NBER WORKING PAPER SERIES

PHARMACEUTICAL INDUSTRY, DRUG QUALITY AND REGULATION: EVIDENCE FROM US AND ITALY

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Working Paper 14567
http://www.nber.org/papers/w14567

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
December 2008

Bhattacharya thanks the National Institute on Aging for partial funding of this work. The views expressed herein are those of the author(s) and do not necessarily reflect the views of the National Bureau of Economic Research.

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NBER Working Paper No. 14567
December 2008, Revised September 2011
JEL No. I1,L51,L65

ABSTRACT

This paper examines 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 a mix of minimum efficacy standards and price control mechanisms (MES+PC). Through a simple model of adverse selection we model the interaction between firms, heterogeneous buyers and the regulator. The theoretical analysis provides two results. First, an MES regime provides greater incentives to produce high quality drugs. Second, an MES+PC mix reduces the difference in price between the highest and lowest quality drugs on the market. The empirical analysis based on US and Italian 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 [10]). 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)* a MES regime combined with a drug price controls (MES+PC). The first regime models the regulatory structure of the pharmaceutical market in the US, 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) it represents the first unified model of drug regulation, drug prices, and drug quality applicable to multiple countries, and (ii) we develop a novel method for measuring drug quality starting from a database of randomized clinical 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 US 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 an incomplete information setting, we derive the properties of the equilibria under the MES and MES+PC regulatory regimes (section 3.1). 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.

[1] Pharmaceutical expenditures represent a substantial component of total health expenditures in all OECD countries (close to 17% in 2007 as OECD average).

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 Medicines Agency (EMEA), in the EU, or by the Food and Drug Administration (FDA), in the US. As such, new drug development is a process that needs time and considerable resources. Country specific differences aside, both the EMEA and the FDA 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 portfolio 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 [14]).

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 [8]

[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 [4])

3 The Model

In this section we develop a simple theoretical framework of the optimal pricing policy of pharmaceutical firms under assumptions of imperfect information about buyers' preferences.

Consider 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 private information and defined only on by efficacy of the drug purchased. The source of heterogeneity stems from the differing *willingness-to-pay* for efficacy.[5]

The main assumptions of the 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*

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

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. Within a monopolistically competitive pharmaceutical market, profit-maximizing firms produce and sell to $N = N_L + N_H$ insurers/providers who differ in their* willingness-to-pay *for efficacy.*[6]

Assumption 4. *Information. The seller does not know buyers' characteristics and she can not discriminate, while buyers perfectly know the efficacy of the drugs sold.*

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

$$\max_{\{p,e\}} \Pi = N_L \cdot \big[p_L - c(e_L)\big] + N_H \cdot \big[p_H - c(e_H)\big] \tag{1}$$

s.t.

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

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 (2) represents the *participation constraints* for types L and H.[7]

[5] In our analysis 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).

[7] 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 (2) would hold as equalities. This solution entails socially optimal efficacy levels that equate the marginal benefit with the marginal cost of efficacy:

$$v'_L(e_L) = c'(e_L) \tag{3}$$

$$v'_H(e_H) = c'(e_H) \tag{4}$$

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*:

$$v_H(e_H) - p_H \geq v_H(e_L) - p_L \tag{5}$$

$$v_L(e_L) - p_L \geq v_L(e_H) - p_H \tag{6}$$

Equations (1-6) represents a *standard adverse selection problem* (see Bolton and Dewatripont [2], Laffont and Tirole [9]). It is easy to show that only L-type *participation constraint* and H-type *incentive compatibility* are binding (see appendix 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

$$v_H(e_H) - p_H = v_H(e_L) - p_L \tag{7}$$

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

Proposition 1. *Solutions for problem (7) entails a* separating equilibrium *where:*

- $p_H^{SB} = v_H(e_H) - \big[v_H(e_L) - v_L(e_L)\big]$*;*
- $p_L^{SB} = v_L(e_L) \Rightarrow$ 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)*

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

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

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

Proof*: see appendix A.3.*

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

3.1 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 [1], 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.

3.1.1 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 US. 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 (4) 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:

$$e_i \geq \underline{e} \qquad for\ i = L, H \tag{8}$$

In the *regulated problem*, the seller maximizes her objective function (eq.1) under the two *participation constraints* (eq.2), the two *incentive compatibility constraints* (eq.6-5) and the two *efficiency constraint* (eq.8).

Proposition 2. *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;*
- $\tilde{p}_L > p_L^{SB}$*;*
- $\tilde{p}_H < p_H^{SB}$ *where and* $\{\tilde{p}_i, \tilde{e}_i\}$ *is the price-efficacy pair delivered to the market under MES regime.*

Proof*: see appendix A.4.*

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

$$\mathcal{W} = \sum_{i=L}^{H} N_i \big[v_i(e_i) - c(r_i)\big] \tag{9}$$

$$\left.\frac{d\mathcal{W}}{d\underline{e}}\right|_{\underline{e}=e_L^{SB}} = \sum_{i=L}^{H} N_i \big[v_i'(e_i) - c'(r_i)\big] \cdot \frac{de}{d\underline{e}} \tag{10}$$

By the last two points of proposition 1 we know that $dv_H(e_H)/d\underline{e} = 0$ and that $dv_L(e_L)/d\underline{e} > 0$. Hence equation (10) 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 [1], 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 $i = H$.

3.1.2 Regulatory mix: MES plus PC

The combination of price-control schemes and quality requirements are very common in pharmaceutical markets. With respect to the former, different mechanisms 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.[8] 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.

For the sake of simplicity, here 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:

$$p_L^{SB} < \hat{p} < p_H^{SB}$$

This implies that, under the MES+PC mandate, pharmaceutical firm solve (7) taking into account the following further constraints: $e_i \geq \underline{e}$ for, $i = L, H$, and $\hat{p} < p_H^{SB}$.

Proposition 3. *The solution for the profit maximimazation problem under MES + PC regulation is characterized as follows:*

- $v_L'(\hat{e}_L) = c'(\hat{e}_L) + \big[\frac{N_H - \mu}{N_L}\big] \cdot \big[v_H'(\hat{e}_L) - v_L'(\hat{e}_L)\big]$;
- $v_H'(\hat{e}_H) = c'(\hat{e}_H)\big[N_H(N_H - \lambda)^{-1}\big]$
- $\hat{p} = v_H(\hat{e}_H) - \big[v_H(\hat{e}_L) - v_L(\hat{e}_L)\big]$

where λ is the Lagrangian multiplier for the constraint $\hat{p} < \tilde{p}_H$ and $\{\hat{p}_i, \hat{e}_i\}$ is the price-efficacy pair delivered to the market under the regulatory mix MES+PC. ***Proof****: see appendix A.5*

Proposition 3 shows that the regulatory mix implies a quality deterioration fot the H-type buyers given that the following relation holds:

$$\hat{e}_H < \tilde{e}_H = e_H^{SB}$$

Hence, MES+PC implies that H-type buyers receive less efficacy then they received in the unregulated case while it induces an improvement of the efficacy delivered to L-type buyers.

[8] 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 [12]).

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

$$\left.\frac{d\mathcal{W}}{d\hat{p}}\right|_{\hat{p}=p_H^{SB}} = \sum_{i=L}^{H} N_i \left[v_i'(e_i) - c'(e_i)\right] \cdot \frac{de_i}{d\hat{p}} \tag{11}$$

From proposition 1 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 11 depends on the distance between $\hat{p}$ and p_H^{SB} and on the sizes of the two group of buyers.[9]

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 effects that the two regimes will produce on drug price and quality (efficacy).

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

	MES	**MES+PC**
Efficacy provided	$\tilde{e}_H = e_H^{SB}$	$\hat{e}_H < \tilde{e}_H$
	$\tilde{e}_L > e_L^{SB}$	$\hat{e}_L > \tilde{e}_L$
Price charged	$\tilde{p}_H < p_H^{SB}$	$\tilde{p}_H > \hat{p} > \tilde{p}_L$
	$\tilde{p}_L > p_L^{SB}$	$\hat{p} = v_H(\hat{e}_H) - \left[v_H(\hat{e}_L) - v_L(\hat{e}_L)\right] > \tilde{p}_L$

From an empirical perspective, three main testable predictions emerge from the theoretical model.

Testable prediction 1. *`High-quality availability`. Only under a MES scheme, the highest quality drugs are delivered to the market.*

Indeed, the theoretical analysis shows that under MES regime, firms have the incentive to produce the highest level of quality and deliver to the H-type buyers the same efficacy lavel obtained at the second best ($\tilde{e}_H = e_H^{SB}$).

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

If we use the difference $(p_H - p_L)$ as a measure of price dispersion, from proposition 3 clearly emerges that

$$(\tilde{p}_H - \tilde{p}_L) > (\hat{p}_H - \hat{p}_L)$$

because $\hat{p}_H < \tilde{p}_H$ and $\hat{p}_L > \tilde{p}_L$.

[9] Vernon [18] describes two potential channels through which a PC 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 PC may also affect R&D through a cash-flow effect.

Testable prediction 3. *Correlation between price and quality. If only a MES scheme is implemented, a higher correlation between price and efficacy is expected for low efficacy drugs. Moreover, if*

$$(\tilde{p}_H - \hat{p}) > (\tilde{e}_H - \hat{e}_H)$$

then MES scheme provides also a higher correlation for the high efficacy drugs compared to MES+PC.

In order to clarify prediction 3 it is worth notice that moving from MES to MES+PC implies a quality improvement for the L-type buyers ($\hat{e}_L - \tilde{e}_L > 0$) but does not generate any effect on the price charged ($\hat{p}_L = \tilde{p}_L$). This result leads to conclude that under MES regime the price's responsiveness of low efficacy drugs is lower than under the regulatory mix. To demonstrate the validity of the second statement provided in prediction 3 it is enough to show that - under the assumption that passing from MES to MES+PC entails a quality deterioration for the high efficacy drugs that is lower than the price reduction ($\tilde{p}_H/\hat{p} > \tilde{e}_H/\hat{e}_H$) - the price's responsiveness of high efficacy drugs realized is higher than under regulatory mix.

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 in US prices are completly free to fluctuate. On the contrary, in Italy several forms of price regulation apply.[10]

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 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 [5]). Mitchell [13] 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.[11]

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).

[10] For the time period to which this study refers, in Italy 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. 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 [8]).

[11] 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 [13]).

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.[12] 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.[13] When the cost-effectiveness ratio is lower, the more QALYs can be accrued per dollar spent: treatments with low levels of `$/QALY` are preferred. According to the Tufts terminology, interventions that reduce cost and simultaneously improve health are defined *cost-saving*. At the opposite poorly performing interventions, that raise costs while improving poorly health status, are defined *dominated*. Therefore, we have obtained a plausible quality indicator (QI hereafter) by simply inverting the `$/QALY` measure. Furthermore, we have assigned the value zero to all *dominated* drugs, while the maximum value in the class has been given to the drugs defined as *cost-saving*.

For different diseases the 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. $/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*.

Our final sample originated contains 500 observations, of which 310 belonging to the Italian market (98 brand names) and 190 to the US market (83 brand names). For each brand name we have then merged in the Italian and US drug prices.[14] 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.[15] We obtained 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

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

[13] See McGregor [11] for a consideration of the strengths and methodological shortcomings of this measure.

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

[15] `www.merck.com/mmhe/index.html`.

in current 2005 US$ per mg.[16] 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
QI	quality indicator	Our calculation on $/QALY provided by 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 QI, 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.

[16]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	$/QALY	US
1	Cardiovascular	aspirin	0.0006	11,000	1
2	Cardiovascular	aspirin & clopidogrel	0.0006	32,000	1
3	Cardiovascular	lovenox	1.7783	3,900	1
...	...	...	...	...	
15	Infectious	adamantane antivirals	0.0149	12	1
16	Infectious	methadone	0.0181	97,000	1
17	Infectious	pneumovax23	73.1000	21,000	1
...	...	...	...	...	
31	Endocrine Disorders	pravachol	0.1357	58,000	1
...	...	...	...	...	
57	Malignant Neoplams	femara	3.8111	8,700	1
58	Malignant Neoplams	tamoxifen	0.1606	32,000	1
...	...	...	...	...	
67	Mus&Rheumatologic	arava	0.6886	0	1
68	Mus&Rheumatologic	fosamax	0.3109	700000	1
...	...	...	...	...	
70	Neuro-Psychiatric	reminyl	0.3779	0	1
71	Neuro-Psychiatric	topamax	0.0640	56,000	1
...	...	...	...	...	
...	...	...	...	...	
...	...	...	...	...	
80	Cardiovascular	aspirina	0.0008	11,000	0
81	Cardiovascular	aspirina and iscover	0.0367	32,000	0
96	Infectious	mantadan	0.0035	12	0
97	Infectious	metadone cloridato	0.0359	97,000	0
...	...	.....			
123	Malignant Neoplams	arimidex	5.6246	14,000	0
124	Malignant Neoplams	femara	2.3423	8,700	0
...	...	...	...		
152	Mus&Rheumatologic	arava	0.5224	0	0
153	Mus&Rheumatologic	fosamax	0.1366	700000	0
...	...	...	...	...	
179	Neuro-Psychiatric	aricept	0.5386	0	0
180	Neuro-Psychiatric	betaferon	445.6173	94,000	0
181	Neuro-Psychiatric	comtan	0.0058	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
$\$/QALY$	181	66157.73	98334.18	0	700,000
QI	181	0.014	0.031	1.43E-06	0.09
$Generics$	181	0.213	0.409	0	1

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.[17] 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.[18] 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 than 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 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 compared to Italy: 3.17 versus 1.30, 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 QI we run the following OLS regression:[19]

$$log(p_i) = \gamma_0 + \gamma_1 QI_i + \gamma_2 US_i + \gamma_3 USQI_i + \varepsilon_i \tag{12}$$

where US_i is a dummy variable which equals to 1 if the price is referred to an US brand name, $USQI_i$ $(= US \cdot QI_i)$ is an interaction term that tests for difference in correlation across the two countries, and ε_i is an *iid* zero-mean error term. $USQI$ works as a sort of dummy 'treatment'variable

The interpretation of equation 12 is straightforward. The value $(\gamma_1 + \gamma_3)$ measures the effect that quality has on drug price in US. At the same time, the parameter γ_3 tells us if there is a difference in the effect that quality has on drug prices between Italy and US.

The effect of the regulation on the price-quality nexus is not identified without further restrictions. To allow differential effects at different quality levels, we have split our drug sample into *low* and *high* quality drugs, using as a threshold the median and the 75% percentile of the QI distribution.

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

[18] 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.

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

Results are shown in table 6. In the regression using the whole sample, a positive relationship between quality and price emerges for US ($(\gamma_1+\gamma_3) > 0$ and statistically significant), with US showing a stronger relationship than Italy ($\gamma_3 > 0$ and significant at 0.05).

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, quality exerts a positive and statistically significant impact on price for *low* quality drugs, with $(\gamma_1 + \gamma_3) > 0$ statistically significant for both thresholds. Along the same line, concerning *high* quality drugs, a positive and statistically significant relationship has been found in both countries, with US characterized by a stronger correlation ($\gamma_3 > 0$ and statistically significant), but only for the threshold at the median. Overall, we can conclude that in Italy price level seems to be less responsive to quality than it is in the US. This is exactly what our model predicts.

As robustness check, we have further controlled our estimates for the presence of *generic* versus *branded* drugs in the two markets and how this may affet price distributions. We have then added to equation (12) a new dummy variable labeled $GENERICS$ that captures whether the drug is generic or branded. Equation (12) then becomes:

$$log(p)_i = \gamma_0 + \gamma_1 QI_i + \gamma_2 US_i + \gamma_3 USQI_i + \gamma_4 GENERICS + \varepsilon_i \tag{13}$$

Looking at table 7, we can observe that the $GENERICS$ dummy displays, as expected, a negative sign that is always statistically significant. More important, the introduction of this dummy does not change the results of our estimates, thus confirming the good predictive power of our theoretical model.

5 Concluding Remarks

In this article we have developed a framework to evaluate the welfare effects of two different types of drug regulation: minimum efficacy standard (MES) and a mix of minimum efficacy standard and price control scheme (MES+PS). 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, MES+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. 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 US than there is in Italy.

Our results have implications for the proper regulation of pharmaceutical markets. Price controls deliver a mix of costs and benefits. On the benefit side of the ledger (apart from lower prices, which, all else equal, benefits patients) is a lower variance for any given set of drugs in the price of drugs. Most people favor social welfare functions that place a positive value on reducing the financial uncertainty associated with getting sick. Price controls deliver such reduced uncertainty by decreasing the variance in the price of drugs. On the cost side of the ledger, price controls reduce the availability of the highest quality drugs. Additionally, they limit the close link between drug quality and price that is present in a market without price controls. To the extent that developing high quality drugs is more expensive than developing lower quality drugs, this reduced correlation further undercuts the incentives that pharmaceutical companies face to produce high quality drugs. While some aspects of the debate over price controls discussed in this paragraph are well known, an important contribution

of this paper is to highlight the reduction in the variance of drug prices and the reduction in the correlation between price and quality of drugs caused by price controls. How policy makers and the population at large should value these costs and benefits is of course beyond our scope here.

Figure 1: Densities plots of price distributions: TUFTS sample

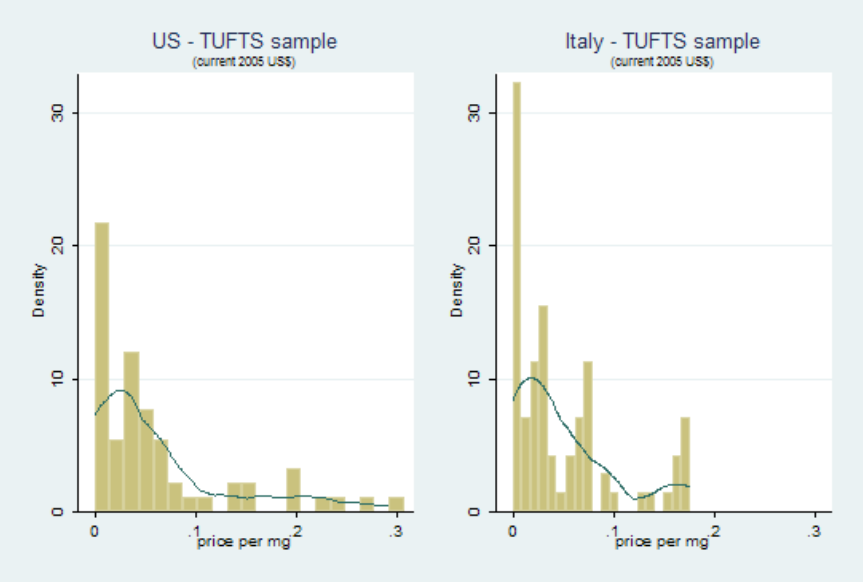


Figure 2: Densities plots of price distributions: MEPS-AIFA sample

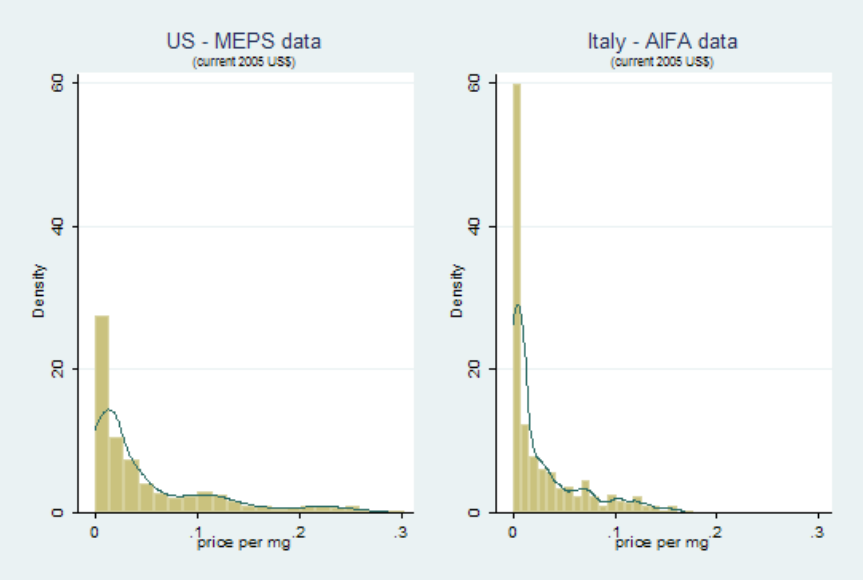


Table 5: Test for equality of price variances

	US	**Italy**	**US**	**Italy**	**Prediction 2**
	Tuft sample		MEPS & AIFA		
Observations	84	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 rejected at significance level = 0.01

Our calculation based on AIFA and MEPS data

Table 6: Results from emprical analysis

Variable	**Parameter**			**Prediction 3**
Overall sample				
QI	γ_1	-20.634*		
US	γ_2	-0.232		
USQI	γ_3	27.878*		
	$(\gamma_1 + \gamma_3)$	F(2,175) = 3.04		`corroborated`
		Prob > F =0.05		
Low efficacy				
		below the median	below the 75^{th} percentile	
QI	γ_1	16800.05**	3318.029**	
US	γ_2	0.579	0.423	
USQI	γ_3	7510.355	442.628	
	$(\gamma_1 + \gamma_3)$	F(2,80) =4.43	F(2,121) =6.24	`partially`
		Prob > F =0.014	Prob > F = 0.003	`corroborated`
High efficacy				
		over the median	over the 75^{th} percentile	
QI	γ_1	-23.366**	-30.303**	
US	γ_2	-0.034	0.017	
USQI	γ_3	23.44**	23.370	
	$(\gamma_1 + \gamma_3)$	F(2,86) = 2.59	F(2,43) =2.37	
		Prob > F = 0.08	Prob > F =0.10	`corroborated`

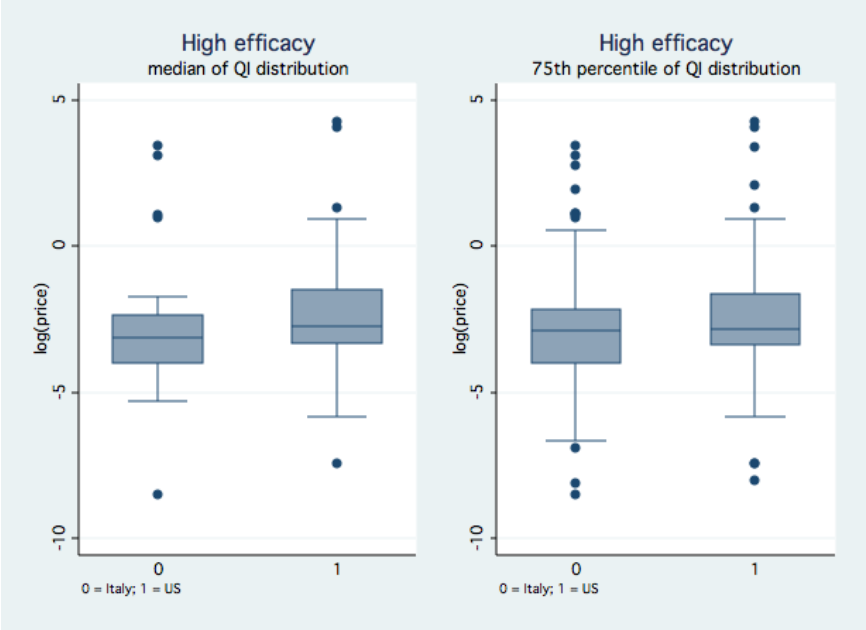
*Our calculation based on AIFA and MEPS data. Legend: * p<0.1; ** p<0.05; *** p<0.01.*

Table 7: Robustness check

Variable	**Parameter**			**Prediction 3**
Overall sample				
QI	γ_1	-13.527		
US	γ_2	-0.041		
USQI	γ_3	22.125*		
GENERICS	γ_4	-2.869***		
	$(\gamma_1 + \gamma_3)$	F(2,169) = 2.36		corroborated
		Prob > F =0.09		
Low efficacy				
		below the median	below the 75^{th} percentile	
QI	γ_1	9883.294	3318.400**	
US	γ_2	0.121	-0.295	
USQI	γ_3	13289.14	708.913	
GENERICS	γ_4	-2.044***	-2.703***	
	$(\gamma_1 + \gamma_3)$	F(2,79) =3.13	F(2,120) =4.89	partially
		Prob > F =0.05	Prob > F = 0.01	corroborated
High efficacy				
		over the median	over the 75^{th} percentile	
QI	γ_1	-12.816	-31.275**	
US	γ_2	-0.010	-0.910	
USQI	γ_3	22.518*	32.163*	
GENERICS	γ_4	-3.280***	-3.121***	
	$(\gamma_1 + \gamma_3)$	F(2,85) = 1.49	F(2,44) =3.44	
		Prob > F = 0.23	Prob > F =0.04	corroborated

*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 QI



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A Appendix

A.1 Symbology

Table 8: 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 MES+PC*

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.

$$v_H(e_H) - p_H \geq v_H(e_L) - p_L \geq v_L(e_L) - p_L \geq 0 \tag{14}$$

A.3 Proof of proposition 1

Constraints (7) provide:

- $p_L = v_L(e_L) = p_L^{FB}$
- $p_H = v_H(e_H) - \underbrace{[v_H(e_L) - v_L(e_L)]}_{<0} < p_H^{FB}$

Plugging p_L and p_H into the profit function yields:

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

FOCs:

- $\partial\Pi/\partial e_L = 0 \Rightarrow v'_L(e_L) = c'(e_L) + \frac{N_H}{N_L} \cdot \underbrace{\left[v'_H(e_L) - v'_L(e_L)\right]}_{>0}$

- $\partial\Pi/\partial e_H = 0 \Rightarrow v'_H(e_H) = c'(e_H)$ ■

A.4 Proof of proposition 2

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. ■

A.5 Proof of proposition 3

Under MES+PC regulation, firm solves the following program:

$$\begin{aligned} &\max_{\{p,e\}} \Pi = N_L \cdot \left[p_L - c(e_L)\right] + N_H \cdot \left[p_H - c(e_H)\right] \\ &\text{s.t.} \\ &\qquad v_L(e_L) - p_L = 0 \\ &v_H(e_H) - p_H = v_H(e_L) - p_L \\ &\qquad \hat{p} < p_H \\ &\qquad e_i \geq \underline{e} \end{aligned}$$

Necessary and sufficient conditions for this problem require that

$N_L[v'_L(\hat{e}_L) - c'_L(\hat{e}_L)] + N_H[v'_L(\hat{e}_L) - v'_H(\hat{e}_L)] - \lambda v'_H(\hat{e}_L) = 0$

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

$N_H\left[v'_H(\hat{e}_H) - c'_H(\hat{e}_H)\right] - \lambda v'_H(\hat{e}_H) \Rightarrow v'_H(\hat{e}_H) = c'(\hat{e}_H)\left[N_H(N_H - \lambda)^{-1}\right]$

$\hat{p} - p_H = 0 \Rightarrow \hat{p} = v_H(\hat{e}_H) - \left[v_H(\hat{e}_L) - v_L(\hat{e}_L)\right]$ ■