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ABSTRACT

The aim of this article is to analyze the relationship between drug price and drug quality and how it varies across two of the most common regulatory regimes in the pharmaceutical market: Minimum Efficacy Standards (MES) and Price Controls (PC). We develop a model of adverse selection where a pharmaceutical company can charge different prices to a heterogeneous group of buyers for its (innovative) drug, and we evaluate the properties of the equilibria under the two regimes. We model consumer heterogeneity stemming from differences in the willingness-to-pay for drug quality, measured through ex-post efficacy. The theoretical analysis provides two main results. First, the average drug quality delivered is higher under the MES regime than in the PC regime or a in combination of the two. Second, PC regulation reduces the difference in terms of high-low quality drug prices. The empirical analysis based on Italian and US data corroborates these results.

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1 Introduction

Regulation plays a crucial role in the pharmaceutical market. The rationale behind the regulator's intervention is dual: to guarantee and improve patient health and safety and to limit expenditures (especially public) on drugs.[1] As a consequence, pharmaceutical markets are characterized by strong interactions between producers and the public sector. This interaction is strongest when governments are both the unique provider of national health insurance and the regulator (for example, Italy, France, Spain) or when they are heavily involved in regulating social insurance funds (for example, U.K.). In such an environment, regulatory agencies generally articulate their strategies with respect to three objectives: drug quality, access (partial or total inclusion in the benefit package), and expenditure control. The definition of these aims varies considerably from country to country, and the authorities rarely rank them or define acceptable trade-offs (Maynard and Bloor [19]). In other cases, such as the United States, this interaction is reduced and it is limited to ensure patient health and safety.

The goal of this paper is to investigate the role that different regulatory schemes can have on the relationship between drug price and drug quality in the pharmaceutical market. We develop a simple model of the market for prescription drugs in which pharmaceutical companies can charge different prices to heterogeneous consumers for innovative drugs. We assume the existence of two different groups of buyers, differing in their *willingness-to-pay* for quality (efficacy). We then derive the properties of the equilibria under two different regulatory regimes: *i)* a regime with minimum efficacy standards (MES) and *ii)* an MES regime combined with a drug price ceilings (PC). The first regime models the regulatory structure of the pharmaceutical market in the U.S., while the second models the structure in many other countries in the developed world, including specifically Italy.

We run empirical tests of some of our theoretical predictions using drug market data from US and Italy. Two main results emerge. First, the average drug quality delivered is higher under a regime of MES regulation alone. Second, price ceiling regulation reduces price differences between highly effective and less effective drugs. Finally, we explore the policy implications of our results. To our knowledge, this paper contributes to the literature in two ways: (i) ours is the first unified model of drug regulation, drug prices, and drug quality applicable to multiple countries, and

[1] Pharmaceutical expenditures represent a substantial component of total health expenditures in all OECD countries.

(ii) we develop a novel data method for measuring drug quality from a database of randomized trials.

We organize the paper as follows. In section 2 we present a short review of the regulatory structure imposed on the pharmaceutical industry in the U.S. and in Europe, along with a short review of the literature. In section 3 we introduce our theoretical framework starting from a simple model where the firm observes only two types of buyers differing in their *willingness-to-pay* for quality (efficacy). In section 3.1, we develop this model under the assumption that consumers are perfectly informed about the quality (efficacy) of innovative medicines and firms observe buyers' *willingness-to-pay*. We then extend the model under the more realistic hypothesis that the firm does not know the buyers' *willingness-to-pay* (section 3.2) and derive the properties of the equilibria under the MES and PC regulatory regimes (section 3.3). In section 4 we discuss the data used to test the theoretical prediction of our model and presents the empirical analysis on the relationship between price and quality (efficacy) in Italy and in US. Finally, section 5 presents the main conclusions, discuss some policy implications of our findings, and highlights some of the caveats that permeates the analysis and that should be resolved in future research in this sector.

2 Background

The setting of minimum quality standards is one of the most important policy tools of the regulator. When an innovative compound is developed, the pharmaceutical firm submits an application for marketing authorization. The firm is then required to undertake an extensive evaluation of the safety and efficacy of the new compound. Approximately, only five in 5,000 compounds that are tested in the laboratory will end up in human trials and only one of these five will be approved by European Agency for the Evaluation of Medicinal Products (EMEA), in the EU, or by the Food and Drug Administration (FDA), in the U.S. As such, new drug development is a process that needs time and considerable resources. Country specific differences aside, both the FDA and the EMEA require companies to establish safety, efficacy, and sound manufacturing of new products for licensing. Standards on efficacy and safety are achieved through positive responses in several randomized clinical trials prior to market launch. If the drug respects the standards and side-effects are acceptable, then it receives approval and can be marketed. This is what we call a regulatory regime that imposes a Minimum Standard Efficacy (MSE).

Once the product is marketed, several other requirements are imposed to allow for reimbursement by public programs. Several forms of price controls (for example, price ceilings, reference pricing, rate of return, and so on) can be imposed together with positive and negative lists. [2] Therefore, regulation can have a substantial impact on the set of drugs available in a market as well as on drug prices. On the most innovative drugs, the regulatory environment can have substantial upstream effects by altering incentives for drug development. For example, a regulatory structure that requires extensive pre-launch clinical trials and detailed data on population risks and benefits in order to pass the MES implies higher R&D costs and increases both the delay in launch of new medicines and the uncertainty about future profits for the firm (see, for example, Peltzman [25]).

The extent of price controls on drugs also differ considerably across countries.[3] Countries such as Germany allow price freedom only for innovative drugs. In the US prices are free, but Health Maintenance Organizations (HMOs) and other Pharmacy Benefit Managers (PBMs) create formularies of "preferred"drugs that physicians and patients are encouraged to use via price incentives[4]. Countries such as Italy, France and Spain provide examples of regulatory frameworks that deter pharmaceutical companies from charging high prices. Drug prices are set through negotiation between the government and industry; firms must agree to the final price to obtain reimbursement from public health insurance. Finally, in the United Kingdom, authorities do not control individual product prices, but rather the profits of individual companies. Pharmaceutical firms can set freely the price of new products at launch; only subsequent price increases require approval. Firms are penalized if profits exceed government guidelines. These guidelines are not universal, but are negotiated company by company and may vary, for instance, with the amount of R&D that company does in the UK. Needless to say that these requirements represent further costs for producers.

[2] A *positive list* is a list that identifies drugs which are eligible for reimbursement, while a *negative list* is a list that identifies drugs which have to be paid out of pocket.

[3] For an extensive review of pharmaceutical regulation across EU countries, see Kanavos [17]

[4] Such price incentives for one or two preferred products within a group of therapeutic substitutes have increased the price elasticity of demand for drugs in the managed care sector in the US. This increase in turn has enabled PBMs to negotiate discounts for branded products. Since 1990 *Medicaid* (a public provider of health insurance for the poor in the US) has required that drug manufacturers provide drugs at a 15% discount off the list price or the "best price"given to any private purchaser, whichever is less (Danzon and Chao [10])

3 The Model

In this section we develop a simple theoretical framework of the optimal pricing policy of pharmaceutical firms under assumptions of perfect and imperfect information about buyers' preferences. We start by considering a market where a monopolistic firm sells its drugs to a set of heterogeneous insurers and providers. Providers behave as surplus maximizing agents whose preferences are known and defined only on by efficacy of the drug purchased. The source of heterogeneity stems from the differing *willingness-to-pay* for efficacy.[5]

3.1 The Complete Information Baseline Model

The main assumptions of the baseline model are the following.

Assumption 1. *Demand-side. There are N surplus maximizing buyers differing in their* willingness-to-pay *for a prescription medication with a certain efficacy. N_L buyers have a low* willingness-to-pay *for efficacy while N_H have a high* willingness-to-pay. *Buyers are price takers.*

Assumption 2. *Preferences. Each buyer chooses* e *to maximize her* gross surplus function $[v_i(e) - p]$. *$v_i(e)$ is the i-type* willingness-to-pay for efficacy *and exhibits the following properties*

$$v_i(e) > 0 \qquad \frac{dv_i(e)}{de} > 0 \qquad \frac{d^2v_i(e)}{de^2} < 0$$

where $i = L, H$. Moreover:

$$v_H(e) > v_L(e) \qquad v'_H(e) > v'_L(e)$$

The net surplus function *for i-th type provider is given by:*

$$v_i(e) - p \geq 0 \qquad for\ i = L, H$$

Assumption 3. *Supply-side (I). Within a monopolistically competitive pharmaceutical market, profit-maximizing firms produce and sell to N heterogeneous buyers a vector ζ_k of k different drugs to treat the same disease, whose efficacy e is function of R&D activities.*[6] *R&D activities exhibit decreasing marginal returns in terms of drug efficacy:*

$$\frac{de(r)}{dr} > 0 \qquad \frac{d^2e(r)}{dr^2} < 0$$

[5] At this stage we are interested in describing the static interaction between the producer and the insurer/provider, hence we do not consider the pharmaceutical product as an experience good.

[6] A good example in the real world of this situation is the market for statins (lipid lowering drugs).

Marginal cost is constant, and producers set a unique price.

Assumption 4. *Information (I). The seller is perfectly informed about buyers' characteristics and the buyers know perfectly the efficacy of the drug sold.*

The firm faces the following maximization problem:

$$\max_{\{p\}} \Pi = \sum_{i=L}^{H} N_i \cdot \{p - c[e(r)]\} \tag{1}$$

s.t.

$$v_i[e(r)] - p \geq 0 \qquad for\ i = L, H \tag{2}$$

where $c[e(r)]$ is unit cost.[7] p is the drug price per unit, N_i is the quantity of drug sold to the i-type insurers/provider, $v_i(e) - p$ is the minimum level of *cost-efficacy* that each insurer/provider is willing to accept for the drug to include it on its reimbursement list, e is the drug's efficacy, and $c > 0$ is constant *average cost*. Equation (2) simply represents the *participation constraints* for i-*th* type buyer. Moreover, cost function is concave in R&D outlay:

$$\frac{\partial C(\cdot)}{\partial r} > 0 \qquad \frac{\partial^2 C(\cdot)}{\partial r^2} < 0$$

Depending on the level of $\frac{e(r)}{p}$ that the producer is able to achieve, three different **strategies** (solutions) can be obtained.

Proposition 1. $v_L[e(r)] < v_H[e(r)] < p(r)$. *Insurers/providers will not buy the drug and the firm will stop its production, eventually leaving the market. This is the trivial case.*

Proposition 2. $v_L[e(r)] < p(r) < v_H[e(r)]$. *In this case only the insurer/provider with a high* willingness-to-pay *for efficacy will buy the product. In that case, the firm will sell to only part of the market. In this solution, profit will be positively affected by the level of R&D activities. At the optimum, the firm will charge a price* p_H *equal to* v_H *and the total profit will be given by:*

$$\Pi = N_H \cdot \Big\{ v_H\big[e(r)\big] - c[e(r)] \Big\} \tag{3}$$

[7]The other fixed costs, known both by the firm and by the regulator, are normalized at zero for notational simplicity.

By differentiating equation (3) with respect to R&D we simply derive the impact of an increasing level of research on profit at the margin:

$$\frac{d\Pi}{dr} \geq 0 \Leftrightarrow \frac{dv_H[e(r)]}{de} \cdot \frac{de}{dr} \geq \left.\frac{dc(\cdot)}{dr}\right|_{e \geq \underline{e}} \tag{4}$$

In many cases high fixed costs may lead the firm to choose not to invest in R&D. However, if it decides to invest and if the level of efficacy achieved is beyond the threshold imposed by the regulation, equation (4) states that R&D is profitable at the margin when the increase of the *willingness-to-pay* for efficacy is greater then (or equal to) the increase of unit cost. In what follows, let the $\underline{e}$ be the minimum drug efficacy permitted under the MES regulation.

Proposition 3. *$p(r) < v_L[e(r)] < v_H[e(r)]$. In this case both insurers/providers will buy the product. The firm will conquer the whole market. Profit maximization will imply that $p = v_L[e(r)]$ and profit will be given by:*

$$\Pi = \big(N_L + N_H\big) \cdot \Big\{ v_L\big[e(r)\big] - c[e(r)] \Big\} \tag{5}$$

where the following equation describes the marginal impact on profit of R&D when both the insurers/providers decide to buy:

$$\frac{d\Pi}{dr} \geq 0 \Leftrightarrow \frac{dv_L[e(r)]}{de} \cdot \frac{de}{dr} \geq \left.\frac{dc(\cdot)}{dr}\right|_{e \geq \underline{e}}$$

For firms that decide to enter the market, they must choose between aiming for the high end market only (high willingness-to-pay insurers) and aiming for the whole market (high and low willingness-to-pay insurers) Simple algebra shows that firms will aim for the whole market if and only if

$$\big(v_L - c\big) \cdot N_L > \big(v_H - v_L\big) \cdot N_H$$

which implies

$$\pi(r) \cdot N_L > \Delta p(r) \cdot N_H$$

where π is the profit per unit of output.

Thus, the firm aims for the whole market (by choosing a lower price) if and only if the profit that derives from extending its market to L-type buyers is higher than the loss in revenues ($\Delta\pi \cdot N_H$) due to the acceptance of a lower price from H-type buyers.

The simple model outlined above allows to infer a set of very important implications concerning optimal pricing strategies: *i)* an increase in marginal costs will

tend to move firms toward "high price"strategy; *ii)* an increase in q_L (the quantity bought by the insurer/provider with lower cost-efficacy ratio) will tend to move firms toward "high price"strategy; *iii)* the greater is e the greater is the market share for a given price. This means that, *ceteris paribus*, a higher efficacy requirement $\underline{e}$ pushes the seller towards H-type buyers, by increasing the ratio $\frac{e(r)}{p}$.

3.2 Incomplete Information: Unobserved Preferences

In this section we extend our reasoning to an environment characterized by incomplete information among agents. The lack of information is related to the buyers *willingness-to-pay* for efficacy. The first three assumptions of the baseline model still hold. The profit-maximizing firm faces the demand of $N = N_L + N_H$ insurers/providers who differ in their *willingness-to-pay* for efficacy as defined in assumption (1). Assumption (4) must, instead, be reformulated.

Assumption 5. *`Information (II).` The seller does not know buyers' characteristics and she can not discriminate, while buyers perfectly know the efficacy of the drugs sold.*

3.2.1 Producer's behavior

Since pharmaceutical firm does not observe the type of the provider/insurer, it will offer a set of choices independent of the type in order to maximize her expected profits. Given that there are only two types of buyer (*low* and *high*), the pharmaceutical firm will produce only two types of drugs ζ_k: $\zeta_k^L(e_L)$, obtained with an investment in R&D equal to r_L and $\zeta_k^H(e_H)$, obtained with an investment in R&D equal to r_H.

Hence, the seller has to solve the following expected profit maximization problem:

$$\max_{\{p,e\}} \Pi = N_L \cdot \big[p_L - c(e_L)\big] + N_H \cdot \big[p_H - c(e_H)\big] \tag{6}$$

s.t.

$$v_i(e) - p_i \geq 0 \qquad for\ i = L, H \tag{7}$$

where $c(e_i)$ with $i = L, H$ is the unit cost of producing i-type drug and $dc(\cdot)/de > 0$, $d^2c(\cdot)/de^2 > 0$. Equation (7) represents the *participation constraints* for types L and H.[8]

[8] We also assume the following regularity conditions: $\lim_{e\to\infty} c'(e) = \infty$; $v_i'(0) > c'(0)$ for $i = L, H$; v_i' is bounded from above.

If the seller could perfectly discriminate, she would extract the entire surplus from each group of buyers, and the constraints (7) would hold as equalities. This solution entails socially optimal efficacy levels that equate the marginal benefit with the marginal cost of efficacy:

$$v'_L(e_L) = c'(e_L) \tag{8}$$

$$v'_H(e_H) = c'(e_H) \tag{9}$$

However, when the provider/insurer's type in not observable, perfect price discrimination is not feasible. Hence the producer is not able any more to maintain all buyers at the zero surplus level and the first best solution $\{p_i^{FB}, e_i^{FB}\}$ is not achievable. Hence the $\{p_i, e_i\}$ pairs offered by the pharmaceutical firm must satisfy also the following *incentive compatibility constraints*:

$$v_H(e_H) - p_H \geq v_H(e_L) - p_L \tag{10}$$

$$v_L(e_L) - p_L \geq v_L(e_H) - p_H \tag{11}$$

Equations (6-11) represents a *standard adverse selection problem* (see Bolton and Dewatripont [6], Laffont and Tirole [18]). It is easy to show that only L-type *participation constraint* and H-type *incentive compatibility* are binding (see A.2). Hence the seller solves her expected profit maximization problem simply by substituting the two remaining constraints in her objective function:

$$\max_{\{p,e\}} \Pi = N_L \cdot \big[p_L - c(e_L)\big] + N_H \cdot \big[p_H - c(e_H)\big]$$

s.t.

$$v_L(e_L) - p_L = 0$$

and

$$v_H(e_H) - p_H = v_H(e_L) - p_L \tag{12}$$

Both the constraints must be binding or else the producer could increase her expected profit simply by raising prices.

Proposition 4. *Solutions for problem (12) entails a* separating equilibrium *where:*

- $p_H^{SB} = v_H(e_H) - \big[v_H(e_L) - v_L(e_L)\big] \Rightarrow$ positive surplus for H-type buyers*;*

- $p_L^{SB} = v_L(e_L) \Rightarrow$ zero surplus for L-type buyers*;*
- *the group of buyers with the lower* willingness-to-pay *for efficacy receives a pair* $\{e_L^{SB}, p_L^{SB}\}$ *and the drug delivered exhibits an efficacy level that is lower then at the social optimum (perfect price discrimination scenario)*

$$v'_L(e_L) = c'(e_L) + \frac{N_H}{N_L} \cdot \left[v'_H(e_L) - v'_L(e_L)\right]$$

- *the buyers with the higher* willingness-to-pay *for efficacy receives a pair* $\{e_H^{SB}, p_H^{SB}\}$*: their medicine exhibits the same efficacy level they received at the social optimum*

$$v'_H(e_H) = c'(e_H)$$

It is worth noticing that the size of this distortion is increasing in the so-called *informational rent* of H-type buyer - $\left[v'_H(e_L) - v'_L(e_L)\right]$ - and in the ratio N_H/N_L.

3.3 Does Regulation Eliminate Distortions?

The following subsections will illustrate the effect that different regulatory mandates can have on the pharmaceutical market described above and how R&D subsidies can contribute to the achievement of higher levels of drug efficacy and welfare.

Following Besanko, Donnenfeld, and White [5], who consider the monopolist's quality choice problem in the presence of regulation, we will analyze two main regulatory approaches: minimum drug efficacy standards and price control regulation.

3.3.1 The Minimum Efficacy Standard (MES) scheme

Consider a pharmaceutical market where regulation requires minimum drug efficacy, but no pure price controls, such as in the U.S. In such a context, when the minimum efficacy level is increased, so are expenditures by firms for research and testing. Once the drug is approved (and presumably patented), the absence of price control allows the firm to enjoy large profits. We define this regulatory mandate as a *Minimum Efficacy Standard* scheme (hereafter MES). Under assumptions (1)-(3) and (5) we will show that a higher efficacy threshold imposed by the government increases the efficacy of the drug marketed to L-type buyers.

Suppose that the government fixes the efficacy requirement $\underline{e}$ such that: $e_L^{SB} < \underline{e} < e_H^{SB}$. Hence the profit maximizer seller has to take into account a further

constraint:

$$e_i \geq \underline{e} \qquad for\ i = L, H \tag{13}$$

In the *regulated problem*, the seller maximizes her objective function (eq.6) under the two *participation constraints* (eq.7), the two *incentive compatibility constraints* (eq.11-10) and the two *efficiency constraint* (eq.13).

Proposition 5. *Simple algebra shows that:*

- $\tilde{e}_H = e_H^{SB} \Rightarrow$ *regulation does not affect the efficacy level delivered to the H-type buyers;*
- $\tilde{e}_L = \underline{e} > e_L^{SB} \Rightarrow$ *the* efficacy constraint *imposed by MES regulatory mandate is binding for L-type buyers;*
- $\tilde{p}_L > p_L^{SB}$;
- $\tilde{p}_H < p_H^{SB}$.

Proof*: see appendix A.3.*

To evaluate how a rise in the minimum efficacy requirement $\underline{e}$ affects welfare, we define the following *Social Welfare Function*:

$$\mathcal{W} = \sum_{i=L}^{H} N_i \big[v_i(e_i) - c(r_i) \big] \tag{14}$$

$$\left. \frac{d\mathcal{W}}{d\underline{e}} \right|_{\underline{e}=e_L^{SB}} = \sum_{i=L}^{H} N_i \big[v_i'(e_i) - c'(r_i) \big] \cdot \frac{de}{d\underline{e}} \tag{15}$$

By the last two points of proposition 4 we know that $dv_H(e_H)/d\underline{e} = 0$ and that $dv_L(e_L)/d\underline{e} > 0$. Hence equation (15) states that marginal increases in $\underline{e}$ improve welfare by raising the utility of L-type buyers, leaving the efficacy provided to the H-type buyers unchanged. Therefore, as pointed out by Besanko, Donnenfeld, and White [5], if MES policy is slight it "can remedy the effects of market failure". However, higher minimum efficacy imposes higher costs on R&D. At an extreme, if regulation imposes too high standards, prices could rise to a point where L-type buyers are excluded from the market.

Given our assumptions, it can be shown that there exists a minimum efficacy threshold that optimally balances the higher R&D costs with the higher efficacy drugs delivered to L-type buyers. This optimal level is just below the level that excludes L-type buyer from the market. To evaluate the welfare effects due to an

increasing in R&D activities by the firm we take the derivative of $\mathcal{W}$ with respect to r:

$$\frac{d\mathcal{W}}{dr} \equiv \sum_{i=L}^{H} N_i \big\{ v_i'[e_i(r)] - c'[r_i(r)] \big\} \cdot \frac{de}{dr}$$

Hence, $d\mathcal{W}/dr \geq 0$ if $\sum_{i=L}^{H} N_i \big\{ v_i'[e_i(r)] - c'[r_i(r)] \big\} \geq 0$ where the term in brackets is positive for $i = L$ and zero for $i = H$.

3.3.2 The Price Control (PC) scheme

Price-control schemes are very common in pharmaceutical markets. Different schemes are in use. For example, in Italy and France prices of new drugs are set through negotiations between firms and the regulator. What producers can charge is strictly related to the reimbursement price (reference pricing). This price is often based on external referencing to foreign prices for the same drug or prices of similar products on the market.[9] In other European countries (e.g. Netherlands, Ireland) pure price-ceiling applies and the maximum that the producer can charge is given by the regulated price.

The aim of this section is to analyze the effect of a price-control scheme on the pair $\{p_i, e_i\}$ delivered to the market. To keep matter simple, we do not focus on the negotiation mechanism and how it occurs. As a consequence, the regulated price is considered as an exogenous variable for the parties.

Consider a regulated price $\hat{p}$ such that: $p_L^{SB} < \hat{p} < p_H^{SB}$. Under this mandate, pharmaceutical firm maximizes the following program:

$$\max_{\{p,e\}} \Pi = N_L \cdot \big[p_L - c(e_L) \big] + N_H \cdot \big[p_H - c(e_H) \big] \tag{16}$$

s.t.

$$v_L(e_L) - p_L \geq 0$$

$$v_H(e_H) - p_H \geq v_H(e_L) - p_L$$

and

$$\hat{p} < p_H$$

Proposition 6. *The solution for the problem (16) under price-ceiling is characterized as follows:*

[9] Though reference pricing differs substantially from the price-ceiling mechanism, a wide evidence supports its efficiency "in cutting drug prices, in controlling relative demand of highly priced drugs, and in encouraging the appropriate use of drugs" (Miraldo [21]).

- $v'_L(\hat{e}_L) = c'(\hat{e}_L) + \left[\frac{N_H - \lambda}{N_L}\right] \cdot \left[v'_H(\hat{e}_L) - v'_L(\hat{e}_L)\right]$;
- $v'_H(\hat{e}_H) = c'(\hat{e}_H) + \left(\frac{N_H}{N_H - \lambda}\right)$
- $\hat{p} = v_H(\hat{e}_H) - \left[v_H(\hat{e}_L) - v_L(\hat{e}_L)\right]$

where λ is the Lagrangian multiplier for the constraint $\hat{p} \geq p_H^{SB}$.

Under this scheme it is interesting to note that H-type buyers' surplus is reduced respect to the unregulated scenario. Hence, PC implies that H-type buyers receive less efficacy then they received in the unregulated case while induces an improvement of the efficacy delivered to L-type buyers.

In order to examine the welfare proprieties of a price control scheme, we evaluate $d\mathcal{W}/d\hat{p}$ at the unregulated equilibrium:

$$\left.\frac{d\mathcal{W}}{d\hat{p}}\right|_{\hat{p}=p_H^{SB}} = \sum_{i=L}^{H} N_i \left[v'_i(e_i) - c'(e_i)\right] \cdot \frac{de_i}{d\breve{p}} \tag{17}$$

From proposition 4 we know that the term in brackets is positive for L-type buyers and null for H-type ones. Furthermore, we pointed out that $de_L/d\hat{p}$ is positive while $de_H/d\hat{p}$ is negative. Hence the sign of equation 17 depends on the distance between $\hat{p}$ and p_H^{SB} and on the sizes of the two group of buyers.[10]

4 Empirical analysis

Complying with pharmaceutical market regulation can be costly. How regulatory mandates affect the pricing and efficacy of marketed drugs is, therefore, an issue of major concern for the pharmaceutical industry. Table 1 summarizes the results obtained from our theoretical model and compares the effect that the two regimes will on drug price and quality (efficacy). From an empirical perspective, three main testable predictions emerge from the theoretical model.

Testable prediction 1. *When pharmaceutical firms compete on price but face a tight regulation on drug quality (efficacy) (MES) the entire market receives more effective medicine. At the opposite, when companies face both a (slight) regulation on drug efficacy and a tight price-ceiling regulation (PCR) the entire market receives (on average) less effective medicines.*

[10] Vernon [34] describes two potential channels through which a PCR scheme may affect R&D investment. Firstly, it may exert a negative influence on the expected returns to R&D. Secondly, if capital market imperfections exist in the market for R&D finance then PCR may also affect R&D through a cash-flow effect.

Table 1: The effects of regulation on price and quality (efficacy)

	Minimum Efficacy Standard	**Price-Ceiling Regulation**
Efficacy provided	$\tilde{e}_H = e_H^{SB}$	$\hat{e}_H < e_H^{SB}$
	$\tilde{e}_L > e_L^{SB}$	$\hat{e}_L > e_L^{SB}$
Price charged	$\tilde{p}_H < p_H^{SB}$	$p_H > \hat{p} > p_L$
	$\tilde{p}_L > p_L^{SB}$	$\hat{p} = v_H(\hat{e}_H) - [v_H(\hat{e}_L) - v_L(\hat{e}_L)]$

Testable prediction 2. *If only a MES scheme is implemented, the market should experience higher price dispersion compared to the case with PC regulation alone.*

Testable prediction 3. *If only a MES scheme is implemented, the correlation between price and efficacy is expected to be higher for low efficacy drugs. If MES and PCR schemes are jointly implemented a low correlation for all drugs is expected.*

The aim of the next sections is to empirically test these predictions. We have collected data on Italian and US pharmaceutical markets, which represent two good examples of the regulatory regimes that we have discussed in our theoretical framework. In fact, while in both markets we observe a MES regime, only the Italian market is characterized by the presence of a PC scheme. There, two different PC schemes coexist: the Average European Price (AEP) - for old products and *me-too* products - and a scheme based on price negotiation - for new medicines registered by EMEA or for all those drugs for which AEP cannot be implemented. The US market is instead characterized by a free price setting scheme.[11]

Unfortunately, as we will clarify later, our data allows only to test prediction 2 and prediction 3. In fact, for what concerns prediction 1, our sample includes, by construction, the same set of drugs across the different regimes. Though Italy and US represent two polar cases with respect to the regulatory schemes associated to drug industry, they are very close for what concerns the other main characteristics of the pharmaceutical market: willingness-to-pay, new drugs availability and affordability. As a consequence, the level of drug efficacy is equalized across the

[11] A free price setting scheme exists in Italy for OTC drugs and for not reimbursable drugs. However, as we will see later, the empirical analysis on the Italian side will concentrate only on prescribed and reimbursable drugs that are all under price control (Kanavos [17]).

two countries and therefore we can not empirically test the difference in the average quality delivered to those markets by the pharmaceutical industry.

Though we cannot test this prediction with our data, we believe that the literature supports it. First, countries with tighter PC regimes tend to experience longer delays in the introduction of new drugs. The existing literature on this topic confirms this statement (Danzon et al [12]). Mitchell [22] reports that, between 2000 and 2005, 73% (52 drugs) of the new medicines approved in both the EU and the US received their approval first from the FDA. On average, FDA approval came 1 year ahead of clearance by the EMEA. This gap does not depend on faster FDA processing, but rather on firm choice to submit drugs first to FDA. [12]

Similar conclusions can be reached within EU. For example, in the European market firm strategies are to market drugs first in the UK or Germany (where price regulation is less stringent) and then in countries with more stringent price regulation (i.e., France, Italy and Spain).

4.1 Data

Our primary source of data comes from the *Tufts - New England Medical Center - Cost Effectiveness Analysis Registry* that allows us to compare cost-effectiveness of a broad range of interventions (among which drugs are the most studied) using standardized cost-utility ratios.[13] The collection consists in detailed abstracted information on published cost-effectiveness studies concerning: *infectious diseases*, *cardiovascular diseases*, *muscular and rheumatological diseases*, *malignant neoplasm* and *neuro-psychiatric diseases*. Each study in the dataset computes the cost-effectiveness of one or more interventions as the incremental costs (converted to 2002 US$) divided by the incremental health benefits quantified in terms of Quality Adjusted Life Years (QALYs).

Though this measure entails important caveats, QALYs enable a comparison between the benefits associated with different drugs in a standardized way, thus allowing us to measure the social value of an innovation in treatment.[14] When the

[12]This has been also confirmed in an interview by Ken Kaitin, Director of the Tufts Center for the Study of Drug Development, who stated "Investors tend to invest in places where there is less control over prices, and it is always better to do your clinical trials in the countries where you plan to market" (Mitchell [22]).

[13]See https://research.tufts-nemc.org/cear/default.aspx

[14]See McGregor [20] for a consideration of the strengths and methodological shortcomings of this measure.

cost-effectiveness ratio is lower, the more QALYs can be accrued per dollar spent. Therefore treatments with low levels of `$/QALY` are preferred. According to Tuft terminology, interventions that reduce cost and simultaneously improve health are defined *cost-saving*. At the opposite poorly performing interventions, that raise costs while improving poorly health status, are defined *dominated*.

For different disease Tufts registry provides cost-effectiveness analyses of several interventions and reports information on the following variables:

1. `intervention treatment`;
2. `comparator treatment`;
3. `cohort of patients`;
4. `QSA` [quality score of the analysis, an index that provides information on the quality of the comparison study carried out and varies from 1 (low quality) to 6 (high quality)];
5. `$/QALY` [cost/effectiveness ratio of the treatment].

Given the aim of our work, we have selected only interventions based on drugs. We have selected 177 interventions of which: 54 concern *cardiovascular diseases*, 43 concern *infectious diseases*, 31 concern *muscular and rheumatological diseases*, 22 concern *neuro-psychiatric diseases*, and 15 concern *malignant neoplasm*. Often the Tufts registry includes comparisons of the same treatments (a single active ingredient or a combination of more medicines) differing in the dosage and/or in the length and/or in the cohort of patients. The following examples clarify this issue.

Example 1: two comparisons involving the same compound, originating from two different studies and conducted on two different cohorts of patients:

- `amantadine` [intervention] **VERSUS** `no treatment` [comparator] **IN** `febrile adult patients with influenza symptoms` [cohort]
- `amantadine` [intervention] **VERSUS** `no treatment` [comparator] **IN** `unvaccinated healthy, working adults between 20 and 50 years of age presenting with influenza-like ill-ness during the influenza season` [cohort]

Example 2: three comparisons involving the same compound originating from the same study:

- tamoxifen [intervention] **VERSUS** no treatment [comparator] **IN** women at very high risk of breast cancer (Gail model RR>1,6) -age 50 [cohort]

- tamoxifen [intervention] **VERSUS** no treatment [comparator] **IN** women at very high risk of breast cancer (Gail model RR>1,6) -age 60 [cohort]

- tamoxifen [intervention] **VERSUS** no treatment [comparator] **IN** women at very high risk of breast cancer (atypical hyperplasia) -age 35 [cohort]

Example 3: two comparisons involving the same compound, originating from two different studies and conducted on two different cohort of patients:

- high-dose adjuvant interferon (IFN) [intervention] **VERSUS** observation only [comparator] **IN** patients with clinical stage II malignant melanoma after surgical excision of their melanoma [cohort]

- interferon-alpha (IFN) in a dose of 5 million units (MU) daily for 16 weeks [intervention] **VERSUS** no treatment [comparator] **IN** patients with chronic hepatitis B infection (HBsAg positive and elevated serum aminotransferase activity for at least 6 months, evidence of active viral replication, and a histological diagnosis of chronic hepatitis but no cirrhosis) - age 30 [cohort]

The size of our dataset will then be equal to the number of comparisons selected (132) times the number of products (brand names) available for each active ingredient in Italy (98 brand names) and US (83 brand names). The final sample originated from this procedure contains **400** observations, of which **310** belonging to the Italian market and **190** to the US market. For each brand name we have then merged in the Italian and US drug prices. [15] We extracted the information on US drugs' brand names from the FDA and Merck Manuals On Line Digital Library. We estimated US prices using information from the Medical Expenditure Panel Survey (MEPS), which is a nationally representative dataset of Americans.[16] We obtained

[15] When the comparison involve a combination of active ingredients we have computed the average price per milligram.

[16] www.merck.com/mmhe/index.html.

Italian brand names and prices from the AIFA, the Italian National Agency for Drug Administration and Control Prices. The prices provided by AIFA have been computed as a average of list prices of all packages available on the Italian market while MEPS provides unit prices (ratios between expenditure and quantity purchased). All prices have been converted in price per milligram and for comparison Italian prices have been expressed in current 2005 US$ per mg.[17] Table 2 provides the variables list, with the relative description and source, used in our empirical analysis.

Table 2: Variables and Data Sources

Variable	**Description**	**Source**
id	active principle	Tufts Center for the Study of Drug Development
$name_{it}$	Italian brand name	Italian Agency for Drug Administration and Control (AIFA)
$company_{it}$	Italian company	Italian Agency for Drug Administration and Control (AIFA)
$name_{us}$	US brand name	Merck Manuals On Line Digital Library; FDA
$company_{us}$	US company	Merck Manuals On Line Digital Library
p	price per mg (US$ 2005)	AIFA for Italy, MEPS for US
QSA	Quality Score of the Analysis (1-6)	Tufts Center for the Study of Drug Development
$\$/QALY$	cost/QALY ratio	Tufts Center for the Study of Drug Development

Given that the same active ingredient (or combination of active ingredients) appears in different comparison yielding different QALY, our final step has been to collapse the dataset with respect to brand name, generating a new sample organized as shown in table 3 and whose summary statistics are reported in table 4.

[17] The exchange rate used are from the Federal Reserve Bank of St. Louis.

Table 3: Selected drugs: brand names and prices per milligram*

n	Disease	Brand name	Price	QSA	$/QALY	US
1	Cardiovascular	aspirin	0.0006	5	11,000	1
2	Cardiovascular	aspirin & clopidogrel	0.0006	5	32,000	1
3	Cardiovascular	lovenox	1.7783	4.5	3,900	1
...	...	...	...	...	...	
15	Infectious	adamantane antivirals	0.0149	6	12	1
16	Infectious	methadone	0.0181	3	97,000	1
17	Infectious	pneumovax23	73.1000	3	21,000	1
...	...	...	...	...	...	
31	Endocrine Disorders	pravachol	0.1357	4.5	58,000	1
...	...	...	...	...	...	
57	Malignant Neoplams	femara	3.8111	3	8,700	1
58	Malignant Neoplams	tamoxifen	0.1606	6	32,000	1
...	...	...	...	...	...	
67	Mus&Rheumatologic	arava	0.6886	4	0	1
68	Mus&Rheumatologic	fosamax	0.3109	4.5	700000	1
...	...	...	...	...	...	
70	Neuro-Psychiatric	reminyl	0.3779	4.5	0	1
71	Neuro-Psychiatric	topamax	0.0640	4.5	56,000	1
...	...	...	...	...	...	
...	...	...	...	...	...	
...	...	...	...	...	...	
80	Cardiovascular	aspirina	0.0008	5	11,000	0
81	Cardiovascular	aspirina and iscover	0.0367	5	32,000	0
96	Infectious	mantadan	0.0035	6	12	0
97	Infectious	metadone cloridato	0.0359	3	97,000	0
...	...	...	...	...	...	
123	Malignant Neoplams	arimidex	5.6246	3	14,000	0
124	Malignant Neoplams	femara	2.3423	3	8,700	0
...	...	...	...	...	...	
152	Mus&Rheumatologic	arava	0.5224	4	0	0
153	Mus&Rheumatologic	fosamax	0.1366	4.5	700000	0
...	...	...	...	...	...	
179	Neuro-Psychiatric	aricept	0.5386	3	0	0
180	Neuro-Psychiatric	betaferon	445.6173	5	94,000	0
181	Neuro-Psychiatric	comtan	0.0058	5.5	10,000	0

**2005 US$. US is a dummy which equals to 1 if the price refers to a brand name sold in US and 0 if sold in Italy.*

Table 4: Summary statistics

Variable	Obs	Mean	Std.Dev.	Min	Max
p	181	6.336	41.327	0.0002	445.6173
$log(p)$	181	-2.912	2.854	-8.517	6.099
QSA	181	4.654	1.111	2.5	6.5
$\$/QALY$	181	66157.73	98334.18	0	700,000
$QALY$	181	0.014	0.031	1.43E-06	0.09

4.2 Empirical Results

4.2.1 Testing Prediction 2: Price Variability

According to our theoretical model, under a PC regime (Italy) we expect a lower price variability compared to a free price regime (US). We test this prediction using two datasets containing active ingredients available in both countries: a small sample of drug prices obtained from the Tuft Cost Effectiveness Analysis Registry, and a larger sample of drug prices for outpatient use only, obtained using data on prices and brand names provided by AIFA for Italy and by MEPS for USA.[18] Given that the types of active ingredients included in the AIFA and MEPS database are different, the first step has been to obtain a common basket of active ingredients across the two countries.[19] We have then identified a list of common active ingredients in both databases and then selected all brand names within that list. Finally, we have obtained average price per milligram by brand names in order to compute an average price per single brand.

We find that US drug prices have a higher variance in drug prices that Italian drug prices, independently of the dataset we use, thus confirming our theoretical prediction. In particular, the statistical analysis shows that the difference in price

[18]The use of this larger sample has been possible because the testing of this prediction does not involve information on drug quality (efficacy).

[19]Italian data concerns all drugs belonging to classes A (fully reimbursed) and H (distributed through hospitals) and include 5003 observations (brand names), while US data concerns all household prescription drugs and include 1526 observations (brand names). The main reason for this discrepancy comes from the different institutional goal that each database has. In fact, MEPS is a household survey that collects information on both over-the-counter and for prescription drugs. Moreover MEPS dataset does not include vaccinations. On the contrary, the AIFA database collects all drugs available in the Italian market.

variances across the two countries is statistically significant at 1% level and that price variance in Italy is lower than price variance in US (see table 5 and figures 1 and 2). Furthermore, in both samples a higher average price per milligram has been found in US: 1.30 versus 3.17, in the Tuft sample, and 0.051 versus 0.026, in the large sample.

4.2.2 Testing Prediction 3: Correlation Between Efficacy and Price

To test the correlation between the log of price and QALY we run the following OLS regression:[20]

$$log(p)_i = \gamma_0 + \gamma_1 QALY_i + \gamma_2 US_i + \gamma_3 USQALY_i + \varepsilon_i \tag{18}$$

where US_i is a dummy variable which equals to 1 if the price is referred to an US brand name, $USQALY_i$ $(= US \cdot QALY_i)$ is an interaction term that tests for difference in correlation across the two countries, and ε_i is an *iid* zero-mean error term. The interpretation of this equation is straightforward. The value $(\gamma_1 + \gamma_2)$ measures the effect that quality has on drug price in US. At the same time, the parameter γ_2 tells us if there is a difference in the effect that quality has on drug prices between Italy and US.

To allow differential effects at different quality levels, we have split our drug sample into *low* and *high* quality drugs, using the median and the 75% percentile of the QSA distribution as thresholds.

Results are shown in table 6. In the regression using the whole sample, we have a positive relationship between quality and price for US $((\gamma_1 + \gamma_3) > 0)$, with US showing a stronger relationship than Italy ($\gamma_3 > 0$ and statistically significant). Similar results hold when we split the sample into *low* and *high* quality drugs, although some differences emerge depending on how we select the threshold to construct the subgroups. In particular, a positive relationship holds for *high* quality drugs in both US and Italy, with US characterized by a stronger relationship. A positive relationship seems to hold also for *low* quality drugs, but in this case there is no difference across the two countries. When we consider the 75% percentile the effect of quality on drug prices does not appear to be different across countries, while it remains positive and statistically significant. Overall, we conclude that in

[20] We use the natural logarithm as dependent variable to reduce the influence of outlier data points.

Italy, price level seems to be less responsive to quality than it is in the US. This is exactly what our model predicts.

5 Concluding Remarks

In this article we have developed a framework to evaluate the welfare effects of two different types of drug regulation—a minimum efficacy standard (MES) for marketed drugs and a price control (PC) scheme. Two main theoretical prediction stem from this model. First, the average drug quality delivered should be higher under the MES regime than in a regime that includes price controls. Second, PC regulation reduces the difference in prices between high and low quality drug. Despite its simplicity, the model's predictions are confirmed in US and Italian drug price and quality data. In particular, we find that *i)* there is more price variability in the US (where drug prices are not controlled) than in Italy; and *ii)* there is a tighter correlation between drug prices and quality in the U.S. than there is in Italy.

Figure 1: Densities plots of price distributions: TUFTS sample

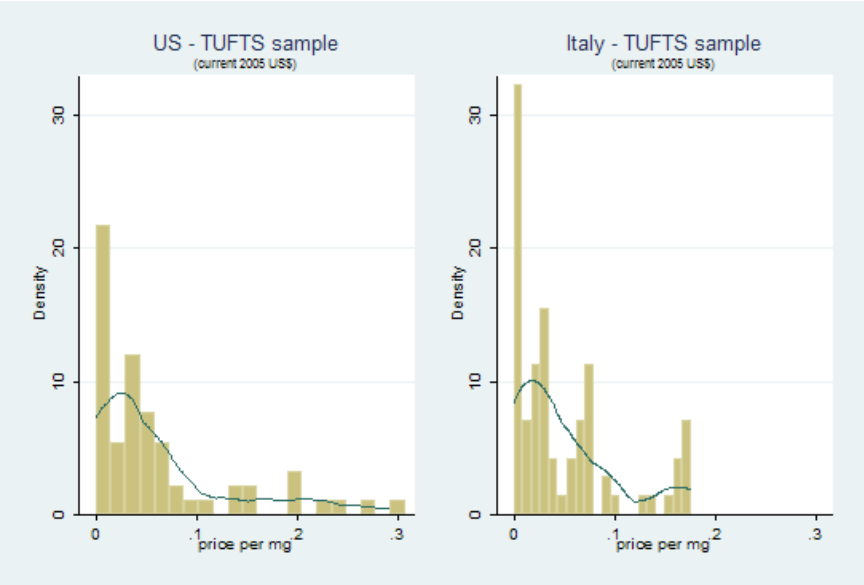


Figure 2: Densities plots of price distributions: MEPS-AIFA sample

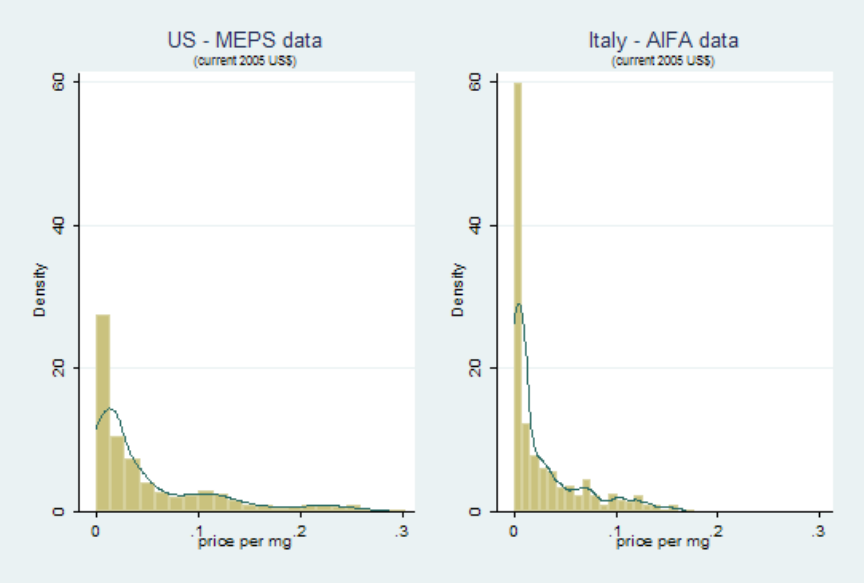


Table 5: Test for equality of price variances

	US	**Italy**	**US**	**Italy**	**Prediction 2**
	Tuft sample		MEPS & AIFA		
Observations	82	97	568	616	
Sample variance	170.39	25.61	0.0036	0.0013	
F test value	6.65		2.9		`corroborated`

For Tuft samples, the null hypothesis $\sigma^2_{US} = \sigma^2_{Italy}$ is rejected at significance level = 0.01

For MEPS & AIFA sample, the null hypothesis $\sigma^2_{US} = \sigma^2_{Italy}$ is accepted at significance level = 0.01

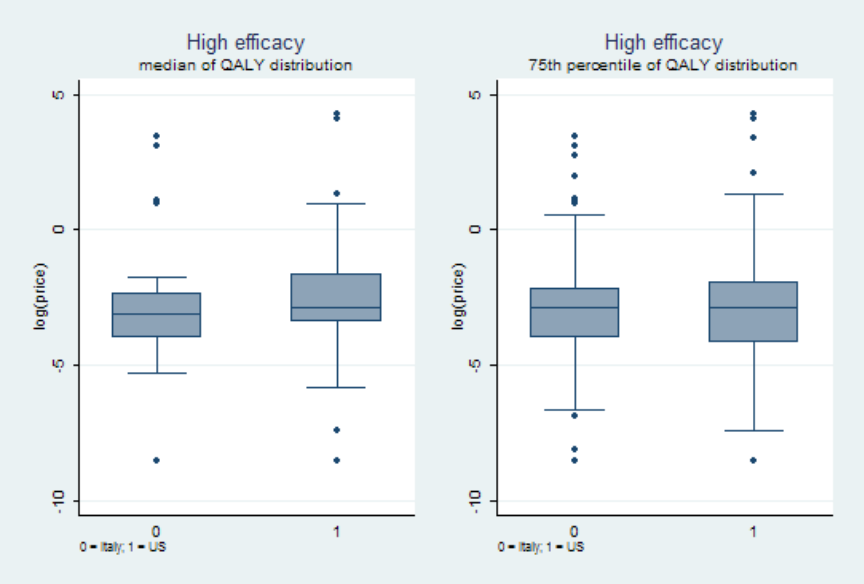
Our calculation based on AIFA and MEPS data

Table 6: Equation (18): estimates

Variable	**Parameter**			**Prediction 3**
Overall sample				
QALY	γ_1	-20.634*		
US	γ_2	-0.232		
USQALY	γ_3	27.878*		`corroborated`
	$(\gamma_1 + \gamma_3)$**	F(2,175) = 3.04	Prob > F =0.05	
Low efficacy				
		below the median	below the 75^{th} percentile	
QALY	γ_1	16799.292*	3318.400**	
US	γ_2	0.222	-0.295	
USQALY	γ_3	2188.264	708.913	`corroborated`
	$(\gamma_1 + \gamma_3)$***	F(2,128) =5.30	Prob > F =0.006	
High efficacy				
		over the median	over the 75^{th} percentile	
QALY	γ_1	-23.366**	-30.303**	
US	γ_2	-0.799	-0.024	
USQALY	γ_3	35.008**	24.739	`corroborated`
	$(\gamma_1 + \gamma_3)$	F(2,43) =2.22	Prob > F =0.1206	

*Our calculation based on AIFA and MEPS data. Legend: * p<0.1; ** p<0.05; *** p<0.01.*

Figure 3: Box-plot, log(price) over QALY



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A Appendix

A.1 Symbology

Table 7: Symbology

Symbol	Description
$\underline{e}$	*efficacy threshold*
e_i	*i-type drug efficacy*
Ω_i	*i-type producer feasibility set*
ζ	*innovative drug*
v_i	*willingness-to-pay for efficacy*
r	*R&D expenditure*
$\{p_i^{FB}, e_i^{FB}\}$	*first best price-efficacy pair*
$\{p_i^{SB}, e_i^{SB}\}$	*second best price-efficacy pair*
$\{\tilde{p}_i, \tilde{e}_i\}$	*price-efficacy pair under MES*
$\{\hat{p}_i, \hat{e}_i\}$	*price-efficacy pair under PCR*

A.2 Second best solution: erasing constraints

First best allocation implies efficient consumption and zero rent for the buyers: $v_i'(e_i) = c'(r_i)$ and $v_i(e_i) = p_i$ with $i = L, H$. However, under incomplete information, this outcome is not incentive compatible because the H-type enjoys a positive rent by choosing the pair $\{e_L, p_L\}$ rather than her own first best allocation. Hence the H-type buyer mimics L-type in order to realize a positive surplus. By doing so she gets:

$$v_H(e_L) - p_L = v_L(e_L) - p_L + \underbrace{[v_H(e_L) - v_L(e_L)]}_{>0}$$

This implies that, even though the principal delivers a e_L to the L-type such as $v_L(e_L) - p_L = 0$, H-type buyer will continue to benefit from an *information rent*.

At the opposite, L-type buyer will not find convenient to consume higher efficacy drug. Hence we can omit *incentive compatibility constraint* for L-type buyer.

$$v_H(e_H) - p_H \geq v_H(e_L) - p_L \geq v_L(e_L) - p_L \geq 0 \tag{19}$$

A.3 Proof of proposition 5

Second best solution for p_H^{SB} implies:

$$p_H^{SB} = v_H(e_H) - \left[v_H(e_L) - v_L(e_L)\right]$$

Regulated price under MES regime for H-type is given by:

$$\tilde{p}_H = v_H(e_H) - \left[v_H(\underline{e}) - v_L(\underline{e})\right]$$

Given that MES regulation does not affect the efficacy level delivered to the H-type buyers and that the efficacy delivered to the L-type buyer is at least $\underline{e}$, $\tilde{p}_H < p_H^{SB}$ requires that

$$\left[v_H(\underline{e}) - v_L(\underline{e})\right] > \left[v_H(e_L) - v_L(e_L)\right] \Rightarrow v_H(\underline{e}) - v_H(e_L) > v_L(\underline{e}) - v_L(e_L)$$

which is always true given assumption 2. ■