients. Monitoring costs are assumed to be borne by the principal. We assume that monitoring the number of treated patients has no cost, while monitoring the cured patient costs $m \geq 0$ per patient. The health authority and the pharmaceutical firm usually share monitoring costs. The model can be easily modified to incorporate shared monitoring costs but this modification does not provide additional insights.

The principal designs the contract to maximize social welfare defined as the expected aggregated benefit net of production and monitoring costs. We take the traditional approach to social welfare and define it as the sum of consumer and producer surplus (i.e. firms revenues and treatment costs offset each other but production costs remain). The firm chooses the size of the market served (in fact, the level of θ above which the drug is prescribed) to maximize its expected profits. It will be assumed that the marginal production cost for the pharmaceutical firm is $c \in (0,1)$. The firm accepts the contract if its expected profits are non-negative. In other words, we assume that the firm gets zero pro-

fits out of the relationship.[2]

We are assuming that both parties are risk-neutral. Alternatively, we could have assumed that the health authority is risk-averse with a concave objective function. The results, qualitatively, would not change.[3]

Notice that risk sharing here means that payments to the firm are made only if the patients are cured. Traditionally, contracts between the principal and the agent were very simple and reimbursement was not linked to outcomes. The pharmaceutical company received a payment (understood as public reimbursement of the drug) per unit sold that was independent on the ex-post observed effectiveness, and the firm had incentives to increase sales, which had a negative impact on public health budgets. When a health authority is concerned with effectiveness, it will be interested in having the number of cured patients (alternatively, the number of patients treated and not cured) as high (low) as possible. In this case, the health authority may be interested in offering a risk-sharing contract to dissuade the firm from selling the drug to too many patients.

3. THE DETERMINATION OF THE OPTIMAL CONTRACT

In this section, we characterize the optimal contract the health authority offers to the firm. There are two types of feasible contracts the health authority can offer. On the one hand, it may offer a contract where the payments to the firm are contingent upon the health outcomes (a risk-sharing contract). On other hand, it may offer a contract where the firm is paid regardless of the effectiveness of the drug (traditional contract). We first derive the best contract within each type, and then find the optimal contract. The type of the optimal contract and its characteristics will depend on the parameters of the model.

3.1. The best traditional contract

When the principal does not make the payments to the company contingent upon the effectiveness of the drug, it will offer a contract that specifies a price per unit sold. Given the assumptions of the model, the principal chooses a price equal to the marginal cost c and all the patients are treated.[4]

Let SW_{nrs} denote the social welfare achieved with this traditional contract, where the subscript nrs stands for no-risk-sharing.

[2] In case of indifference, the firm accepts the contract.

[3] The analysis when the health authority is risk-averse is available from the authors upon request.

[4] Notice that the firm will be indifferent between any $\theta \in [0,1]$ as its profits are zero. Strictly speaking, the principal pay the firm a price slightly above the marginal cost, and the firm, optimally, will choose $\theta = 0$. Therefore, the firm chooses to serve the entire market.

$$SW_{nrs} = 1 - \theta_t + \int_0^{\theta_t} \left(1 - s + \frac{s\theta}{\theta_t}\right) d\theta - c = 1 - \theta_t + (1-s)\theta_t + \frac{s\theta_t^2}{2\theta_t} - c = 1 - \frac{s\theta_t}{2} - c \quad (1)$$

Patients with $\theta \geq \theta_t$ are cured with probability 1, and their aggregated benefit is $1-\theta_t$. A patient with $\theta < \theta_t$ gets cured with probability $\frac{\theta}{\theta_t}$, and his benefit is 1. With probability $1-\frac{\theta}{\theta_t}$ he is not cured, and his benefit is $1-s$. Thus, his expected benefit is $1-s+\frac{s\theta}{\theta_t}$. The aggregate expected benefit of the patients with $\theta < \theta_t$ is given by the integral in (1). Notice that, given the assumptions, the principal does not incur the monitoring costs.

3.2. The best risk-sharing contract

If the principal decides to make the payments contingent upon the health outcomes, it will offer a contract specifying a price per cured patient $p \in [c,1]$ to be paid to the firm.

3.2.1. The behaviour of the firm

Given the price $p \in [c,1]$, the firm chooses the level of θ that maximizes its expected profits:

$$E\pi(p,\theta) = pN_c(\theta) - c(1-\theta) \quad (2)$$

where $N_c(\theta)$ is the expected number of cured patients. If the firm sells the drug to patients with $\theta \geq \theta_t$, all the patients are cured given the assumptions of the model, and the expected number of cured patients is equal to the treated patients. If the firm sells the drug to some patients that are not indicated to receive the treatment, the expected number of cured patients is $1-\theta_t + \int_\theta^{\theta_t} \left(\frac{\theta}{\theta_t}\right) d\theta$. Thus, we have:

$$N_c(\theta) = \begin{cases} 1-\theta & \text{if } \theta \geq \theta_t \\ 1 - 0.5\theta_t - 0.5\dfrac{\theta^2}{\theta_t} & \text{if } \theta < \theta_t \end{cases}$$

Let $\theta^*(p)$ be the value of θ that maximizes the firm's expected profits. If $p = c$, the firm will never sell to patients with $\theta < \theta_t$ as its profits would be negative. The firm will be indifferent between any $\theta \in [\theta_t, 1]$. We assume that it chooses θ_t. Thus, $\theta^*(c) = \theta_t$.

For $p \in (c, 1]$, the firm may opt for selling only to patients indicated to receive the treatment according to the clinical trial, in which case, it will choose $\theta = \theta_t$ and its expected profits are:

$$E\pi(p, \theta_t) = (1 - \theta_t)(p - c) \tag{3}$$

Alternatively, it can sell to patients with $\theta < \theta_t$. In this case, the firm chooses the level of θ that maximizes its expected profits:

$$E\pi(p, \theta) = p\left(1 - 0.5\theta_t - 0.5\frac{\theta^2}{\theta_t}\right) - c(1 - \theta)$$

Thus, we have:

$$\frac{dE\pi(p, \theta)}{d\theta} = 0 \Rightarrow c\theta_t - p\theta = 0 \Rightarrow \theta(p) = \frac{c\theta_t}{p} < \theta_t$$

Firm's expected profits are:

$$E\pi\big(p, \theta(p)\big) = p\left(1 - 0.5\theta_t - 0.5\frac{c^2\theta_t}{p^2}\right) - c\left(1 - \frac{c\theta_t}{p}\right) \tag{4}$$

From (3) and (4), it follows that:

$$E\pi\big(p, \theta(p)\big) - E\pi(p, \theta_t) = \frac{0.5\theta_t(p - c)^2}{p} > 0$$

Thus, when $p \in (c, 1]$, the firm prefers to sell to some patients that are not indicated to receive the treatment according to the clinical trial: $\theta^*(p) = \frac{c\theta_t}{p}$. In this case, the firm's profits are strictly positive.

In summary, the firm's optimal decision is:

$$\theta^*(p) = \begin{cases} \theta_t & \text{if } p = c \\ \dfrac{c\theta_t}{p} & \text{if } p \in (c, 1] \end{cases}$$

3.2.2. The determination of the best risk-sharing contract

The principal anticipates the behaviour of the firm and selects the price per

cured patient that maximizes social welfare.

The principal can induce the firm to sell $1-\theta_t$ by choosing $p=c$. Let $SW_{rs}(\theta_t)$ denote social welfare when the firm chooses $\theta^*=\theta_t$, where the subscript rs stands for risk sharing. Social welfare $SW_{rs}(\theta_t)$ is given by:

$$SW_{rs}(\theta_t)=(1-\theta_t)(1-c)+\theta_t(1-s)=1-c+\theta_t(c-s) \qquad (5)$$

In this case, $1-\theta_t$ patients get cured (all the treated patients) and θ_t patients are not treated, being their benefit $\theta_t(1-s)$. Notice that there are no monitoring costs, as the principal knows that, given the assumptions of the model, all the treated patients are cured.

Alternatively, the principal can design a contract with a price per cured patient such that the firm finds optimal to sell to some patients not indicated to receive the treatment according to the clinical trial. The principal chooses the price per cured patient $p\in(c,1]$ that solves the following problem:

$$Max\ 1-\theta_t+\int_{\theta^*(p)}^{\theta_t}\left(1-s+\frac{s\theta}{\theta_t}\right)d\theta+\theta^*(p)(1-s)-(c+m)(1-\theta^*(p))$$

where $\theta^*(p)=\dfrac{c\theta_t}{p}$. Patients with $\theta\geq\theta_t$ are cured with probability 1, and their aggregated benefit is $1-\theta_t$. The aggregate expected benefit of the patients with $\theta\in[\theta^*(p),\theta_t]$ is given by the integral in the above expression. Patients with $\theta<\theta^*(p)$ are not treated and their benefit is $\theta^*(p)(1-s)$. Notice that, in this case, the principal needs to monitor all the treated patients to know the number of cured patients as he is not able to distinguish *a priori* the patients that get cured with probability 1. An interior solution for this problem is $p^*=\dfrac{cs}{c+m}$ as long as $c+m<s$. It follows that $\theta^*(p^*)=\dfrac{(c+m)\theta_t}{s}<\theta_t$. Expected social welfare $SW_{rs}(\theta^*)$ is given by:

$$SW_{rs}(\theta^*)=1-\frac{s\theta_t}{2}-c-m+\frac{(c+m)^2\theta_t}{2s} \qquad (6)$$

The principal compares both levels of social welfare in (5) and (6) and chooses the contract (the price) for which social welfare is higher:

$$SW_{rs}(\theta^*) - SW_{rs}(\theta_t) = \theta_t \left[\frac{s}{2} - c + \frac{(c+m)^2}{2s}\right] - m$$
$$= \theta_t \left[\frac{s^2 + (c+m)^2 - 2sc}{2s}\right] - m$$
$$\Downarrow$$
$$SW_{rs}(\theta^*) \geq SW_{rs}(\theta_t) \Leftrightarrow \theta_t \geq \hat{\theta}(s,c,m)$$

where the threshold value $\hat{\theta}(s,c,m) = \frac{2sm}{2sm + [s-(c+m)]^2} < 1$. It is very easy to check:

$$\frac{\partial \hat{\theta}(s,c,m)}{\partial s} < 0 \qquad \frac{\partial \hat{\theta}(s,c,m)}{\partial c} > 0 \qquad \frac{\partial \hat{\theta}(s,c,m)}{\partial m} > 0$$

When the condition $c+m<s$ is not met, the principal cannot induce the firm to sell to patients with $\theta < \theta_t$, and the only feasible risk-sharing contract implies that the firm sells only to patients indicated to receive the treatment according to the clinical trial.

Proposition 1

Let $s > c+m$. If $\theta_t < \hat{\theta}(s,c,m)$, the optimal risk-sharing contract sets a price per cured patient equal to the marginal cost, and only the patients indicated in the clinical trial to receive the treatment are treated. If $\theta_t \geq \hat{\theta}(s,c,m)$, the optimal risk-sharing contract sets a price above the marginal costs and the firm sells to some patients that are not indicated to receive the treatment. In this case, some patients are not cured. When $s \leq c+m$, the optimal risk-sharing contract sets a price per cured patient equal to the marginal cost.

The optimal contract that the principal chooses when the incentives to the firm are based on the health outcomes depends on the monitoring costs m, the marginal cost c, the parameter θ_t from the clinical trial and the health cost parameter s. Intuitively, if the health cost the patient gets when the treatment fails is relatively large, the threshold value $\hat{\theta}(s,c,m)$ will be low, and the more likely the parameter θ_t will be above $\hat{\theta}(s,c,m)$. *Ceteris paribus*, for a given *s*, the lower the monitoring costs m or the marginal cost c, the lower $\hat{\theta}(s,c,m)$, and the more likely the treatment will be applied to patients that are not indicated to receive it. Thus, the principal prefers that the firm sell to a higher number of patients even though not all of them are cured. When the parameter

s is relatively low, it is better to treat only to patients eligible to receive the treatment according to the clinical trial to save monitoring costs.

3.3. The optimal contract

In this section, we characterize the optimal contract. In Table 1 we summarise the expected social welfare for each type of contract from equations (1), (5) and (6).

Table 1
Expected social welfare

Type of contract	*Expected Welfare*
No risk – sharing	$SW_{nrs} = 1 - 0.5s\theta_t - c$
Risk – sharing $\left(\theta^* = \theta_t\right)$	$SW_{rs}\left(\theta_t\right) = 1 - c + \theta_t\left(c - s\right)$
Risk – sharing $\left(\theta^* < \theta_t\right)$	$SW_{rs}\left(\theta^*\right) = 1 - 0.5s\theta_t - \left(c + m\right) + \dfrac{\left(c + m\right)^2 \theta_t}{2s}$

Source: Own elaboration.

Let us assume that $s \leq c + m$. According to Proposition 1, if the principal restricts himself to offer only risk-sharing contracts, he would choose a contract such that the firm sells only to patients that are indicated to receive the treatment according to the clinical trial $(\theta^* = \theta_t)$. Alternatively, he may opt for a traditional contract. If we compare the expected welfare for each contract, we obtain:

$$SW_{nrs} \geq SW_{rs}\left(\theta_t\right) \Leftrightarrow 1 - 0.5s\theta_t - c \geq 1 - c + \theta_t\left(c - s\right)$$

$$\Downarrow$$

$$s \geq 2c$$

Proposition 2

Let $s \leq c + m$. If $s \leq 2c$, the principal prefers the risk-sharing contract such that the firm sells only to patients with $\theta \geq \theta_t$. Otherwise, the optimal contract does not include risk sharing, and the firm sells to all the patients.

Intuitively, although s is relatively low, only patients with $\theta \geq \theta_t$ receive the treatment if c is large compared to s. The principal reduces health expenditures, and allows the firm to sell the treatment only to those patients for which

the treatment works. When the payment to the firm (the marginal cost) is low, the principal allows the firm to sell to all patients.

Let us assume that $s > c + m$ and $s \leq 2c$. In this case, the principal always chooses a risk-sharing contract. The health cost when the treatment fails is so large that the principal offers a contract based on health outcomes. The optimal contract depends on the relationship between θ_t and $\hat{\theta}(s,c,m)$ as shown in Proposition 1.

Let us assume that $s > c + m$ and $s > 2c$. In this situation, the three types of contracts are feasible. However, the principal will never choose a risk - sharing contract such that the firm sells only to the patients indicated to receive the treatment as the no-risk-sharing contract dominates that type of contract: $SW_{nrs} > SW_{rs}(\theta_t)$. Thus, in order to find the optimal contract, we need to compare the expected social welfare $SW_{rs}(\theta^*)$ with SW_{nrs}. It is easy to check:

$$SW_{rs}(\theta^*) \geq SW_{nrs} \Leftrightarrow \theta_t \geq \tilde{\theta}(s,c,m)$$

where $\tilde{\theta}(s,c,m) = \dfrac{2sm}{(c+m)^2}$. Notice that $\tilde{\theta}(s,c,m) > \hat{\theta}(s,c,m)$. When s is relatively large and c is relatively low, the optimal contract will depend on the relationship between θ_t and $\tilde{\theta}(s,c,m)$. When few patients are eligible for the treatment (θ_t is high), the principal prefers to pay per cured patient. When most patients are eligible to receive the treatment (θ_t is low), all patients are treated. The treatment works well and the principal does not mind paying for treated patient although some patients are not cured.

Proposition 3

Let $s > c + m$. If $s \leq 2c$, the principal always offers a risk-sharing contract. The type of risk-sharing contract depends on the efficacy of the clinical trial. If $\theta_t < \hat{\theta}(s,c,m)$, the contract implies that only the patients to receive the treatment according to the clinical trial will be treated. If $\theta_t \geq \hat{\theta}(s,c,m)$, it is optimal to treat some patients with $\theta < \theta_t$. When $s > 2c$, the principal prefers that all the patients receive the treatment (a traditional contract) if the efficacy in the clinical trial is relatively high ($\theta_t < \tilde{\theta}(s,c,m)$). Otherwise, the optimal contract is a risk-sharing contract such that the firm sells the treatment to some patients with $\theta < \theta_t$.

In Table 2, we summarize the results from Propositions 2 and 3. When the health cost derived from being sick is lower than the sum of the marginal production costs and the follow-up costs, the principal -the health authority- is not interested in monitoring the use of the drug. He will either fix a price per treated patient (all the patients are treated) or will offer a risk-sharing contract such that the drug is only prescribe to the patients that fulfil the requirements of the clinical trial.

Table 2
Optimal contracts

$s > c + m \text{ and } s \leq 2c$	$Risk - sharing \begin{cases} \theta^* = \dfrac{(c+s)\,\theta_t}{s} & if\ \theta_t \geq \hat{\theta} \\ \theta^* = \theta_t & if\ \theta_t < \hat{\theta} \end{cases}$
$s > c + m \text{ and } s > 2c$	$Risk - sharing \left(\theta^* = \dfrac{(c+s)\,\theta_t}{s} \right) if\ \theta_t \geq \tilde{\theta}$ $No\ risk - sharing\ if\ \theta_t < \tilde{\theta}$
$s \leq c + m \text{ and } s \leq 2c$	$Risk - sharing \left(\theta^* = \theta_t \right)$
$s \leq c + m \text{ and } s > 2c$	$No\ risk - sharing$

Source: Own elaboration.

On the contrary, if the health cost derived from being sick is larger than the sum of the marginal costs and the follow-up costs, the optimal contract depends on the relationship between the efficacy of the clinical trial and the threshold values $\hat{\theta}$ and $\tilde{\theta}$. When the health cost derived from being sick is relatively low -less than twice the marginal production costs-, the principal prefers that only patients indicated by the clinical trial were treated as long as the efficacy of the clinical trial is high. Otherwise, it will be socially profitable to allow the firm to sell the treatment to some patients whose personal characteristics that differ from those in the clinical trial. Notice that the simultaneous fulfilment of both conditions ($s > c + m$ and $s \leq 2c$) implies $c \geq m$. If the health cost derived from being sick is relatively high (greater than twice the marginal production cost), the principal will prefer to open the possibility of treatment to the maximum number of patients. The principal will fix a price by patient treated if the efficacy of the clinical trial is high. Otherwise, it will offer a risk-sharing agreement such that the firm is allowed to distribute the product between pa-

tients whose characteristics are different from those of the participants in the clinical trial.

In order to check the crossed influences of the parameters in the election of the optimal contract, a simulation analysis with some selected parameter values has been carried out. In particular, we have fixed the marginal production cost at 0.1, and θ_t at 0.6 and we have chosen the values for *s* and *m* such that the conditions in Propositions 2 and 3 are fulfilled. The simulation allows to determine the optimal contract under different sets of parameter values. For instance, when $s = 0.19$ and $m = 0.11$, the maximum welfare is obtained for the risk-sharing schemes reaching 0.846. However, if $s = 0.21$ and everything else remains the same as in the previous scenario, then the optimal contract is the traditional one, being the welfare 0.837. Interestingly, the welfare values do not vary in a wide range under different scenarios due to the constrains derived from the assumptions and the formulation of the model.

4. THE DECISION BASED ON THE COST-EFFECTIVENESS RATIO

So far, we have considered that the patients' benefit was known, and the principal designed the contract to maximize expected benefits net of production and monitoring costs. However, in the real world, the benefit attached to health is unlikely to be known. In these circumstances, health authorities often base their decisions on the incremental cost-effectiveness ratio. In this section, we assume that, before the new drug is traded, there existed another drug to treat the disease without any uncertainty about its effectiveness. For the sake of simplicity, that effectiveness is assumed zero, as well as its price. Thus, in the context of our model, the incremental cost-effectiveness ratio is simply defined as the cost per cured patient with the new drug. Health authorities will be interested in minimizing this ratio, and will choose the contract for which the cost-effectiveness ratio is lower.

According to the analysis in the previous section, the cost-effectiveness ratio when the principal does not make the incentives contingent on the effectiveness results is $CER_0 = \dfrac{c}{1-0.5\theta_t}$. Note the numerator is the payment to the firm, and the denominator is the expected number of cured patients when all the patients are treated.

The cost-effectiveness ratio when the firm sells only to the patients indicated to receive the treatment according to the clinical trial is $CER_{\theta_t} = \dfrac{(1-\theta_t)c}{1-\theta_t} = c$.

It is easy to see that $CER_{\theta_t} < CER_0$.

Finally, the cost-effectiveness ratio when the firm sells to some patients not indicated to get the treatment is equal to the price per cured patient p plus the monitoring costs per cured patient. As the firm has to be paid a unit price above the marginal cost, it follows that the CER_{θ_t} is also lower than the cost-effectiveness ratio when the firm sells to some patients not indicated to get the treatment.

Proposition 4

When the decision is based on the cost-effectiveness ratio, the principal offers the firm a risk-sharing contract and the firm sells to the patients indicated to receive the treatment.

The methodological approach adopted by the health authority has implications for the optimal contract. When the health authority is concerned about the cost per cured patient, it will always offer a risk-sharing contract. However, the health authority may be concerned instead about the well-being of the untreated patients. Some of these patients are not eligible to receive the treatment although they might be cured if they are treated. In this case, the health authority will prefer to pay a price per treated patient, and all the patients will be treated. This will happen either if the health cost derived from treatment failure is relatively low or if the efficacy of the drug in the clinical trial is relatively high. Otherwise, the health authority prefers to offer a risk-sharing contract.

5. CONCLUSIONS

In this article, we have modelled the relationship between a health authority and a pharmaceutical firm when the effectiveness of the drug manufactured by the firm is uncertain. The *ex-ante* information on the efficacy of the new drug is provided by the outcomes of a clinical trial. Within the framework of the model, the firm is interested in maximizing sales while the health authority is concerned about the health outcomes (patients' benefit) and the budget, i.e. efficiency.

We have considered two types of contracts. On the one hand, the health authority may offer a contract where the payments to the firm are not conditioned to the health outcomes. In this case, all the risk is borne by the health authority as the firm receives the same payment regardless of the ex-post observed effectiveness. On the other hand, the health authority can offer a contract where the payments are contingent upon the health outcomes. Now, all the risk is borne by the firm.

The optimal contract depends on the trade-off between the monitoring costs,

the production costs and the health cost derived from treatment failure. When the drug performs relatively well in the clinical trial, the health authority may either choose a contract such that all the patients eligible to receive the treatment are treated or a traditional contract. The decision depends on the relationship between the parameter s and the marginal cost c. When c is low, a traditional contract will be chosen. If the drug does not perform well in the clinical trial, the optimal contract makes the payments contingent upon the results unless the monitoring costs are too low and the health cost derived from treatment failure is relatively large.

We have also analysed the relationship between the health authority and the pharmaceutical firm when the decisions by the health authority are based on the cost-effectiveness ratio. In this case, the health authority will always offer a risk-sharing contract.

The model we have developed, although stylized as it is, can be used in real world to decide the type of contracts that can be used in pharmaceutical markets when there are uncertainties related to the effectiveness of a particular treatment. Decisions may be based on the parameters we have included in the analysis, and the optimal contract should be chosen by taking into account the relationships between them.

The basic model can be extended in several directions. The analysis suggests that the pharmaceutical firm prefers a risk-sharing contract that allows it to sell to patients not eligible to receive the treatment, as its profits are strictly positive. However, the type of contract that the health authority offers depends, among other things, on the results of the clinical trial. Pharmaceutical firms have usually private information about the efficacy of their products before performing the clinical trials. Therefore, firms may be interested in designing the clinical trials to show efficacy results such that the health authority offers their most preferred contract.

The model can be modified by adding a first stage in which firms with private information about the efficacy of their products design the clinical trial by choosing θ_t. The firm sends a signal to the health authority about the efficacy of the drug and the health authority, depending on the observed clinical trial, decides on the contract. Likewise, we have assumed for analytical tractability that the monitoring costs are borne by the principal. In the real world, such costs are probably shared (and perhaps, duplicated) between the principal and the firm, and therefore, the model could be extended to contemplate this circumstance. We have also assumed that treatment failure does not cause negative effects. The basic framework could be modified to differentiate the levels of benefit that untreated and uncured patients obtain. We hope to explore these issues in future research.

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