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THREE ESSAYS ON HEALTH ECONOMICS

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To Vì, Nichi & Gattogiallo

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Abstract

The present doctoral thesis is based on three different essays on health economics. Even though the topics differ across the three chapters, they share two main features: *i)* they are all based on micro analyses and *ii)* they all aim to explain some specific aspects of the pharmaceutical market. In particular, the first two chapters shed light on the nexus between regulation and drug Innovation, while the third presents an econometric analysis of the demand of production factors in the Italian pharmaceutical industry. It is worth noticing that the first and the third chapter both present an empirical analysis based on novel and *ad hoc* datasets.

The first chapter *Pharmaceutical industry, drug quality and regulation. Evidence from US and Italy*, co-authored by Vincenzo Atella and Jay Bhattacharya, studies the interactions existing between pharmaceutical companies and regulators and how these interactions affect the quality (i.e. *ex post* efficacy) of the drug delivered to the market. This contribution is the first attempt, to our knowledge, to provide an empirical assessment of the nexus between regulation and the pairs price, efficacy realized in drug market. In particular, the goal is to analyze the effects on drug price and drug quality of the two most common regulatory regimes in the pharmaceutical market: Minimum Efficacy Standards (MES) and Price Controls (PC). Following Besanko, Donnenfeld, and White [5], we develop a very simple 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 regimes. Second, PC regulation reduces the difference in terms of high-low quality drug prices. The empirical analysis has been conducted on a common sample of drugs available both in Italy and in US. Drug quality has been measured using data from *Tufts - New England Medical Center - Cost Effectiveness Analysis Registry* that allows to compare cost-effectiveness of a broad range of interventions (among which drugs are the most studied) using standardized cost-utility ratios. Despite its simplicity, the theoretical model produces testable predictions that are corroborated by the empirical analysis.

The chapter *Information and regulation in drug market* explores the trade-off faced by the pharmaceutical firms whether to innovate or not and the related problem of designing a regulatory framework that provides incentives for firms to produce breakthrough drug rather than incremental modifications to the existing pharmaceutical product lines (the so-called me-too drugs). We consider the interaction between the innovative firm and the regulator when the innovative process is assumed to be stochastic. The relationship between the regulated price and the efficacy of the entrant drug is established through a bargaining approach. The model suggests that regulators should apply a value-based approach to pricing in order to relate the price to the incremental therapeutic benefit delivered to patients. In light of this purpose, the regulator should use her bargaining power to penalize the production of *me-too* drugs and incentivate firm's innovative effort acknowledging higher prices to more effective drug.

Finally, the third chapter *How variable is labor input in the Italian manufacturing: the case of the pharmaceutical industry* analyzes the labor demand in the Italian manufacturing, using firm-level data on pharmaceutical industry. The Italian pharmaceutical industry is characterized by the existence of long-term labor contracts, and this fact suggests to consider labor as quasi-fixed input. In order to characterize firms' behavior we base our analysis on the restricted Generalized Leontief cost function. The choice of this flexible functional form is due to its ability to capture the input substitution patterns in presence of more than one quasi-fixed input. Therefore demand and substitution elasticities are estimated with respect to two different theoretical models: the first, QFI(1), with capital as quasi-fixed input and the second, QFI(2), with two quasi-fixed inputs, capital and labor. The choice among the two alternative specifications is based on an elasticity comparison criterion, since the two models are not nested. Our results confirm the a priori on the labor market rigidity and point out the high heterogeneity between the firms, even controlling for size and nationality.

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Rome, Lorenzo Carbonari
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Chapter 1

Pharmaceutical industry, drug quality and regulation. Evidence from US and Italy

1.1 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

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

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 (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 (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 1.2 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 1.3 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 1.3.1, 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 1.3.2) and derive the properties of the equilibria under the MES and PC regulatory regimes (section 1.3.3). In section 1.4 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 1.5 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.

1.2 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 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].

[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 [48]

[4] Such price incentives for one or two preferred products within a group of therapeutic substitutes have increased

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.

1.3 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]

1.3.1 The Complete Information Baseline Model

The main assumptions of the baseline model are the following.

Assumption 1.3.1. *`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 1.3.2. *`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*

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

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])

[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.

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 1.3.3. *`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:*

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

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

Assumption 1.3.4. *`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:

$$\max_{\{p\}} \Pi = \sum_{i=L}^{H} N_i \cdot \big\{p - c[e(r)]\big\} \tag{1.3.1}$$

s.t.

$$v_i[e(r)] - p \geq 0 \qquad for\ i = L, H \tag{1.3.2}$$

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 (1.3.2) 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 1.3.1. *$v_L[e(r)] < v_H[e(r)] < p(r)$. Insurers/providers will not buy the drug and the firm will stop its production, eventually leaving the market. This is the trivial case.*

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

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

Proposition 1.3.2. *$v_L[e(r)] < p(r) < v_H[e(r)]$. 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:*

$$\Pi = N_H \cdot \Big\{ v_H\big[e(r)\big] - c[e(r)] \Big\} \tag{1.3.3}$$

By differentiating equation (1.3.3) with respect to R&D we simply derive the impact of an increasing level of research on profit at the margin:

$$\frac{d\Pi}{dr} \geq 0 \Leftrightarrow \frac{dv_H[e(r)]}{de} \cdot \frac{de}{dr} \geq \frac{dc(\cdot)}{dr}\bigg|_{e \geq \underline{e}} \tag{1.3.4}$$

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 (1.3.4) 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 1.3.3. *$p(r) < v_L[e(r)] < v_H[e(r)]$. 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:*

$$\Pi = \big(N_L + N_H\big) \cdot \Big\{ v_L\big[e(r)\big] - c[e(r)] \Big\} \tag{1.3.5}$$

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

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

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 $\frac{e(r)}{p}$.

1.3.2 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 (1.3.1). Assumption (1.3.4) must, instead, be reformulated.

Assumption 1.3.5. *`Information (II)`. The seller does not know buyers' characteristics and she can not discriminate, while buyers perfectly know the efficacy of the drugs sold.*

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:

$$\max_{\{p,e\}} \Pi = N_L \cdot \big[p_L - c(e_L)\big] + N_H \cdot \big[p_H - c(e_H)\big] \tag{1.3.6}$$

s.t.

$$v_i(e) - p_i \geq 0 \qquad for\ i = L, H \tag{1.3.7}$$

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 (1.3.7) represents the *participation constraints* for types L and H.[8]

If the seller could perfectly discriminate, she would extract the entire surplus from each group of buyers, and the constraints (1.3.7) would hold as equalities. This solution entails socially optimal efficacy levels that equate the marginal benefit with the marginal cost of efficacy:

$$v'_L(e_L) = c'(e_L) \tag{1.3.8}$$

$$v'_H(e_H) = c'(e_H) \tag{1.3.9}$$

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*:

$$v_H(e_H) - p_H \geq v_H(e_L) - p_L \tag{1.3.10}$$

$$v_L(e_L) - p_L \geq v_L(e_H) - p_H \tag{1.3.11}$$

Equations (1.3.6-1.3.11) represents a *standard adverse selection problem* (see Bolton and Dewatripont [6], Laffont and Tirole [51]). It is easy to show that only L-type *participation constraint* and H-type *incentive compatibility* are binding (see 1.6.2). 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

$$v_H(e_H) - p_H = v_H(e_L) - p_L \tag{1.3.12}$$

[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.

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

Proposition 1.3.4. *Solutions for problem (1.3.12) entails a* separating equilibrium *where:*

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

1.3.3 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.

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 (1.3.1)-(1.3.3) and (1.3.5) 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:

$$e_i \geq \underline{e} \qquad for\ i = L, H \tag{1.3.13}$$

In the *regulated problem*, the seller maximizes her objective function (eq.1.3.6) under the two *participation constraints* (eq.1.3.7), the two *incentive compatibility constraints* (eq.1.3.11-1.3.10) and the two *efficiency constraint* (eq.1.3.13).

Proposition 1.3.5. *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 1.6.3.*

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

$$\mathcal{W} = \sum_{i=L}^{H} N_i \big[v_i(e_i) - c(r_i) \big] \tag{1.3.14}$$

$$\left. \frac{d\mathcal{W}}{d\underline{e}} \right|_{\underline{e}=e_L^{SB}} = \sum_{i=L}^{H} N_i \big[v_i'(e_i) - c'(r_i) \big] \cdot \frac{de}{d\underline{e}} \tag{1.3.15}$$

By the last two points of proposition 1.3.4 we know that $dv_H(e_H)/d\underline{e} = 0$ and that $dv_L(e_L)/d\underline{e} > 0$. Hence equation (1.3.15) 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 $i = H$.

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:

$$\max_{\{p,e\}} \Pi = N_L \cdot \big[p_L - c(e_L) \big] + N_H \cdot \big[p_H - c(e_H) \big] \tag{1.3.16}$$

[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 [53]).

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 1.3.6. *The solution for the problem (1.3.16) under price-ceiling is characterized as follows:*

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

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:

$$\left.\frac{d\mathcal{W}}{d\hat{p}}\right|_{\hat{p}=p_H^{SB}} = \sum_{i=L}^{H} N_i \left[v'_i(e_i) - c'(e_i)\right] \cdot \frac{de_i}{d\hat{p}} \tag{1.3.17}$$

From proposition 1.3.4 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 1.3.17 depends on the distance between $\hat{p}$ and p_H^{SB} and on the sizes of the two group of buyers.[10]

1.4 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 1.1 summarizes the results obtained from our theoretical model and compares the

[10] Vernon [34] 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.

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.

Table 1.1: 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 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 (PC) the entire market receives (on average) less effective medicines.*

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 PC 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

[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 [48]).

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 [42]). Mitchell [54] 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).

1.4.1 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

[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 [54]).

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

of an innovation in treatment.[14] When the 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 illness during the influenza season` [cohort]

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

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 in-`
  `fection (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

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

representative dataset of Americans.[16] 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 in current 2005 US$ per mg.[17] Table 1.2 provides the variables list, with the relative description and source, used in our empirical analysis.

Table 1.2: 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 1.3 and whose summary statistics are reported in table 1.4.

[16] `www.merck.com/mmhe/index.html`.
[17] The exchange rate used are from the Federal Reserve Bank of St. Louis.

Table 1.3: 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.*

1.4.2 Empirical Results

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

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

Table 1.4: 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

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 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 2.2 and figures 1.1 and 1.2). 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.

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]

$$log(p)_i = \gamma_0 + \gamma_1 QALY_i + \gamma_2 US_i + \gamma_3 USQALY_i + \varepsilon_i \tag{1.4.1}$$

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

[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.

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

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.

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

1.5 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 1.1: Densities plots of price distributions: TUFTS sample

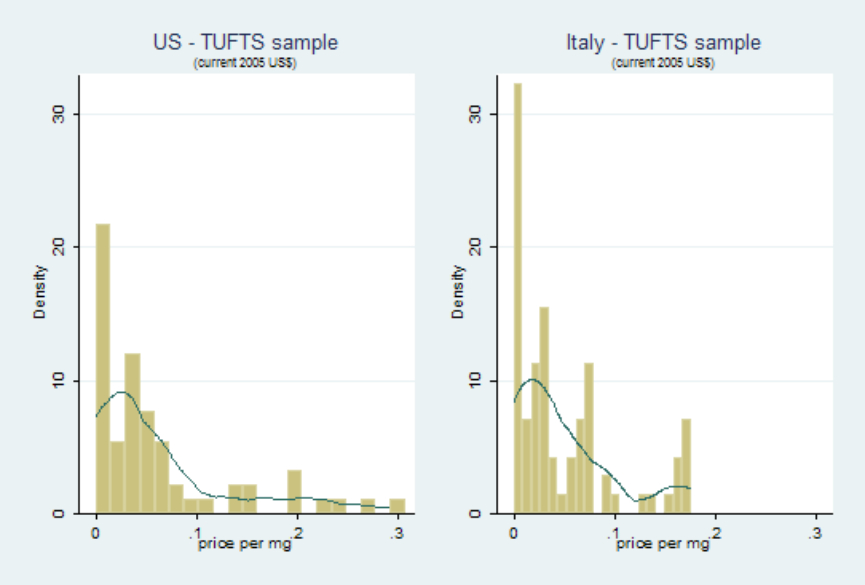


Table 1.5: Test for equality of price variances

	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 rejected at significance level = 0.01

Our calculation based on AIFA and MEPS data

Figure 1.2: Densities plots of price distributions: MEPS-AIFA sample

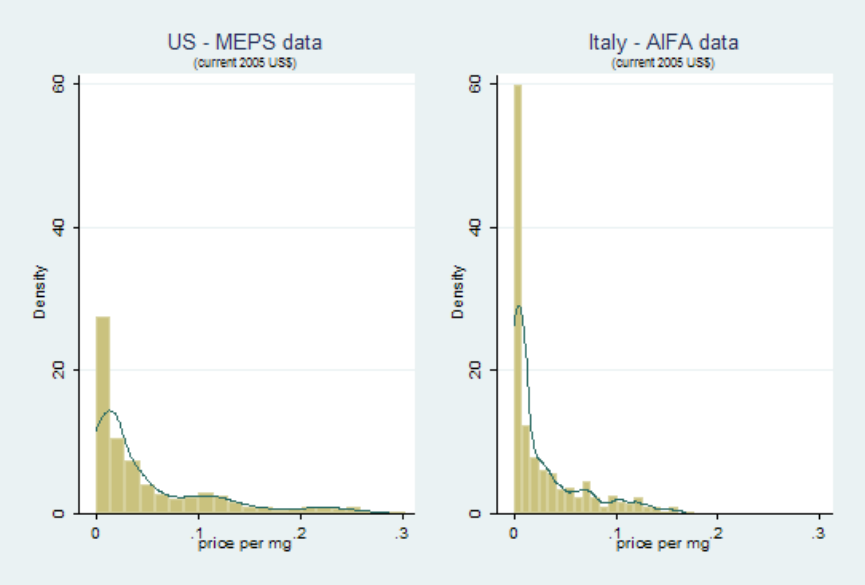
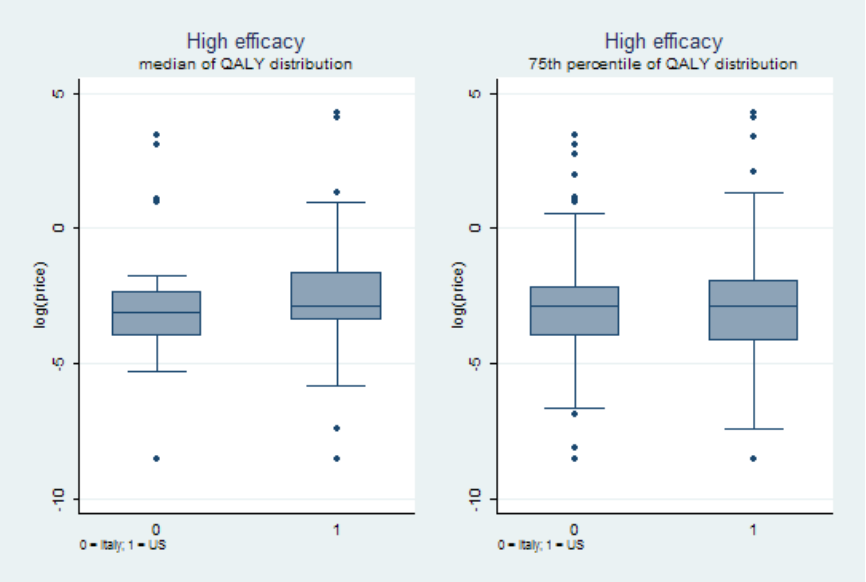


Table 1.6: Equation (1.4.1): estimates

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 1.3: Box-plot, log(price) over QALY



1.6 Appendix

1.6.1 Symbology

Table 1.7: 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*

1.6.2 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.

$$v_H(e_H) - p_H \geq v_H(e_L) - p_L \geq v_L(e_L) - p_L \geq 0 \tag{1.6.1}$$

1.6.3 Proof of proposition 1.3.5

Second best solution for p_H^{SB} implies:

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

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 1.3.2. ■

Chapter 2

Information and regulation in drug market

2.1 Introduction

Pharmaceutical industry has recently undergone increasing criticism for the extent to which investments appear to be addressed on developing drugs, the so-called *me-too*, which do not exhibit substantial improvement over the existing products (Angell [36], Avron [38], Lee [52]).

The medical literature does not provide an unambiguous definition of what a *me-too* drug really is. Usually, this term refers alternatively to the biological equivalent of existing molecular entities or to the new versions of existing drugs (e.g. the isomers), produced by the same firm that initially developed the drug. In both cases, it is clear that *me-too* drugs display virtually the same ingredients as previously approved ones and, because of their high profitability (due to low R&D investment costs), they represent one of the most important causes of the lack of innovation within the pharmaceutical industry (Hollis [47]).

Data provided by the Food and Drug Administration (FDA) show that 80 percent of the new drugs marketed over the last ten years were not even new chemical compounds (see figure 2.1). They were merely new combinations or different formulations of drugs already on the market. Meanwhile, the pharmaceutical industry has continued to be one of the most profitable in the world. That is mainly because, as pointed out by Avron [38], in many circumstances FDA approves new drugs which result only a little bit better than a placebo at improving a surrogate measure in short and modest-sized clinical trials. Moreover, the FDA "rarely comments on the therapeutic importance of

a new drug and never on its cost-effectiveness. Clinical trials comparing a new drug with existing treatments are typically required only when placebo controls are ethically unacceptable".[1]

Presently, there is an intense and growing debate whether the production of these drugs should be limited (DiMasi [43], Lee [52], Frothingham et al. [46], Morgan et al. [55]). Most critics of *me-too* drugs depict the pharmaceutical market as a place where a breakthrough (first-in-class) drug appears and is marketed successfully for a while before other firms decide to enter, facing little production cost and innovative effort, with minor modification of the first-in-class molecule. From our point of view, this description is unrealistic and overemphasize the role played by imitation: such simplifications are misleading and as such should be rejected. Indeed, *me-too* products explosion does not necessarily imply that imitation has replaced innovation in health care. As a matter of fact, in several circumstances new drug development is conducted *de facto* in parallel, rather than sequentially, and some of the most famous cases of *me-too* drugs are the result of companies racing for the same target (DiMasi [43]). Furthermore *me-too* products trigger a competitive mechanism among drug and manufacturers that is a powerful driver for lowering costs. Lee [52] provides evidence that such competition has reduces prices within the same therapeutical class (see table 2.1).

In our view, two are the main potential criticisms that can be raised against the *me-too* drugs. First of all, *me-too* drugs may expose patients at risk that may increase with the potential for cost saving.[2] That is because, the existing approval procedure does not require any *head-to-head* trials that compare the new drugs with the existing ones and does not provide systematic post-marketing studies. Secondly, despite their potential benefits in lowering price, *me-too* drugs contribute substantially in increasing drug expenditure.[3]

That said, and recalling that *me-too* drugs are not the evil, the relevant question for a policy maker is then to design a regulatory policy able to foster the discovery of new chemical entities. Several proposals have been brought forward over the years: *i)* patent laws have been suggested

[1] "Sometimes a company creates a *me-too* drug as a way of extending a patent on an older one. For example, AstraZeneca created `Nexium` to replace the virtually identical `Prilosec` when its patent was about to expire. By putting out these *me-too*'s, the companies can get new exclusive marketing rights on what are essentially the same old drugs. Other companies come in with their own *me-too*'s because markets are expandable. It's been shown that when you advertise one me-too drug, you increase the sales of all of them".(Marcia Angell interviewed by Claudia Dreifus, `http://www.nytimes.com/2004/09/14/health/policy/14conv.html`)

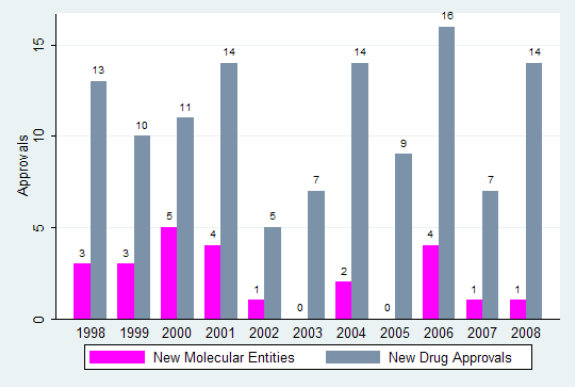
[2] Frothingham et al. [46] report that "five me-too drugs in the statin and quinolone classes have been withdrawn or restricted because of serious adverse effects that were not recognized until months or years after their approval".

[3] Morgan et al. [55] find that between 1996 and 2003, the drug expenditure in the Canadian province of British Columbia doubled, and that 80% of this increase was induced by *me-too* drugs.

to increase rewards for the basic science upon which drug discovery stands; *ii)* purchasers (insurers/providers) and physicians have been invited to focus only on critical reviews of the clinical and economic evidence (e.g. cost/effectiveness analysis)(Avron [38]); *iii)* tighter regulation on efficacy requirements have been invoked to improve the approval procedures (Ray and Stein [58]).

With respect to this last point, we claim that a regulator who can use both price control schemes and minimum efficacy standards should be more concerned with the latter rather than the former. Indeed, if the drugs are *de facto* functionally identical they tend to drive each other's prices down. Hence, assuming that higher efficacious drugs grant higher utility to the patients, a surplus-consumer maximizing regulator should be able to provide the right incentives to produce innovative drugs with adding therapeutic value. In practise, the regulator could require more useful and demanding pre-marketing studies and ask its advisory committees to comment on whether a newly approved drug is an important therapeutic contribution or a simple addition to an already long list of available drugs.[4]

Figure 2.1: FDA new drugs and new molecular entities approvals



Source: FDA

Several articles have recently analyzed the nexus between pricing policy and innovation in pharmaceutical (Atella et al [37], Bommier et al [39], Danzon et al [42], Domínguez et al [44]). Among them two deserve to be mentioned for their proximity to our research.

Domínguez et al [44] propose a model that focuses on the distortions induced on drug innovation

[4]The development of this regulatory approach might be particularly useful when the research in drug discovery is publicly funded. In fact *me-too* products lines divert resources that could be used to develop innovative compound for life-threatening diseases.

by the interaction between patients, practitioners and firms. Relying on the assumption that doctors exhibit low price elasticity, their model suggests that the firms' innovative effort depends not only on the extent of the rent, but also on the rewards that the firm obtains for any size of innovation it might achieve. Consequently pharmaceutical firms has incentives to produce small innovations (e.g. *me-too*) rather than pioneer drugs.

Bommier et al [39] develop a model to analyze the effects of reference pricing regulation on the innovative effort of pharmaceutical companies. Within a deterministic innovation model, according to which each firm chooses the time devoted to develop the new drug (breakthrough or *me-too*), those authors show that a price regulation based on uniform pricing rule produces ambiguous effects. Indeed, in such an environment, a reduction in price due to the production of *me-too* drugs implies both an ambiguous effect on profits related to the breakthrough - positive effects occurs only for some parameter values - and a delay in the introduction of followers, which instead provides positive incentives to launch innovative drugs.

Our main contribution with respect the existing literature is that our approach relies on the uncertainty related to the innovation process, which is assumed be stochastic. Indeed, this assumption seems to be more appropriate in order to capture the trade-off implicit in the decision whether to innovate or compete in the *me-too* market. Furthermore we contribute to the debate on whether drug regulation and drug innovation are necessarily at odds with each other by designing a regulatory framework that could provide incentives to produce new chemical entities rather than incremental modifications of existing drugs.[5] We then analyze the case of a pharmaceutical company that faces the dilemma whether to develop a new chemical entity or compete in the *me-too* drugs' market. The lack of full information concerns both the realized efficacy of the innovative drug and the buyers' preferences distribution.

The structure of the paper is the following. Section 2.2 describes the environment as well as the optimization problem for the producer. Section 2.2.2 illustrates the negotiation between the innovative firm and the regulator. Section 2.4 briefly discusses the characteristics of the *me-too* market. Finally, section 2.5 provides conclusions and policy implications.

[5]It is worth noticing that our line of reasoning will not assert that it would be better if the regulator forces only one company in the race for a single target. We are aware that if were so, the pharmaceutical market would experience a bad equilibrium where many firms, not necessary inefficient, might fail and where many therapeutical class might end up with no drug.

Table 2.1: Costs of Various Drugs in US

Class	Drug and Dose	FDA Approval Date	Average Cost/Mo
Statins	Simvastatin (`Zocor`) 80 mg orally daily*	Dec-91	137.56
	Atorvastatin (`Lipitor`) 40 mg orally daily	Dec-96	109.31
	Rosuvastatin (`Crestor`) 10 mg orally daily	Aug-03	75.6
Angiotensin II	Losartan (`Cozaar`) 100 mg orally daily	Apr-95	64.8
-receptor blockers	Olmesartan (`Benicar`) 40 mg orally daily	Apr-02	40.32
Proton-pump	Omeprazole (`Prilosec`) 20 mg orally daily	Sep-89	138.44**
inhibitors	Pantoprazole (`Protonix`) 40 mg orally daily	Feb-00	110
COX-2	Celecoxib (`Celebrex`) 200 mg orally twice a day	Dec-98	171
inhibitors	Valdecoxib (`Bextra`) 10 mg orally daily	Nov-01	115
ACE	Captopril (`Capoten`) 25 mg orally three times a day	Jan-82	106.20**
inhibitors	Trandolapril (`Mavik`) 4 mg orally daily	Apr-96	29.55

Data on cost are from Redbook, October 2003. * Simvastatin at a dose of 80 mg was approved by the FDA in 1998 but the product was originally approved in lower-dose preparations in 1991. ** The price is for the brand-name preparation. Source: Lee [52]

2.2 The theoretical framework

Our model involves three types of agents: the pharmaceutical firm, the buyers (insurers/providers), and the regulator.

The main assumptions of the model are the following.

Assumption 2.2.1. `Supply-side`. *In order to treat a single specific pathology, we assume that the pharmaceutical firm can choose whether to produce a* me-too *drug or an innovative drug. In the former case, she engages in the modification of an existing product which exhibits a deterministic efficacy e^{mt}, and obtains a deterministic positive profit with no cost in R&D. In the latter case, she undertakes positive R&D outlays, and sells, within a monopolistically competitive market, a single drug ζ^n, which exhibits a random efficacy $e^n \in \left[e^{mt}, \overline{e}\right]$. The probability of obtaining a high effective drug increases with the firm's innovative effort $\varrho \in [0, \infty)$.*[6] *Thus e^n is assumed to be distributed according to $\mathcal{G}(e, \varrho)$, with density $g(e, \varrho)$. Furthermore we assume that producer can not discriminate.*

Assumption 2.2.2. `Demand-side`. *The demand side is characterized by a continuum of surplus maximizing buyers differing in their* willingness-to-pay *for efficacy, parameterized by θ, embodied in the drug acquired and unobservable before the purchase. For mathematical simplicity, θ is assumed to be positive and bounded within some known interval $\left[\underline{\theta}, \overline{\theta}\right]$. Buyers are price taker and equate their own marginal utility derived from the innovative drug consumption to the price. Without loss of generality the mass of consumers is normalized at 1. The heterogeneity stems from the random component θ that is supposed distributed according to the distribution function $\mathcal{F}(\theta)$ with strictly positive density $f(\theta)$ on $\left[\underline{\theta}, \overline{\theta}\right]$.*

[6] *As in Domínguez et al [44], $\mathcal{G}$ is ordered in the first stochastic sense, so that if $\varrho' > \varrho \Rightarrow \mathcal{G}(e, \varrho') < \mathcal{G}(e, \varrho)\ \forall e$. The economic interpretation of such assumption is that the higher is the innovative effort the higher is the probability of obtaining a high quality drug.*

Given the deterministic nature of e^{mt}, we can represent the demand function faced by pharmaceutical firm as:

$$\mathcal{D} = \begin{cases} \mathcal{D}(\mathcal{F}(\theta), e^n, p^n) & \text{innovative drug} \\ \mathcal{D}(e^{mt}, p^{mt}, \xi, \mathcal{M}) & \textit{me-too} \text{ drug} \end{cases} \tag{2.2.1}$$

where:

- p^n and p^{mt} are respectively the price charged on the innovative drug and on the *me-too*;

- ξ is the degree of substitutability between *me-too* in the same therapeutical class;[7]

- $\mathcal{M}$ is the number of firm that produce the *me-too* drug.

As it happens in several European countries, we consider a regulator that might combine price control and minimum efficacy standard.[8] The former applies through price negotiation mechanisms held at country level while the latter consists in a threshold in terms of efficacy that the new drug must achieve in order to be marketed, held at EU level through the European Medicines Agency (EMEA).

The time structure of the model is the following (see figure 2.2).

- At time t_0, firm chooses whether to produce an *innovative drug* or not. If firm decides for a *me-too* drug, she enters the market with a modest investment in R&D (i.e. imitation, $\varrho \simeq 0$). On the contrary, if firm chooses to produce an innovative drug, her innovative effort produces a new drug with a random efficacy. Indeed at the time 0, the future realization of e is unknown and the innovative firm selects optimal innovative effort ϱ^* in order to maximize her expected profit $\mathbb{E}(\pi)$;

- At the end of the innovative process (t_e), firm discovers if the new drug provides a significant incremental benefit in terms of efficacy or not (i.e. $e^n \geq e^{mt}$). The probability to obtain a small improvement or a breakthrough is given by the shape of the distribution $\mathcal{G}$.

- At the negotiation time (t_n) regulator observes the efficacy level of the drug. If firms obtains an innovative drug (e^n) she negotiates the price (p^R) with the regulator. If innovation does

[7] The higher is the degree of substitutability the closer to 1 is the value of the parameter ξ.
[8] For a detailed overview of regulations in the European pharmaceutical market see Kanavos [48]

not occur, firm decides whether to enter in the *me-too* market where the price is "officially"set by the regulator. However, as it will be shown in section 2.4, market forces tend to push the "real"price below that level, *de facto* realizing a Cournot competition.[9]

- At the competition time (t_c) innovative firm behaves as a monopolist, while *me-too* drug producer competes *á la Cournot* with the other companies that sell similar drugs within the therapeutical class.

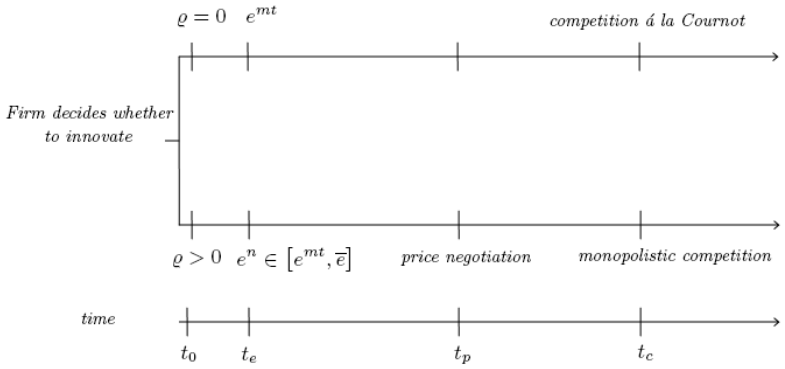


Figure 2.2: Time structure of the model

2.2.1 The producer's optimization problem

Given this set up, the next step is to define the optimization problem for the firm. In terms of figure 2.2, at t_0, firms must compare the expected profits related to the different production plans in order to decide whether innovate. A crucial role is played by the knowledge of the characteristics of the demand side that the producer has. According to assumption 2.6.2, the buyer will acquire the new drug if she derives positive utility: $\theta e^n - p^n \geq 0$. Let define the consumer with the lowest *willingness-to-pay* when the efficacy is e^n and the price is p^n as $\underline{\theta}$ such that $\underline{\theta} = p^n/e^n$. Once normalized to one the mass of consumers, following Creane [41] who develops a model of product quality under uncertainty, we can derive the demand for a new high effective drug ζ^n simply as $\mathcal{D} = [1 - \mathcal{F}(p^n/e^n)]$.

[9]The careful reader will recognize that in describing the above process patent law does not play any role. Though, we are aware of the potential benefit of this tool (i.e. it may enable firm to fund R&D outlays and new drug discovery), we prefer, at this stage, focus only on the nexus price regulation - efficacy. We leave this issue for future exploration.

Pharmaceutical firm maximizes her expected profit (over e) choosing ϱ and p:

$$\max_{\{p,\varrho\}} \mathbb{E}_e(\pi) = \begin{cases} \int_{e^{mt}}^{\overline{e}} \left[1 - \mathcal{F}\left(\frac{p^n}{e}\right)\right](p^n - c^n)g(e,\varrho) - \psi(e,\varrho)de & \textit{innovative drug} \\ \underline{\pi} \equiv \left[1 - \mathcal{F}\left(\frac{p^{mt}}{\varepsilon^{mt}}\right)\right](p^{mt} - c^{mt}) \geq 0 & \text{me-too } \textit{drug} \end{cases} \tag{2.2.2}$$

where:

- c^n is the known unit cost of ζ^n and c^{mp} is the known unit cost of ζ^{mt};[10]
- ϱ is the technological parameter that captures the firm's innovative effort which can be normalized to zero if firm produces ζ^{mt} and strictly positive otherwise;
- $\psi(e,\varrho)$ is the *disutility* of the innovative effort which satisfies $\psi_e < 0$, $\psi_{ee} < 0$,$\psi_\varrho > 0$, $\psi_{\varrho\varrho} > 0$ and $\psi(e,0) = 0$.

The innovative effort ϱ is private information to the firm. Firm invests in R&D only in the expected profit from producing ζ^n is greater than the deterministic profit she can earn from ζ^{mt}:

$$\mathbb{E}_e[\pi(p^n, \mathcal{G}(e,\varrho))] - \Phi \geq \mathbb{E}_e[\pi(e^{mt}, p^{mt})] \equiv \underline{\pi} \tag{2.2.3}$$

where Φ is the R&D fixed cost. If condition (2.2.3) holds, profit maximizing firm solves program (2.2.2), choosing p^n and ϱ that satisfy the first order conditions, which are sufficient if we do not allow for corner solutions:

$$\frac{\partial \mathbb{E}(\pi)}{\partial p^n} = \int_{e^{mt}}^{\overline{e}} \left[1 - \mathcal{F}\left(\frac{p^n}{e^n}\right)\right] g(e,\varrho) - \frac{f(\cdot)(p^n - c^n)g(e,\varrho)}{e} de = 0 \tag{2.2.4}$$

$$\frac{\partial \mathbb{E}(\pi)}{\partial \varrho} = \int_{e^{mt}}^{\overline{e}} \left[1 - \mathcal{F}\left(\frac{p^n}{e^n}\right)\right](p^n - c^n)g' - \left[1 - \mathcal{F}\left(\frac{p^n}{e^n}\right)\right] g(e,\varrho) - \psi_\varrho de = 0 \tag{2.2.5}$$

From the above FOCs, the following proposition emerges.

[10] As in the real world, both the unit costs in our framework are set equal to zero.

Proposition 2.2.1. *Optimal solution for the unregulated problem entails an equilibrium price that depends on the distribution $\mathcal{G}(e,\rho)$ rather then on the realized efficacy.* ***Proof****: it follows from first order conditions (2.2.4-2.2.5).* ■

Lemma 2.2.2. *If*

$$\frac{\partial^2\pi}{\partial e^2} = \frac{(p-c)p}{e^3}\left[f'\left(\frac{p^n}{e^n}\right)\frac{p^n}{e^n} + 2f\left(\frac{p^n}{e^n}\right)\right] + \psi_{ee} \tag{2.2.6}$$

is negative then the profit function is concave in e. This implies that, in an unregulated market, the firm prefers to invest less in R&D (i.e. less risky activity). ***Proof****: see appendix 2.6.1.* ■

Lemma 2.2.3. *If lemma 2.2.2 applies, then the more risky is the drug the lower is the expected profit.* ***Proof****: see appendix 2.6.2.* ■

2.2.2 The regulator's problem

In countries where new drugs prices are not set freely, regulation works basically at two levels. At the first level, the regulator (e.g. FDA, EMEA) reviews the safety and efficacy of new compound that manufacturers would bring to the market. At the second level, regulator negotiate with the firm the price and/or reimbursement and decides whether to limit their availability through the use of positive and negative lists (see Kanavos [48] for further details).

Let consider now the regulator's problem once e^n is realized. The regulator sets the price in order maximize consumer surplus $\mathcal{S}$. We assume that neither the realized θ nor the realized ϱ are known by the regulator while she knows the distribution of the *willingness-to-pay* $\mathcal{F}(\theta)$.

$$\mathcal{S}(e,\theta,p^R) = \begin{cases} \overline{\mathcal{S}} \equiv \displaystyle\int_{p^R/e^n}^{\overline{\theta}} e^n\theta^n f(\theta)d\theta - \left[1-\mathcal{F}\left(\frac{p^R}{e^n}\right)\right]p^R & \textit{innovative drug} \\ \underline{\mathcal{S}} \geq 0 & \text{me-too } \textit{drug} \end{cases} \tag{2.2.7}$$

Assumption 2.2.3. *`Consumers' surplus`. We assume that $\underline{\mathcal{S}}$ is very close to zero.*[11]

Recalling that the marginal new drug buyer had been defined by $\theta^n e^n - p^n = 0$, regulator solves the following problem:

$$\max_{\{p^R\}} \mathcal{S} = \int_{p^R/e^n}^{\overline{\theta}} e^n\theta^n f(\theta)d\theta - \left[1-\mathcal{F}\left(\frac{p^R}{e^n}\right)\right]p^R \tag{2.2.8}$$

[11] *One of the main benefit provided by* me-too *drugs is that they may have different side-effect profiles than the innovator drugs. This is not of secondary importance because different patients may respond differently to the same drug. Then, having a portfolio of similar drugs to choose from may enhance consumer welfare. Assumption 2.2.3 does not deny the existence of such advantages. It simply emphasizes that patient assigns a greater marginal valuation to the pioneer drug with respect to the* me-too.

such that:

$$\pi(p^R, \mathcal{G}(e,\varrho)) \geq 0 \qquad \forall e^n \in \left[e^{mt}, \overline{e}\right] \tag{2.2.9}$$

$$\mathbb{E}_e[\pi(p^R, \mathcal{G}(e,\varrho))] - \Phi \geq \mathbb{E}_e[\pi(e^{mt}, p^{mt})] \equiv \underline{\pi} \tag{2.2.10}$$

Constraint (2.2.9) ensures that, irrespectively to the realization of e^n and the price-ceiling p^R, the innovative production plan is profitable for the firm. Constraint (2.2.10) guarantees that the firm prefers to invest in R&D rather than producing a *me-too* drug.

2.3 Price negotiation: a Nash bargaining approach

An agreement between the regulator and the pharmaceutical company is a price-efficacy pair $\{p^R, e^n\}$. The gain of the innovative firm from that agreement is her expected (over e) profit such as defined in equation (2.2.2), while that of the regulator is the sum of the buyers' net utility, $\mathcal{S}$.

Recalling that the profit obtained through the production of the *me-too* medicine ζ^{mt} has been set equal to $\underline{\pi}$ and that the profit associated to an innovative drug is assumed to be non-negative, the set of utility pairs that can result from the agreement is

$$\Omega = \left\{ \left(\int_{p^R/e^n}^{\overline{\theta}} e^n \theta^n f(\theta) d\theta - \left[1 - \mathcal{F}\left(\frac{p^R}{e^n}\right)\right] p^R, \int_{e^{mt}}^{\overline{e}} \left[1 - \mathcal{F}\left(\frac{p^n}{e}\right)\right] (p^n - c^n) g(e,\varrho) - \psi(e,\varrho) de \right) : \right.$$
$$\left. \pi(p^R, \mathcal{G}(e,\varrho)) \geq 0, \mathbb{E}_e[\pi(p^R, \mathcal{G}(e,\varrho))] \geq \underline{\pi} \right\} \tag{2.3.1}$$

If the two parties fail to agree, then the firm switches to the *me-too* plan, obtaining a profit of $\underline{\pi}$ and the regulator receives $\underline{\mathcal{S}}$, so that the disagreement utility pair is $\Delta = \{\underline{\pi}, \underline{\mathcal{S}}\}$.

Assuming Ω be compact and convex (that is when both the regulator and the firm are risk averse), the generalized Nash bargaining solution is the price p^R that solve:

$$\max_{\{p^R\}} \left(\mathcal{S} - \underline{\mathcal{S}}\right)^{\alpha} \left(\pi - \underline{\pi}\right)^{1-\alpha} \tag{2.3.2}$$

where $\alpha \in (0,1)$ is the arbitrary bargaining power.

If both the firm and the regulator are indifferent to the timing of the agreement (i.e. delays are costless), the solution of problem (2.3.2) is a perfect equilibrium outcome.

First order conditions with respect to p are:[12]

$$\frac{f(p\overline{\theta}e^n - p^2 - pe^n) + 2pe^n + \mathcal{F}(\frac{p}{e})(e^n\overline{\theta} - 2e^n p)}{(e^n)^2} - \overline{\theta} = 0$$
$$\int_{e^{mt}}^{\overline{e}} \frac{-f(p-c^n)}{e}\left[1 - \mathcal{F}\left(\frac{p}{e^n}\right)\right] g(e,\varrho)de = 0 \tag{2.3.3}$$

Proposition 2.3.1. *Optimal solution for regulated problem entails a regulated price p^R that is monotonically increasing in the realized efficacy e^n and depends on the distributions $\mathcal{F}(\theta)$ and $\mathcal{G}(e,\rho)$. A higher bargaining power for the regulator implies lower p^R.* ***Proof****: it follows from first order conditions (2.3.3).* ■

Once negotiation is successfully completed, innovative firm chooses the optimal quantity to produce at price p^R.

2.3.1 A simple numerical example

In order to evaluate numerically the properties of the regulated equilibrium in proposition 2.3.1, two further (reasonable) assumptions on the distributions $\mathcal{F}(\theta)$ and $\mathcal{G}(e,\rho)$ must be made.

Assumption 2.3.1. *`Willingness-to-pay`. Let θ be a random variable distributed uniformly with a density:*

$$f(\theta) = \begin{cases} \frac{1}{\overline{\theta}-\underline{\theta}} & \text{if } \theta \in [\underline{\theta}, \overline{\theta}] \\ 0 & \text{otherwise} \end{cases}$$

Assumption 2.3.2. *`Realized efficacy`. $\mathcal{G}(e,\varrho)$ is assumed distributed according to a Weibull distribution with pdf $\mathcal{G}(e,\gamma) = \gamma\beta e^{\beta}\exp(-\gamma e^{\beta})$ where $\gamma \equiv 1/\varrho$ and $\beta = 2$.*

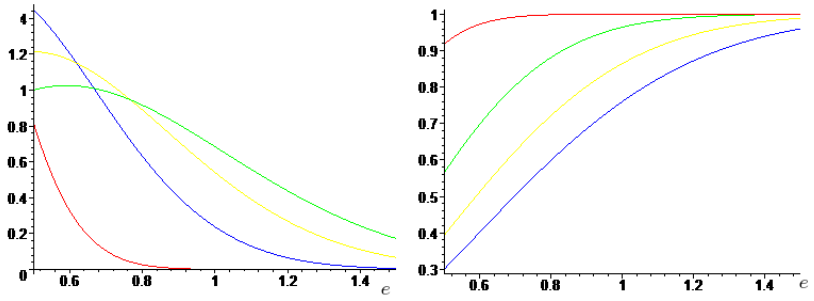


Figure 2.3: The $\mathcal{G}$ distribution (pdf and density): $\beta = 2$, $e \in (0.5, 1.5)$, $\rho \in (0,1)$

[12] Further requirements for the existence and uniqueness of the solution is that the objective function is continuous and quasi-concave.

Assumption 2.3.2 is consistent with assumptions 2.2.1-2.2.2. In particular, setting the shape parameter equal to 2 implies that $\mathcal{G}$ does not match the perfect symmetry of the normal bell-shaped distribution. The choice of a Weibull distribution supports our attempt to build a model that matches what really happens in terms of expected returns of drug discovery investment. As shown in figure 2.3, the mass of $\mathcal{G}$ is concentrated on the left of graph.[13] Indeed, existing literature on pharmaceutical research suggests that the majority of R&D outlays produce incremental rather than breakthrough innovation (i.e. high level of e^n).[14]

Given these assumptions, the negotiation between the regulator and the firm can be rewritten as:

$$\left\{ \frac{e\theta}{(t-p/e)} - p\left(1-\frac{p}{e}\right) - \underline{\mathcal{S}} \right\}^{\alpha} \left\{ \int_{e^{mt}}^{\overline{e}} \frac{(1-p/e)(p-c^n)2e\exp(-e^2/\varrho)}{\varrho} - \frac{1}{2}\psi(\varrho^2-e^2)de - \underline{\pi} \right\}^{1-\alpha} \tag{2.3.4}$$

where the parameter β in $\mathcal{G}(\cdot)$ has been set equal to 2 and, without loss of generality, $\psi(e,\varrho)$ has been assumed quadratic.

Appendix 2.6.3 provides a simulation based on the set of assumptions (2.2.1-2.3.2). The main results can be displayed through a simple graphical analysis. Not surprisingly the negotiated price p^R is monotonically increasing in drug efficacy e^n (figure in appendix 2.6.3). Though it also monotonically decreases in the regulator negotiation power α, when the realized efficacy grows it tends to decline only if the regulator increases more than proportionally her bargaining power (figure in appendix 2.6.3).

Profit function for the innovative firm is a S-shaped function of the innovative effort ϱ (right graph of figure 2.6 in appendix 2.6.3). This result suggests the existence of threshold effect: if the firm can not achieve the minimum requirement of *innovative effort*, she finds more profitable to enter in the *me-too* market rather than trying to develop an innovative drug.

Our theoretical results indicate clearly the existence of a relationship between regulated price and realized efficacy. *Ceteris paribus*, price control regulation (i.e. α close to 1) reduces the opportunity for profit and disincentives to invest resources in R&D. When the investment is risky, as it happens in new drug development, this policy leads to less innovation. On the contrary, the possibility for

[13] For simplicity we assume also that $e \in (0.5, 1.5)$.

[14] The Weibull distribution is also frequently used, in the medical literature, to model the distribution of the trials results (e.g. survival rate), with shape and scale parameters determined from cohort data.

the producer to charge freely the price and then to extract as much revenues as possible from the new drug represents a strong incentive to undertake the innovative effort.[15]

Some empirical analyses on global pharmaceutical market support this result. For instance, Danzon et al. [42] find that countries with lower expected prices have fewer products launched and longer delays for those products that are launched abroad.

2.4 *Me-too* market: oligopoly á la Cournot

Consider now the *me-too* market for a given class of medicines. All the drugs delivered by this market show, by definition, the same therapeutical properties. The bargaining process described above implies that the regulated price for the entrant should be equal to the one charged by the incumbents. The reason lies in the fact that regulator does not acknowledge any significant difference in the efficacy of the new drug with respect to the efficacy of the existing one. In other words, the role played by the regulator is negligible because market force is sufficient to keep prices for similar compounds close to their marginal cost. As a consequence, as usually happens in the real world, we do not consider the bargaining process for *me-too* drugs and we assume that the equilibrium price is determined only through a competitive mechanism.

From a theoretical standpoint we can describe this situation as follows. We have assumed that there are $\mathcal{M}$ firms are in this stage. Each of them competes in an oligopolistic market where rival companies offer a slightly differentiated drugs. Recalling that ξ provides a measure for the substitutability of the drug with respect to the other *me-too*s, firm m's inverse demand function can be written as:[16]

$$p_m(q_m, \mathbf{q_{-m}}, e^n) = \Delta(e)_m - q_m - \xi \sum_{k \neq m} q_k \tag{2.4.1}$$

where:

- q_m is quantity produced by firm m;

- $\mathbf{q_{-m}}$ is quantity produced by the $\mathcal{M} - 1$ rivals;

[15] As pointed out by Mitchell [54], price control regulation has doubtlessly contributed both to limit R&D investments by European drug companies and to reduce the number of new molecular entities launched.

[16] Hereafter we omit the apex mt for notational simplicity.

- $\Delta(e)_m \equiv (e_m - e^n)$ measures the distance in terms of efficacy of the drug provided by firm m and the innovative drug.

Assuming c be normalized at zero, firm m's reaction function can be expressed as:

$$q_m(\mathbf{q_{-m}}, e^n) = \frac{\Delta(e)_m - \xi \sum_{m \neq k} q_k}{2} \tag{2.4.2}$$

Simple algebra shows that, under Cournot competition, the equilibrium is characterized as follows:

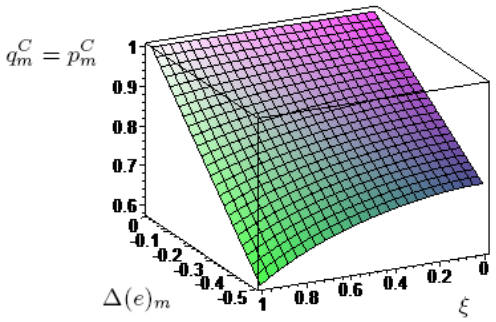
$$q_m^C = p_m^C = \frac{\Delta(e)_m \left[\xi\left(\mathcal{M}-2\right)+2\right] - \xi \sum_{k \neq m} \Delta(e)_k}{(2-\xi)\left[\xi\left(\mathcal{M}-1\right)+2\right]} \tag{2.4.3}$$

From equation (2.4.3) we can derive the following proposition.

Proposition 2.4.1. *Cournot competition between* me-too *drugs yields firm* m*'s equilibrium pair* $\{p_m^C, q_m^C\}$ *that is affected negatively by the degree of substitutability with other drugs* ξ *and the distance from the first-in-class* $\Delta(e)_m$. ***Proof****: see appendix 2.6.4.* ■

Figure 2.4 provides a graphical representation of the equilibrium price and quantity for the m^{th} firm in the *me-too* market.

Figure 2.4: Cournot equilibrium



It is worth notice that if the firm undertook a positive effort ϱ on developing her drug then she earns a profit equal to:

$$\pi_m^C = \left\{ \frac{\Delta(e)_m \left[\xi\left(\mathcal{M}-2\right)+2\right] - \xi \sum_{k \neq m} \Delta(e)_k}{(2-\xi)\left[\xi\left(\mathcal{M}-1\right)+2\right]} - \psi(e_m, \varrho) \right\} \tag{2.4.4}$$

If the above expression is positive m^{th} firm finds entry profitable, otherwise the optimal response is to stay out of the market.

Finally, it is worth notice that the simple mechanism described in this section is also suitable to describe innovative drug pricing in country where regulation does works only at efficacy level (eg. US). Indeed, the higher are the new drug therapeutical properties the lower are the values of $\Delta(e)$ and ξ, which tends to 0. Both those factors lowers dramatically the price charged and the quantity sold by the incumbents.

The statins market provides evidence which is consistent proposition 2.4.1.[17] In 2005, Medical Expenditure Panel Survey (MEPS) reports that in US there were available six different statins: lovastatin, pravastatin, simvastatin, atorvastatin, fluvastatin and rosuvastatin. Despite these molecules exhibit very similar performances in reducing cholesterol (ξ very close to one), a growing literature has recently defined rosuvastatin as the most powerful compound currently on the market (i.e. $\Delta(e)_m \equiv (e_r - e_m)\ \forall m$ where e_r is the efficacy level of rosuvastatin).[18]

The high degree of substitutability prevents firms from charging a price greater than p^C. Moreover, the introduction of a more effective compound (i.e. rosuvastatin) implies a fall in the price of the rivals (see figure 2.5) and in the companies' bargaining power.[19]

2.5 Conclusion and policy implications

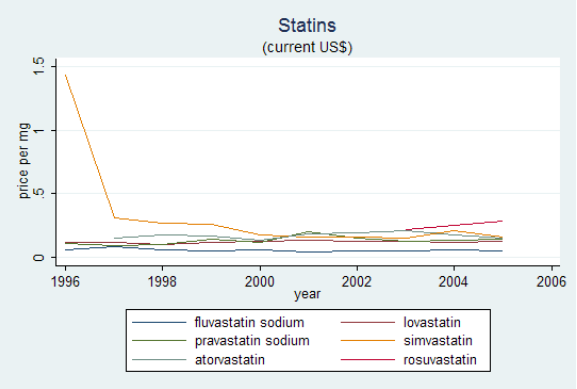
There is growing concern that the current procedures followed in drug regulation are inadequate in providing incentives to innovation. Several papers have recently called for tighter approval procedure and post-marketing studies (among the others see Ray and Stein [58]). Comparisons involving *me-too*

[17] The statins are effective cholesterol lowering medications. The major clinical effect of statin therapy on the lipid profile is the reduction in levels of low-density-lipoprotein (LDL) cholesterol, which carries the bulk of circulating cholesterol, accompanied by a variable decrease in the concentration of very-low-density-lipoprotein (VLDL).

[18] For instance, Efthimiadis [45] showed the greatest efficacy of rosuvastatin in lowering total cholesterol and low-density lipoprotein cholesterol, and in increasing high-density lipoprotein cholesterol. Stender and coauthors [59] pointed out that, compared to atorvastatin 10 mg, simvastatin 20 mg and pravastatin 40 mg, treatments with rosuvastatin (10 mg) are more effective ($p < 0.0001$ for all comparisons). Olsson et al. [59] found that rosuvastatin provides advantages in LDL-C goal attainment over existing lipid-lowering therapies. Moreover Olsson et al. [57] reported that rosuvastatin has a number of advantageous pharmacological properties, including enhanced HMG-CoA reductase binding characteristics, relative hydrophobicity, and selective uptake into/activity in hepatic cells.

[19] The companies' bargaining power is generally greater in US than in Italy. The reason is twofold. Firstly, because government, through the agency AIFA, controls both the price and efficacy. Secondly, because in Italy the regulator is also the most important provider and then firm can not benefit from the possibility of switching to another buyer (insurer/provider).

Figure 2.5: Price and *me-toos* (US data)



drugs and existing products have been also required before the formers' unrestricted use (Lee [52]). Sharing this feeling, we analyzed the effect of price negotiation on firm's behavior.

In order to highlight the distinctions between our approach and previous work, we assume that innovation process is stochastic and that the firm might choose whether to innovate or compete in the *me-too* market. A key feature of our model is that the firm does not know in advance the level of efficacy that the drug will exhibit. Hence, our analysis showed that, in a very simple set up, *me-too* drugs production is chosen because there is no uncertainty about the future profit (i.e. e^{mt} is not stochastic). In other words they are less risky. From appendix 2.6.1 we know that firm is risk lover if and only if:

$$\Upsilon\left[f'\left(\frac{p}{e}\right)\frac{p}{e}+2f\left(\frac{p}{e}\right)\right]+\psi_{\varepsilon e}>0$$

Thus regulation may work to compensate the disutility that arises from the *innovative effort*. Along this way, regulator should simultaneously negotiate higher prices for more effective drugs and lower for the *me-too* ones. The rationale for this regulatory strategy is twofold. First, it reduce the uncertainty about price which also depends on $\mathcal{F}(\theta)$ and $\mathcal{G}(e,\varrho)$. Second, it renders *me-too* plan less profitable.

Under mild assumptions on $\mathcal{F}$ and $\mathcal{G}$, we have also found that p^R is increasing monotonically in the realized efficacy. It is not a standard result. It suggest that the existence of a trade-off between expenditure control and the (average) efficacy delivered matters.[20]

[20]Using data on US and Italy, Atella et al [37] find that the link between price and efficacy is weak in a tight

The positive analysis developed indicates also that the level *willingness-to-pay* θ exerts a positive effect on the regulated price especially for the low efficacy drug. Moreover the distribution of θ and the level of effort ϱ affect the curvature of the profit function and then the propensity to invest in developing new drug.

The model developed so far has been built on reasonable assumptions aimed at obtaining an analytical friendly framework. Some further extensions are going to be introduced in future works. *i)* The patents issue should be address in order to refine the the trade-off between innovation and *me-too* products. *ii)* An empirical analysis on US and Italian data should be also carried out to evaluate the impact of the regulatory regime on the production (and registration) of new chemical entities and the proliferation of *me-too*. In particular, it should take into account the evolution of the {price, efficacy} pairs experienced in several therapeutical class. Anti-hypertensive medications might constitute a further area for empirical tests. Indeed, this group of drugs include more different types of medication with different mechanisms of action (beta-blockers, diuretics, ACE-inhibitors, calcium channel blockers).

price-regulated pharmaceutical market.

2.6 Appendix

2.6.1 Proof of Lemma 1

Assumption 2.2.1 states that e^n is stochastic for the firm. Then concavity of $\pi(\cdot)$ represents risk aversion. Second derivative of profit function yields:

$$\frac{\partial^2 \pi}{\partial e^2} = -\frac{f'\left(\frac{p}{e}\right)p^2(p-c)}{e^4} - \frac{2f\left(\frac{p}{e}\right)p(p-c)}{e^3} - \psi_{ee} \tag{2.6.1}$$

Hence:

$$\Upsilon\left[f'\left(\frac{p}{e}\right)\frac{p}{e} + 2f\left(\frac{p}{e}\right)\right] + \psi_{ee} < 0, \ \textit{firm invests in risky drug} \tag{2.6.2}$$

$$\Upsilon\left[f'\left(\frac{p}{e}\right)\frac{p}{e} + 2f\left(\frac{p}{e}\right)\right] + \psi_{ee} = 0, \ \textit{firm is neutral w.r.t. to riskiness} \tag{2.6.3}$$

$$\Upsilon\left[f'\left(\frac{p}{e}\right)\frac{p}{e} + 2f\left(\frac{p}{e}\right)\right] + \psi_{ee} > 0, \ \textit{firm does not invests in risky drug} \tag{2.6.4}$$

where $\Upsilon \equiv [(p-c)p/e^3]$. ■

2.6.2 Proof of Lemma 2

If the profit function is concave in e then the expected profit decreases with more risky product. Let consider two different distributions $\mathcal{G}(e,\varrho)$ and $\mathcal{H}(e,\varrho)$ with the same mean and $e \in \left[e^{mt}, \overline{e}\right]$. We say that $\mathcal{G}$ is more risky than $\mathcal{H}$ if

$$\int_{e^{mt}}^{e} \mathcal{G}(e,\varrho)de \geq \int_{e^{mt}}^{e} \mathcal{H}(e,\varrho)de \qquad \forall e \in \left[e^{mt}, \overline{e}\right]$$

If condition (2.6.4) holds, from the previous definition follows:

$$\mathbb{E}\Big[\pi\big(p(\mathcal{G}), \mathcal{G}(e,\varrho)\big)\Big] = \int_{e^{mt}}^{\overline{e}} \left[1 - \mathcal{F}\left(\frac{p(\mathcal{G})}{e}\right)\right](p-c)\mathcal{G}(e,\varrho) - \psi(e,\varrho)$$

$$< \int_{e^{mt}}^{\overline{e}} \left[1 - \mathcal{F}\left(\frac{p(\mathcal{H})}{e}\right)\right](p-c)\mathcal{H}(e,\varrho) - \psi(e,\varrho) = \mathbb{E}\Big[\pi\big(p(\mathcal{H}), \mathcal{H}(e,\varrho)\big)\Big] \qquad \blacksquare \tag{2.6.5}$$

2.6.3 Numerical simulations: figures

Table 2.2: Simulation: numerical values

parameters	*values*
θ	1
ψ	0.35
e^{mt}	0.5
$\overline{e}$	1.5
$\underline{\pi}$	0
$\underline{\mathcal{S}}$	0
$\overline{\theta}$	0.5
c^n	0

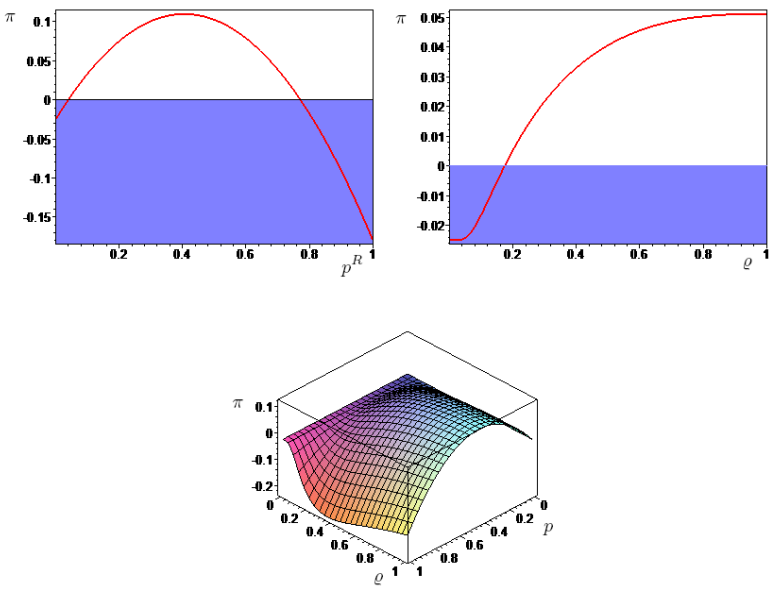


Figure 2.6: The profit function (right panel: p=0.034)

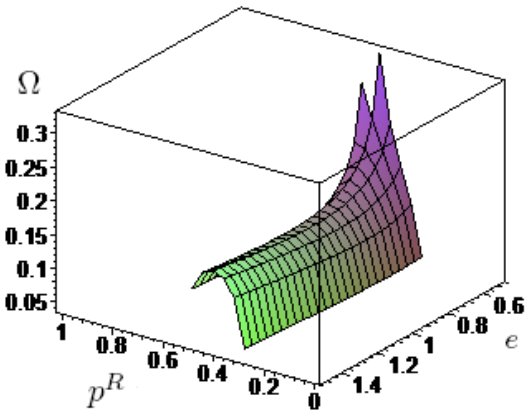


Figure 2.7: The negotiation: regulated price & new drug efficacy

Changes in the observed efficacy e^n

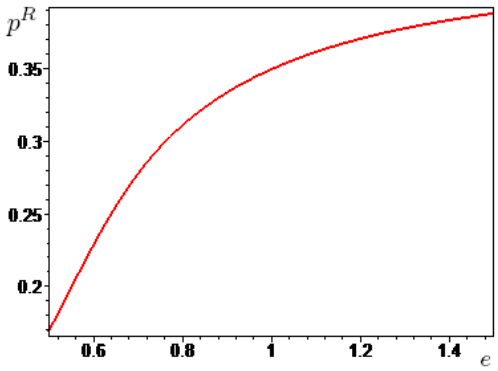


Figure 2.8: Regulated price and the efficacy observed

Changes in the regulator's bargaining power α

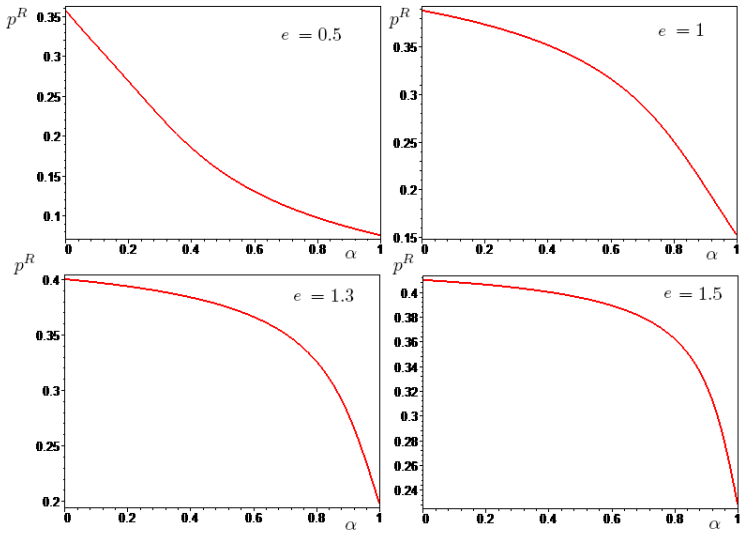


Figure 2.9: Regulated price and the bargaining power when e^n is equal to 0.5, 1, 1.3, and 1.5

Changes in the *willingness-to-pay* θ

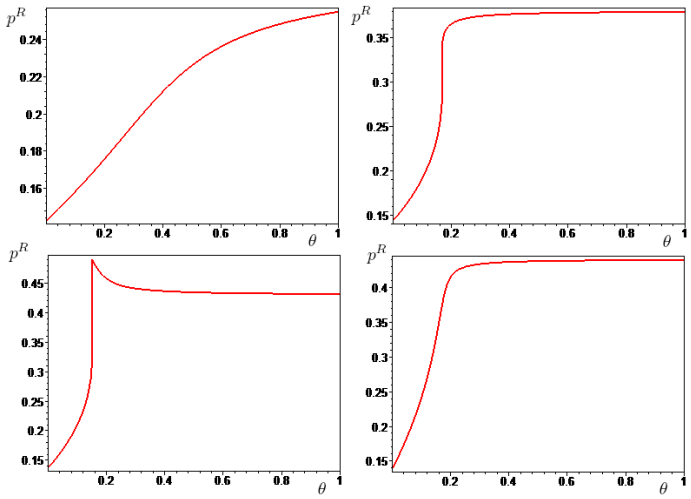


Figure 2.10: Regulated price and the bargaining power when e^n is equal to 0.5, 0.7, 1, and 1.5

2.6.4 Proof of proposition 2.4.1

Deriving equation (2.4.3) with respect to ξ yields:

$$\frac{-4\Delta_m\xi + 2\Delta_m\xi^2 + \xi^2\sum_{k\neq m}\Delta_k + 4\Delta_m\xi\mathcal{M} + \Delta_m\xi^2\mathcal{M}^2 - 3\Delta_m\xi^2\mathcal{M} - \xi^2\sum_{k\neq m}\Delta_k\mathcal{M} - 4\sum_{k\neq m}\Delta_k}{(\xi-2)^2/(\xi\mathcal{M}-\xi+2)^2} < 0 \tag{2.6.6}$$

where $\Delta \equiv \Delta(e)$. ■

Chapter 3

How variable is labor input in the Italian manufacturing: the case of the pharmaceutical industry

3.1 Introduction

In recent times, most surveys have underlined the Italian transition towards a more flexible labor market (e.g. OECD [75] [76]). Indeed, starting from early 90's, a series of legal reforms has been introduced to render labor market more efficient.[1] The main result of such a policy is that *flexible* workers are the overwhelming majority of overall new hired. Nevertheless, especially in the manufacturing, where the use of flexible contracts is less frequent, available data tell that labor demand, at least in the short-run, is irresponsive to the change in the production scale (Carbonari [64]).[2] In line with this evidence, we claim that labor input evinces an adjustment pattern very close to the one of physical capital.

There are only few papers in the literature that focus on this issue, referring to the Italian case

[1] In 1994 the use of the *training on the job contracts* (*Contratti di Formazione e Lavoro*) - originally introduced ten year before to reduce youth unemployment - was extended to a wider range of situations. In 1995 there was the introduction of the *ongoing collaboration contracts* while in 1997 the *temporary work agencies* broke the monopoly of public employment agencies. In 2001 the use of fixed-term contracts for subordinate workers as well became legal. Finally, in 2003, the so-called *Biagi Law* has given the variety of *atypical labor contracts* a common framework (Russo and Veredas [79]).

[2] For example, focusing on the period 1993-2003, the Italian Central Statistical Office reports that while the deseasonalized index of production in industry has grown by an estimated 1.7 percent, the number of workers has remained substantially unchanged (ISTAT [69]).

and using firm-level data. The majority of those moves from a *labor economics* perspective and investigates the effectiveness of the deregulation policies or the employment dynamics (e.g. Bertola and Ichino [63] and Russo and Veredas [79]). Differently, the present paper, that belongs to the strand of the empirical literature that applies flexible functional forms to characterized productive behavior (e.g. Morrison [71] [72] [73], Atella and Quintieri [61], Pierani and Rizzi [77]), is intended to focus on firms' labor demand and to provide insights into substitution patterns. In order to test the hypothesis of labor rigidity, we will use a new dataset on the Italian pharmaceutical industry. We base our analysis on the restricted Generalized Leontief cost function proposed by Morrison [72] [73]. The choice of this flexible functional form is due to its ability to describe factors demand, when both physical capital and labor behave as a quasi-fixed input. This approach is suitable to analyze the Italian case given that teh pharmaceutical industry, as the rest of the Italian manufacturing, is highly characterized by the existence of long-term labor centralized contracts, that exacerbate labor rigidity.[3]

The paper is organized as follows. Section 3.2 describes the key features of the Italian Pharmaceutical sector. Section 3.3 outlines the theoretical framework. Section 3.4 displays the results of the estimations, and evaluates the short and the long-run elasticities in alternative models with one or two quasi-fixed inputs. Section 3.5 provides conclusions.

3.2 The Italian pharmaceutical industry: figures and trend

The Italian economy has historically been characterized by a large pharmaceutical sector. From the end of WWII until the end of mid-sixties many Italian entrepreneurs contributed to develop a modern, fast-growing industry, able to respond to the increasing demand of medicines. Since then, despite this encouraging beginning, national firms started to decline in terms of competitiveness and innovation.

Currently, the Italian pharmaceutical market displays the same structure of other developed ones: high entry barriers, a strong governmental intervention, and high profits for the sellers. As

[3]This rigidity arises also from the *Charter of Workers' Rights* that have tightly regulated employment relationships in Italy since 1970. Particularly, the *Statuto dei Lavoratori* sets the procedures for hiring and firing, and defines the compensation structure and the rules for workers mobility. Most of all, it prevents the dismissal of workers in absence of appropriately motivation and prescribes that guilty employers must "compensate dismissed workers in kind, restoring their employment status and paying back wages for all the period of litigation plus other monetary penalties"(Bertola and Ichino [63]).

shown in table 3.1, it is the third largest in Europe by total sales and by number of workers, and the fifth largest with respect to the number of companies. Moreover, it has historically attracted a relevant flow of foreign direct investments. The reason of these inflows of investments is twofold. On one hand, until the late 70s, foreign investors had been attracted by the large amount of funds granted by the Cassa del Mezzogiorno. On the other hand, the increasing demand for drugs led multinational enterprises to locate plants and commercial activities in Italy (Carbonari [65]). These facts contribute to explain why, during the last thirty years in Italy, the world leaders' market share has been constantly increased (see the right graph of figure 3.3 in the appendix).

The most relevant features of this industry, with respect to the rest of the Italian manufacturing sector, are the following:

- it exhibits a high segmentation due to the low substitutability among the drugs belonging to different therapeutic classes. The overall market is highly concentrated: in 2005, the top ten vendors represented the 50% of the total market, while the top hundred cover the 96.5% of the entire market (Farmindustria [68]);

- it operates within a tightly regulated environment. In fact, the regulatory system affects the drug's safety/effectiveness, and its pricing.[4] There is also a unique institutional buyer, the National Health System, which is managed at regional level;

- it is characterized by high investment in R&D. Even though there is an extreme lack in terms of research facilities in Italy, in 2004 the pharmaceutical industry invested 839 billions euros into R&D and the drug companies based in Italy employed 4,314 individuals in R&D (Farmindustria [67]).[5] Despite this positive element, only few firms develop new drugs in Italy. The reason for this apparent contrast is dual. First, Italy has historically suffered a lack of incentives to innovation. Second, R&D expenditure, derived from balance sheets, is only a proxy (often unreliable) of the research led by firms, because it also includes large resources invested on advertising, marketing and lobbying. Drugs' patent protection was introduced in Italy only in 1978. Since then, the Italian pharmaceutical industry has started to face an increasing number of difficulties, especially because of the high costs associated to the research

[4] As in other EU countries price regulation includes the entry price and any posterior increases.
[5] Around 5% of the entire national expenditure in R&D and the 9% of the whole manufacturing.

in this sector. Hence, keeping aside the new generation of *biotech* firms, the majority of Italian companies usually prefers *co-marketing* techniques. Moreover, multinational companies find it more productive to invest in R&D abroad rather than in Italy (Carbonari [65]).

Table 3.1: European pharmaceutical industry (2004)

Country	Total sales	Number of workers	Number of firms
France	25,392	98,900	256
Germany	23,242	119,800	313
Italy	21,989	73,550	241
United Kingdom	16,850	73,000	362
Spain	13,042	39,000	245
Greece	7,141	11,200	-
Netherlands	4,250	15,500	130
Sweden	3,117	21,600	60
Switzerland	2,953	29,613	230
Portugal	2,852	10,691	-
Denmark	1,839	15,131	41
Norway	1,684	4,603	156
Finland	1,651	7,032	69

Million US$ PPP. Source: OECD Health Data (2006)

An other important feature of this sector is the labor demand evolution. In the period 1985-2005, the number of workers employed in the Italian pharmaceutical industry has grown only at 0.8% per year, whereas the growth rate of fixed assets accumulation has been around 7.8% (Farmindustria [67]). This evidence suggests to test the hypothesis that labor behaves as a quasi-fixed input.

3.3 The theoretical model

The existing literature (e.g. Morrison [73]) has shown the usefulness of considering firm's behavior in terms of cost rather than production function. This choice allows to avoid the main problem that arises when production function specification is implemented for econometric purposes: endogeneity versus exogeneity of right hand side variables. Moreover, by using cost function, input demand can be easily derived through *Shephard's lemma*. This section offers the theoretical structure of our analysis and the specification chosen in order to address the issues highlighted in the introduction.

3.3.1 The dynamic optimization problem with static expectations

In this analysis we will consider an industry composed by H technologically independent firms facing a competitive input market. Suppose also there are K quasi-fixed inputs x_k $(k = 1...K)$, subjected to increasing internal cost as in Berndt and Morrison [74] and J variable inputs v_j $(j = 1...J)$, which are available at constant price. Let $\mathbf{p} = \{p_j\}$ be the vector of (exogenous) prices of variable inputs and let $C(\dot{x}_k)$ be the change total costs due a variation of quasi-fixed input. Furthermore, the cost function exhibits the following properties:

$$C(0) = 0 \qquad C'(|\dot{x}_k|) > 0 \qquad C''(|\dot{x}_k|) > 0 \tag{3.3.1}$$

where $\dot{x}$ (net investment) is the first derivative of x_k with respect to time. The firm's optimization problem firm consists in to choosing the sequences of variable inputs $\{v_{j,t}\}$ and quasi-fixed inputs $\{x_{k,t}\}$ that minimize the present value of the stream of future cost subject to the production constraint $Y(t) = F(\mathbf{v,x}, \dot{\mathbf{x}}, t)$:

$$C(0) = \int_0^\infty e^{-rt}\left(\sum_j w_j v_j + \sum_k q_k z_k\right)dt \tag{3.3.2}$$

where:

- r is the real discount rate;
- δ is the depreciation rate and r is the real interest rate;
- $q_k = p_k/(r + \delta)$ is the asset price of x_k;
- p_k is the rental price of new quasi-fixed input;
- $z_k = \dot{x}_k(t) + \delta x_k(t-1)$ is the gross investment in terms of k^{th} quasi-fixed input x_k.

As in Berndt and Morrison [74] and Morrison [71], in order to minimize 3.3.2, first we derive the restricted cost function G that incorporates the solution of the short run optimization problem, and then we find the optimality conditions with respect quasi-fixed inputs. It is worth noticing that $G(\mathbf{p,x}, \dot{\mathbf{x}}, Y, t)$, which is dual with $Y(t)$, evinces the following properties:

- $\partial G(\cdot)/\partial p_j = v_j$ is the optimal short run for variable input j (*Shephard's lemma*);
- $-\partial G(\cdot)/\partial x_k = \lambda_k$ is the shadow value of the quasi-fixed input k.

Hence, to define the pattern of quasi-fixed inputs accumulation, we must take into account the *Euler equation* corresponding to the following optimal control problem:

$$\min_{x,\dot{x}} C(0) + \sum_k q_k x_k(0) = \int_0^\infty e^{-rt}\left[G(\mathbf{p},\mathbf{x},\dot{\mathbf{x}},Y,t) + \sum_k p_k x_k\right]dt \tag{3.3.3}$$

where $x_k(0)$ is the initial stock of quasi-fixed input.

Using the *calculus of variation* to solve problem (3.3.3), we obtain the following first order conditions:

$$\frac{\partial G}{\partial x_k} = \frac{\partial}{\partial t}\frac{\partial G}{\partial \dot{x}_k} \tag{3.3.4}$$

which implies:

$$(G_x + \mathbf{u}) - (-rG_{\dot{x}} + G_{\dot{x}x}\dot{x} + G_{\dot{x}\dot{x}}\ddot{x} + G_{\dot{x}t}) = 0 \tag{3.3.5}$$

where:

- $\mathbf{u}$ is the vector of p_k;
- $\ddot{x}$ is the second derivative of x_k with respect to time;
- $\dot{\mathbf{p}}$, the derivative of the vector of variable input prices with respect to time, and $\dot{Y}$ are set equal to zero, given the assumption of static expectations.[6]

In order to solve the second order differential equation 3.3.5, we expand linearly around $(x,\dot{x},t)=(x(t)^*,0,t)$ at time t, where $x(t)^*$, in the simplest case of only one quasi-fixed input (e.g. the physical capital), is the unique value that solves:

$$-G_x(\cdot) - rG_{\dot{x}}(\cdot) = p_k \tag{3.3.6}$$

where the LHS is the shadow value and the RHS is the market rental.

3.3.2 The choice of flexible functional form: a Generalized Leontief approach

The flexible functional form chosen for our purpose is the *Generalized Leontief* used by Morrison [72] to compare firms' behavior in U.S. and Japanese manufacturing. The advantages of this cost function is that it is relative parsimonious of parameters and, above of all, it allows an analytical computation

[6] For that reason we omit the term $G_{\dot{x}p}\dot{\mathbf{p}} + G_{\dot{x}Y}\dot{Y}$ in equation (3.3.5).

of the "desired"level of input stocks x_k^*. The *Generalized Leontief* for multiple quasi-fixed inputs can be expressed as:

$$\tilde{G} = Y\left[\sum_i \sum_i \alpha_i p_i^{.5} p_j^{.5} + \sum_i \sum_m \delta_{im} p_i s_m^{.5} + \sum_i p_i \sum_m \sum_n \gamma_{mn} s_m^{.5} s_n^{.5}\right] +$$

$$Y^{.5}\left[\sum_i \sum_k \delta_{ik} p_i x_k^{.5} + \sum_i p_i \sum_m \sum_k \gamma_{mk} s_m^{.5} x_k^{.5}\right] + \sum_i p_i \sum_k \sum_l \gamma_{lk} x_k^{.5} x_l^{.5} \tag{3.3.7}$$

where:

- p is the price vector of variables inputs identified by the subscripts i, j;
- x is the stock of quasi-fixed input identified by the subscripts k, l;
- Y stands for the level of output;
- s captures other exogenous argument of $\tilde{G}$ not included in the return to scale specification;
- m, n are the subscripts denoting the exogenous arguments of $\tilde{G}$ not included in the return to scale specification (e.g. state of technology, net investment in quasi-fixed inputs Δx_k, etc...).

In equation (3.3.7) $\tilde{G}$ is linear homogeneous in price, and the global convexity in x_k, as it happens with many other flexible functional forms, is not guaranteed. Furthermore, differently from Morrison [71]- [72], we do not impose any restriction on the parameter in order to allow for non constant returns to scale.[7]

Following Morrison [72], we can easily obtain the explicit shadow value of capital Z_k by deriving equation (3.3.7) with respect to x_k:

$$Z_k = -.5\left[Y^{.5} x_k^{-.5}\left(\sum_i \delta_{ik} p_i + 2\sum_i p_i \gamma_{tk} t^{.5}\right) + \sum_i p_i \sum_l \gamma_{kl} x_k^{-.5} x_l^{.5}\right] \tag{3.3.8}$$

Then at the equilibrium:

$$Z_k = \tilde{G}_x(\cdot) - r\tilde{G}_{\dot{x}}(\cdot) = p_k \tag{3.3.9}$$

[7] In fact, as explained in section 3.1, pharmaceutical industry exhibits high entry barriers and profits that suggest significant returns to scale.

and the desired stock of the quasi-fixed input is given by

$$x_k^* = \digamma(\mathbf{p}, p_k, Y, t, \dot{x}_k) \tag{3.3.10}$$

Demand equations suitable for empirical analysis may be derived from equation (3.3.7) simply by applying Shepard's lemma and by dividing the I input demand for Y in order to reduce possible heteroscedasticity:

$$\frac{v_i}{Y} \equiv \frac{\partial \tilde{G}}{\partial p_i}\frac{1}{Y} = \sum_j \alpha_{ij}(p_j/p_i)^{.5} + \sum m\delta_{im}s_m^{.5} + \sum m \sum n\gamma_{mn}s_m^{.5}s_n^{.5}$$

$$+Y^{-.5}\left[\sum_k \delta_{ik}x_k^{.5} + \sum m \sum k\gamma_{mk}s_m^{.5}x_k^{.5}\right] + Y^{-1}\sum_k\sum_l \gamma_{lk}x_k^{.5}x_l^{.5} \tag{3.3.11}$$

The system of estimable equations comprised in equation (3.3.11) represents the firm demand behavior in the short-run.

Given the restrictions made on the cost function, short-run elasticities are defined as

$$\varepsilon_{ij}^{SR} \equiv \frac{\partial lnv_i}{\partial lnp_j} = \frac{\partial v_i}{\partial p_j}\cdot\frac{p_j}{v_i}\Big|_{x_k=x^*} \tag{3.3.12}$$

$$\varepsilon_{iY}^{SR} \equiv \frac{\partial lnv_i}{\partial lnY} = \frac{\partial v_i}{\partial Y}\cdot\frac{Y}{v_i} \tag{3.3.13}$$

and the long-run ones as:

$$\varepsilon_{ij}^{LR} = \frac{p_j}{v_i}\cdot\left[\frac{\partial v_i}{\partial p_j} + \sum_{k=1}^{n}\frac{\partial v_j}{\partial x_k}\cdot\frac{\partial x_k}{\partial p_j}\right] \tag{3.3.14}$$

3.4 Empirical implementation

Given the traditional rigidity exhibited by the Italian labor market, we test the dynamic model described above in two different versions: one where only physical capital is quasi-fixed, and the other where also labor is treated as a quasi-fixed input. This section provides the results of the empirical implementation of these two models carried out on firm level panel data. Our database Pharmapanel Top100 was built from balance-sheet files collected by *Bureau van Dijk Electronic Publishing* (*BvDEP*), that sets up computer-readable files from the original balance-sheet reports. It contains information on the top hundred companies, ranked by revenue, which represent the 96.5% of the entire Italian market (Farmindustria [68]). The data cover the period from 1991 through 2004

- not all firms are present in all years. - and are relative to gross production, labor, materials, services, fixed assets, and investments.[8] We also use additional information on the real interest rate, the depreciation rate, and consumer price indexes.[9] It is worth noticing that, while fixed assets are deflated using the one-digit industry specific deflator from ISTAT, labor cost is obtained through a firm-specific index (p_L) that is equal to the average wage per worker. The technological change is represented by a non-firm-specific time trend (t) and finally, in order to capture the effects of firm size and nationality, specific dummy variables are defined.[10]

Summary statistics are presented in table 3.2.

Table 3.2: Summary statistics of selected variables

Variable	Definition	Unit	Obs	Mean	Std.Dev.	Min	Max
Y	production	10^6 current Euros	695	142.119	221.081	0.081	1812.924
v_S	services demand	10^6 current Euros	695	27.926	38.576	0.001	272.800
v_I	materials demand	10^6 current Euros	695	77.567	120.210	0.010	900.718
x_K	capital demand	10^6 current Euros	695	19.113	29.409	0.000	223.189
v_L	labor demand	10^2 # of workers	695	6.827	12.467	0.010	110.420
p_S	services price index	2000=1	695	1.004	0.082	0.729	1.136
p_I	materials price index	2000=1	695	0.993	0.045	0.801	1.081
p_L	labor price index	2000=1	695	1.071	0.703	0.014	14.137
p_C	capital price index	2000=1	695	0.993	0.042	0.787	1.050

3.4.1 Descriptive analysis

Table 3.3 provides a brief sketch of the Pharmapanel Top100 through the most relevant indicators of firm performance. The existence of high heterogeneity for many of the variables of interest suggests to focus on median values.

An interesting feature emerging from descriptive analysis is the evolution of capital and labor demands, that corroborates our *a priori* on the labor market rigidity. Figure 3.1 plots the evolution of physical capital demand and labor demand with respect to aggregate production. This graph shows that the pattern of labor demand is very close to the one of physical capital.[11]

[8] Services include the outside labor and and/or materials for specialized or overflow work. Physical capital is given by the sum of equipment, machineries and structures.

[9] The source for the interest rate data is the Bank of Italy; depreciation rate has been set equal to 10%; the source for consumer price index is the Italian Institute of Statistics (ISTAT).

[10] Dummy variables are used in order to evaluate the effects of firms' size and their nationality. The former is given by the (average) total revenues, the latter is given by the ownership nationality. The number of workers has also been used in order to capture the size, but any statistically significant difference in the results has been found. See the table 3.9 in the appendix for further details on data construction.

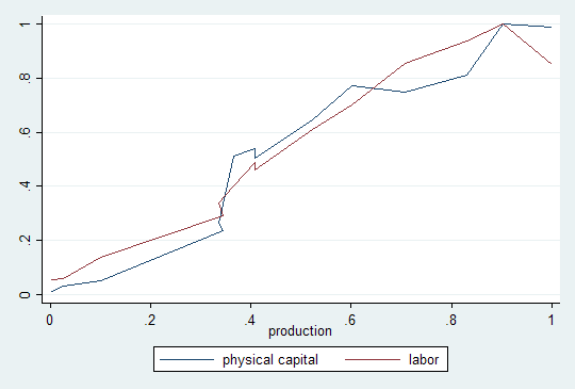
[11] Annual average values for input demands and production level have been computed and than properly rescaled

Table 3.3: Pharmapanel Top100, relevant indicators

	Total Revenues	Value Added	Ebit	Cash flow	Equity	Working capital
2004	252.163	81.679	9.151	21.597	18.813	86.682
	106.615	**29.731**	**2.453**	**7.636**	**7.748**	**31.672**
2003	226.108	77.309	7.204	20.336	16.588	70.636
	89.096	**26.930**	**2.857**	**6.973**	**7.006**	**24.515**
2002	203.132	66.038	11.102	21.852	13.472	55.997
	80.319	**24.107**	**2.563**	**6.123**	**5.168**	**16.255**
2001	166.606	55.159	9.147	18.060	12.975	61.832
	74.368	**24.149**	**2.571**	**7.662**	**5.170**	**17.554**
2000	166.156	55.183	8.382	16.500	13.836	58.138
	69.730	**22.347**	**2.162**	**4.866**	**5.165**	**17.174**

Value added is defined as total revenues less non-labor costs of inputs. Net result is defined as total revenues minus total costs (business, depreciation, interest, and taxes). Cash flow is equal to net result plus amounts charged off for depreciation, and amortization. Working capital is given by the difference between current assets and current liabilities. Millions of current euros; means and ***medians****. Source: our calculations based on* Pharmapanel Top 100

Figure 3.1: Do capital and labor behaves as QFIs?



Source: our calculations based on Pharmapanel Top100

Our data confirms also that, keeping aside the early 90's when pharmaceutical aggregate production was hit by a strong exogenous shock (the so-called *pharma bribery scandal*), the labor demand exhibits a substantial degree of rigidity until late the 90's. Another interesting issue arising from the descriptive analysis concerns the distribution of capital across workers. Table 3.4 provides the correlation between capital/labor ratio and price ratio p_K/p_L. As suggested by the theory all values are negative, though statistically insignificant.

to the interval [0,1].

Table 3.4: Capital & Labor (1991-2004)

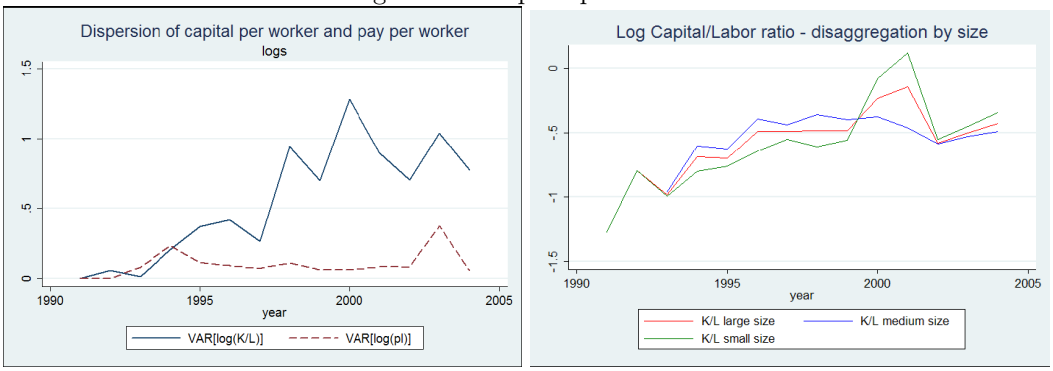
	Correlation ($x_K/x_L, p_K/p_L$)
Pharmapanel Top100	-0.0271
small size	-0.0340
medium size	-0.0884
large size	-0.0748

x_K is the stock of physical capital, x_L is equal to the number of workers $p_k$is the rental price of x_K and p_L is the average wage. Source: our calculations based on Pharmapanel Top100.

The left-hand side graph of figure 3.2 plots the evolution of the dispersion of the logarithm of the capital/labor ratio and of the logarithm of the average wage (not deflated by the CPI). The remarkable fact documented in figure 3.2 is that, while the cross-firm dispersion of the capital/labor ratios has increased significantly during the period 1991-2004, the dispersion of wages remains almost constant. As mentioned before, this phenomenon is likely due the existence, in pharmaceutical sector as well as in the entire Italian manufacturing, of long-term labor contracts that provide a source of rigidity in wage. In fact, as measured by the intra-quartile range, the dispersion of the capital/labor ratio within the pharmaceutical industry appears fairly stable throughout the first half of the 90s', then it increases sharply and reaches a peak in 2000. In contrast, consistently with the transition towards a more flexible labor market, the path followed by the average wage, which is stable along nineties, started to exhibit more volatility only from 2002. In the period 2002-2004 we found an increased inequality both in wages, and in capital-labor.

The right-hand side panel shows that the average capital/labor ratio, for small firms in particular, has sharply increased. Therefore, we find an increasing heterogeneity not only between different size groups but also within groups.

Figure 3.2: Capital per worker



K is the stock of physical capital, L is the number of workers.
Source: our calculations based on Pharmapanel Top100.

3.4.2 Estimation

In order to evaluate the demand factors patterns of the Italian pharmaceutical industry, the restricted Generalized Leontief cost function is employed under two different specifications. The first, QFI(1), with one quasi-fixed input and the second, QFI(2), with two quasi-fixed inputs. Technology describes how variable inputs (e.g. services, materials, and labor in the first model tested), quasi-fixed inputs (capital, and labor in the second model tested), and a proxy to capture the impact of technical change are used to create output.

In line with the existing literature, we apply the technique of iterated *seemingly unrelated regressions* (Zellner[80]) in order to estimate the system of equations (3.3.11) and the *Euler equation* (3.3.9) presented in section 3.3.

Full results from the two alternative dynamic models with static expectations are presented in the appendix (see tables 3.10,3.11).

According to the economic theory, relative prices parameters α_{ij} are largely positive, even if sometimes non-significant. The parameters δ_{it} of the technological change are generally negative. This result shows that most of the firms in the sample, during the period 1991-2004, have applied factor saving procedures, except for those of small size and Italian nationality.[12] Actually, in an environment where physical capital complements labor, innovative procedures presumably require increasing demand for (high skilled) workers and services, at least in the short-run. The interaction

[12]The 55.4% of the Italian companies in Pharmapanel Top100 are small size.

between input prices and the stock of quasi-fixed input, captured by δ_{ik}, presents different results according to the model implemented.

The estimation of the two models used to test the effective rigidity of labor provides results consistent with our set of assumptions. The regularity conditions hold under both specifications, yet under the QFI(2) model we obtain better results with respect to $\partial\tilde{G}/\partial x_k$ and $\partial^2\tilde{G}/\partial x_k^2$ (see tables 3.5-3.6). The global fit is higher in the QFI(2) model, and the parameter $\gamma_{L\Delta L}$, that catches directly the labor adjustment effects, is significant and negative.

Elasticities

The best global fit and the lower values of B.I.C. (see table 3.8) are not the only reasons to consider the QFI(2) model the better to interpret the Italian case. Further useful insights arise from the assessment carried out through the elasticity estimates (tables 3.7).

In both models, the intermediate input demand and the labor demand are much more responsive to the scale of production than to their own prices, regardless of the model implemented. In contrast, short-run and long-run changes in demand of services seem to depend more on their price then on production level. These results are consistent with the existence of economy of scale especially for small-size companies (see tables 3.5-3.6).[13]

[13]Short-run price and substitution elasticities of capital in QFI(1) model and capital and labor in QFI(2) model with respect to the other inputs are zero by definition because they are evaluated for a constant value of the quasi-fixed input.

Table 3.5: QFI(1) model, regularity conditions

	Pharmapanel Top100	**Small size**	**Medium size**	**Large size**
$\tilde{G} > 0$	100.0%	100.0%	100.0%	100.0%
$d\tilde{G}/dp_L > 0$	79.4%	67.6%	91.0%	80.5%
$d\tilde{G}/dp_S > 0$	78.7%	66.6%	93.4%	72.6%
$d\tilde{G}/dp_I > 0$	83.0%	67.2%	99.0%	83.2%
$d\tilde{G}/dY > 0$	51.8%	16.7%	95.2%	31.9%
$d\tilde{G}/dt < 0$	17.0%	0.0%	33.0%	18.0%
not all $dx_k/dY > 0$	100%	100%	100%	100%
$d\tilde{G}/dx_K < 0$	100%	100%	100%	100%
$d^2\tilde{G}/dx_K^2 > 0$	50.9%	46.1%	45.0%	78.8%

When considered as a variable input, labor exhibits a short-run own-price elasticity that indicates a relative degree of responsiveness that tends to disappear in the long-run under both specifications.

The elasticity of the demand for physical capital with respect to its own price exhibits values less than 1 under both specifications. Only the one evaluated when labor is treated as quasi-fixed input is consistent with economic theory.

As the scale of production increases, interesting results are provided by the values of ε_{LY} that emphasizes the differences between the two specification implemented. In the QFI(1) model, labor appears very sensitive to changes in output: in the short run, a unit increase in Y reduces significantly the labor demand (around 13%). The reason of such a high and non-realistic level of ε_{LY} is that in QFI(1) labor is a variable input, then when firms experimented a negative shock - e.g. the *pharma bribery scandal* - that remarkably reduced the output level (see left graph of figure 3.3 in appendix) the effect on labor demand is considerably overestimated. At the opposite, in the long run, values of ε_{LY} strengthen the idea that Italian firms have applied labor saving procedures and that labor demand adjusts slowly.

The QFI(2) model moving from the assumption that labor is a quasi-fixed input displays a slightly different pattern. Indeed, even though positive (the mean of the ε_{LY} is less than unit while the median value is null), the elasticity witnesses the labor input relative rigidity.

Production level exerts a slight effect also on capital demand. Indeed the mean value of ε_{KY} is

Table 3.6: QFI(2) model, regularity conditions

	Pharmapanel Top100	**Small size**	**Medium size**	**Large size**
$\tilde{G} > 0$	100%	100%	100%	100%
$d\tilde{G}/dp_S > 0$	56%	63%	47%	61%
$d\tilde{G}/dp_I > 0$	69%	68%	66%	81%
$d\tilde{G}/dY > 0$	58%	17%	86%	91%
$d\tilde{G}/dt < 0$	80.6%	99.7%	66.8%	66.4%
$dx_L/dp_L < 0$	88%	86%	91%	84%
not all $dx_k/dY > 0$	100%	100%	100%	100%
$d\tilde{G}/dx_K < 0$	100%	100%	100%	100%
$d\tilde{G}/dx_L < 0$	100%	100%	100%	100%
$d^2\tilde{G}/dx_K^2 > 0$	70.1%	99.7%	74.4%	91.2%
$d^2\tilde{G}/dx_L^2 > 0$	90.2%	57.7%	99.7%	41.6%

Note: percentages in tables 3.5-3.6 indicate the times in which regularity conditions have been satisfied along the period 1991-2004. Source: our calculations based on Pharmapanel Top100.

equal to 0.594 (median 0.177) in the QFI(1) model and is close to zero, 0.153 (median 0.100), in the QFI(2) model. These results are presumably due to the numbers of years taken into account. In fact, thirteen years may be not enough to capture physical capital adjustments in manufacturing.

Cross-price elasticities indicate a high substitutability between materials and labor in the short-run. Finally, according to the theory, we have found that the intermediate input and services own-price elasticities, ε_{II} and ε_{SS} show negative values.

3.5 Concluding remarks

In this paper a restricted Generalized Leontief function with multiple quasi-fixed inputs has been applied using a novel firm-level panel data. Two different specifications have been tested in order to analyze the productive behavior of the top hundred pharmaceutical companies operating in Italy, ranked by revenue.[14] The econometric analysis provides important insights on the relationship between input substitution patterns and firms' performances. Although the two models can not be directly compared (statistically), since they are not nested, important questions are addressed

[14]We also use the number of workers as a proxy for firm size, without any significant change in the results.

Table 3.7: Short-run and long-run selected elasticities

	Short Run					
	QFI(1) model			**QFI(2) model**		
	Mean	Median	Std.Dev	Mean	Median	Std.Dev
ε_{LL}	-1.341	-0.143	2.437			
ε_{LS}	0.318	0.300	0.501			
ε_{LI}	0.962	-0.066	2.283			
ε_{SS}	-6.263	-0.711	21.780	0.689	4.086	85.843
ε_{II}	-4.286	-0.591	9.601	-0.575	1.908	7.387
ε_{LY}	-13.911	-3.155	24.725			
ε_{SY}	-4.876	0.210	16.346	3.857	0.952	57.764
ε_{IY}	-5.398	-0.262	12.389	0.019	0.847	3.474
	Long Run					
	QFI(1) model			**QFI(2) model**		
	Mean	Median	Std.Dev	Mean	Median	Std.Dev
ε_{LL}	0.316	0.460	0.942	0.027	0.000	0.439
ε_{LY}	-1.060	0.467	1.642	0.723	0.000	16.590
ε_{IY}	1.466	0.987	1.714	-4.908	1.416	70.994
ε_{CL}	0.991	0.000	0.696	0.327	0.000	4.720
ε_{CC}	0.053	0.000	0.459	-0.417	-0.336	0.367
ε_{CY}	0.594	0.177	0.135	0.153	0.100	1.100
ε_{GY}	0.052	0.000	0.504	0.501	0.364	1.442

Source: our calculations based on Pharmapanel Top100.

Table 3.8: Comparing models

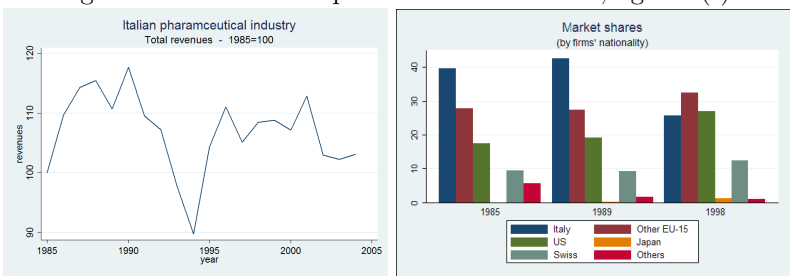
Model	**Schwarz B.I.C.**
QFI(1)-short run	5970.41
QFI(1)-long run	6182.84
QFI(2)-short run	2885.07
QFI(2)-long run	2834.32

Source: our calculations based on Pharmapanel Top100.

by comparing the elasticities. In particular, three main results emerge: i) significant returns to scale ($\varepsilon_{GY} < 1$) have been found under both specification; ii) cross-prices elasticities suggest a general substitution pattern among capital and labor that is more slight in the QFI(2) model; iii) estimations confirm the *a priori* on the labor market rigidity. The QFI(2) model provides a better interpretation of the labor demand in this sector and elasticities more consistent with the economic theory. Moreover, from an econometric standpoint, the QFI(2) model exhibits a better global fit and lower values of Schwarz B.I.C. both in the short run and in the long run.

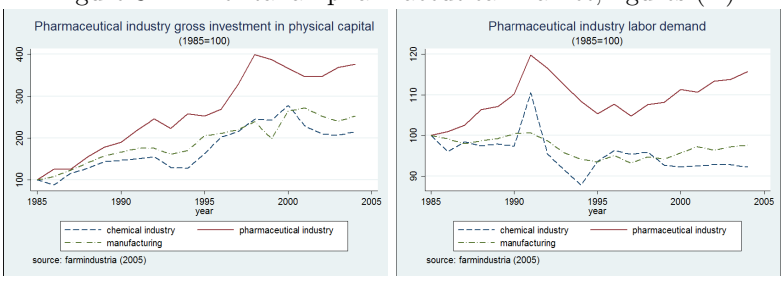
3.6 Appendix

Figure 3.3: The Italian pharmaceutical market, figures (I)



Source: our calculations based on Farmindustria [67] (left panel). Our calculations based on Pammolli et alii [78] (right panel)

Figure 3.4: The Italian pharmaceutical market, figures (II)



Classification of firms and sectors adopted in ISTAT Surveys apply. Source: our calculations based on Farmindustria [67]

Table 3.9: Pharmapanel Top100, disaggregation

	Italian	**MNE**	**Total**
Large size	47	66	113
Medium size	174	115	289
Small size	169	124	293
Pharmapanel Top100	390	305	695

Notation: Large size *= (avg.) total revenues > 300 millions euros.* Medium size *= 300 millions euros < (avg.) total revenues < 60 millions euros.* Small size *= (avg.) total revenues < 60 millions euros. Source: our calculations based on* Pharmapanel Top100.

Table 3.10: Estimations (I)

SUR Estimations					
QFI(1) model			**QFI(2) model**		
Parameter	Estimate	P-value	Parameter	Estimate	P-value
$\alpha_{SS}1$	6.662	[.810]	$\alpha_{SS}1$	8.402	[.743]
$\alpha_{SS}2$	7.141	[.620]	$\alpha_{SS}2$	15.214	[.243]
$\alpha_{SS}3$	-4.098	[.747]	$\alpha_{SS}3$	-0.548	[.962]
$\alpha_{SS}4$	0.566	[.979]	$\alpha_{SS}4$	8.781	[.646]
$\alpha_{SS}5$	5.396	[.719]	$\alpha_{SS}5$	11.336	[.401]
$\alpha_{SS}6$	-2.824	[.823]	$\alpha_{SS}6$	21.515	[.061]
α_{SI} 1	-1.743	[.941]	α_{SI} 1	1.114	[.959]
α_{SI} 2	-1.870	[.874]	α_{SI} 2	-2.222	[.832]
α_{SI} 3	10.851	[.310]	α_{SI} 3	13.710	[.152]
α_{SI} 4	-0.215	[.991]	α_{SI} 4	-0.706	[.965]
α_{SI} 5	-0.023	[.999]	α_{SI} 5	0.336	[.977]
α_{SI} 6	9.021	[.418]	α_{SI} 6	-0.636	[.949]
α_{SL} 1	-0.119	[.971]	$\delta_{SL}1$	-0.093	[.944]
α_{SL} 2	-0.304	[.730]	$\delta_{SL}2$	-0.868	[.054]
α_{SL} 3	0.646	[.072]	$\delta_{SL}3$	-0.921	[.000]
α_{SL} 4	5.607	[.060]	$\delta_{SL}4$	-1.122	[.000]
α_{SL} 5	-0.696	[.585]	$\delta_{SL}5$	-0.583	[.056]
α_{SL} 6	2.973	[.002]	$\delta_{SL}6$	-2.322	[.000]
$\delta_{ST}1$	-2.576	[.425]	$\delta_{ST}1$	-9.020	[.005]
$\delta_{ST}2$	-3.660	[.179]	$\delta_{ST}2$	-9.820	[.000]
$\delta_{ST}3$	2.838	[.286]	$\delta_{ST}3$	-4.454	[.098]
$\delta_{ST}4$	-1.714	[.559]	$\delta_{ST}4$	-8.812	[.003]
$\delta_{ST}5$	-3.465	[.195]	$\delta_{ST}5$	-9.325	[.001]
$\delta_{ST}6$	1.054	[.674]	$\delta_{ST}6$	-5.203	[.041]
$\delta_{SY}1$	-0.165	[.848]	$\delta_{SY}1$	1.031	[.283]
$\delta_{SY}2$	0.480	[.530]	$\delta_{SY}2$	0.953	[.231]
$\delta_{SY}3$	-11.269	[.000]	$\delta_{SY}3$	-7.702	[.000]
$\delta_{SY}4$	-0.637	[.440]	$\delta_{SY}4$	1.231	[.187]
$\delta_{SY}5$	0.405	[.601]	$\delta_{SY}5$	0.847	[.293]
$\delta_{SY}6$	-8.757	[.000]	$\delta_{SY}6$	-9.186	[.000]
$\delta_{S\Delta K}$	-0.025	[.730]	$\delta_{S\Delta K}$	0.010	[.000]
$\delta_{SK}1$	0.346	[.089]	$\delta_{SK}1$	-0.167	[.000]
$\delta_{SK}2$	0.147	[.000]	$\delta_{SK}2$	-0.050	[.000]
$\delta_{SK}3$	0.182	[.000]	$\delta_{SK}3$	-0.026	[.001]
$\delta_{SK}4$	0.657	[.000]	$\delta_{SK}4$	-0.144	[.000]
$\delta_{SK}5$	0.134	[.000]	$\delta_{SK}5$	-0.044	[.000]
$\delta_{SK}6$	0.191	[.000]	$\delta_{SK}6$	-0.030	[.002]
α_{IL} 1	-0.569	[.908]	$\delta_{IL}1$	-1.511	[.259]
α_{IL} 2	-0.243	[.860]	$\delta_{IL}2$	-1.053	[.016]
α_{IL} 3	-0.132	[.764]	$\delta_{IL}3$	-0.770	[.000]
α_{IL} 4	12.183	[.006]	$\delta_{IL}4$	-0.693	[.001]
α_{IL} 5	-0.154	[.937]	$\delta_{IL}5$	-1.279	[.000]
α_{IL} 6	8.074	[.000]	$\delta_{IL}6$	0.194	[.279]
α_{II} 1	7.551	[.736]	α_{II} 1	10.247	[.606]
α_{II} 2	6.757	[.566]	α_{II} 2	14.657	[.162]
α_{II} 3	0.659	[.950]	α_{II} 3	2.718	[.772]
α_{II} 4	-2.855	[.876]	α_{II} 4	8.208	[.597]
α_{II} 5	5.006	[.687]	α_{II} 5	12.011	[.274]
α_{II} 6	0.797	[.939]	α_{II} 6	19.568	[.037]

Notation: 1) large size national firms; 2) medium size national firms; 3) small size national firms; 4) large size multinational firms; 5) medium size multinational firms; 6)small size multinational firms.

Table 3.11: Estimations (II)

SUR Estimations					
QFI(1) model			**QFI(2) model**		
Parameter	Estimate	P-value	Parameter	Estimate	P-value
$\delta_{IT}1$	-2.496	[.492]	$\delta_{IT}1$	-9.184	[.007]
$\delta_{IT}2$	-3.434	[.213]	$\delta_{IT}2$	-9.508	[.000]
$\delta_{IT}3$	4.861	[.081]	$\delta_{IT}3$	-2.891	[.295]
$\delta_{IT}4$	-1.772	[.590]	$\delta_{IT}4$	-8.745	[.004]
$\delta_{IT}5$	-3.470	[.224]	$\delta_{IT}5$	-9.196	[.001]
$\delta_{IT}6$	7.693	[.005]	$\delta_{IT}6$	-1.300	[.630]
$\delta_{IY}1$	-0.174	[.853]	$\delta_{IY}1$	1.075	[.278]
$\delta_{IY}2$	0.493	[.560]	$\delta_{IY}2$	1.033	[.217]
$\delta_{IY}3$	-16.446	[.000]	$\delta_{IY}3$	-11.794	[.000]
$\delta_{IY}4$	-0.837	[.344]	$\delta_{IY}4$	1.354	[.157]
$\delta_{IY}5$	0.451	[.608]	$\delta_{IY}5$	0.811	[.343]
$\delta_{IY}6$	-22.924	[.000]	$\delta_{IY}6$	-14.605	[.000]
$\delta_{I\Delta K2}$	-0.019	[.764]	$\delta_{I\Delta K2}$	-0.011	[.000]
$\delta_{IK}1$	-0.480	[.022]	$\delta_{IK}1$	0.148	[.002]
$\delta_{IK}2$	-0.153	[.000]	$\delta_{IK}2$	0.033	[.000]
$\delta_{IK}3$	-0.194	[.000]	$\delta_{IK}3$	8.72S-03	[.210]
$\delta_{IK}4$	-0.867	[.000]	$\delta_{IK}4$	0.125	[.000]
$\delta_{IK}5$	-0.124	[.000]	$\delta_{IK}5$	0.027	[.000]
$\delta_{IK}6$	-0.193	[.000]	$\delta_{IK}6$	0.012	[.173]
α_{LL} 1	5.993	[.776]	γ_{KY}	0.032	[.491]
α_{LL} 2	5.417	[.616]	γ_{LY}	0.144	[.000]
α_{LL} 3	22.175	[.022]	$\gamma_{L\Delta L}$	-0.037	[.083]
α_{LL} 4	32.998	[.043]	δ_{LL}	0.176	[.000]
α_{LL} 5	5.371	[.629]	δ_{KK}	-0.499	[.000]
α_{LL} 6	11.866	[.225]	δ_{KL}	0.162	[.000]
$\delta_{LT}1$	-2.644	[.718]	$\delta_{S\Delta L}$	0.034	[.487]
$\delta_{LT}2$	-3.316	[.402]	$\delta_{I\Delta L}$	-0.059	[.271]
$\delta_{LT}3$	12.942	[.001]	$\gamma_{T\Delta L}$	-8.61E-03	[.002]
$\delta_{LT}4$	1.037	[.866]	$\gamma_{Y\Delta L}$	4.13E-03	[.000]
$\gamma_{Y\Delta K}$	-2.97E-05	[.649]	$\gamma_{Y\Delta K}$	-6.96E-06	[.000]
γ_{YY}	0.076	[.089]	γ_{YY}	-5.61E-03	[.828]
γ_{TY}	-0.161	[.223]	γ_{TY}	-0.073	[.286]
γ_{TT}	0.767	[.091]	γ_{TT}	0.902	[.000]
γ_{TK}	-3.88E-03	[.000]	γ_{TK}	2.85E-03	[.000]
$\gamma_{T\Delta K}$	2.21E-03	[.033]	$\gamma_{T\Delta K}$	2.69E-05	[.000]
γ_{KY}	6.61E-06	[.972]	γ_{KY}	-1.96E-04	[.004]
$\gamma_{K\Delta K}$	2.17E-03	[.356]	$\gamma_{K\Delta K}$	-1.28E-04	[.004]
$\delta_{LT}5$	-2.747	[.535]			
$\delta_{LT}6$	11.863	[.003]			
$\delta_{LY}1$	-0.139	[.928]			
$\delta_{LY}2$	0.279	[.852]			
$\delta_{LY}3$	-35.440	[.000]			
$\delta_{LY}4$	-8.160	[.000]			
$\delta_{LY}5$	-0.117	[.944]			
$\delta_{LY}6$	-31.045	[.000]			
$\delta_{L\Delta K}$	-2.75E-03	[.741]			
δ_{KK}	-0.647	[.000]			
$\delta_{LK}1$	0.138	[.003]			
$\delta_{LK}2$	0.038	[.000]			
$\delta_{LK}3$	0.046	[.000]			
$\delta_{LK}4$	0.227	[.000]			
$\delta_{LK}5$	0.025	[.000]			
$\delta_{LK}6$	0.035	[.000]			

Notation: 1) large size national firms; 2) medium size national firms; 3) small size national firms; 4) large size multinational firms; 5) medium size multinational firms; 6)small size multinational firms.

Table A.4: QFI(1) model *versus* QFI(2) model

QFI(1) model

Dependent variable: $\frac{v_L}{Y}$			
Mean of dep. var.	5.21184	Std. error of regression	17.8762
Std. dev. of dep. var.	22.9291	R-squared	0.395179
Sum of squared residuals	221775	LM het. test	8.86965 [.003]
Variance of residuals	319.56	Durbin-Watson	1.4235
Dependent variable: $\frac{v_S}{Y}$			
Mean of dep. var.	1.26042	Std. error of regression	3.56282
Std. dev. of dep. var.	4.4179	R-squared	0.456939
Sum of squared residuals	8809.41	LM het. test	70.9963 [.000]
Variance of residuals	12.6937	Durbin-Watson	0.757202
Dependent variable: $\frac{v_I}{Y}$			
Mean of dep. var.	2.71918	Std. error of regression	6.06963
Std. dev. of dep. var.	9.4487	R-squared	0.601098
Sum of squared residuals	25567.3	LM het. test	153.912 [.000]
Variance of residuals	36.8404	Durbin-Watson	0.59381
Dependent variable: p_K			
Mean of dep. var.	0.993294	Std. error of regression	0.092055
Std. dev. of dep. var.	0.041722	R-squared	0.14784
Sum of squared residuals	5.88099	LM het. test	137.804 [.000]
Variance of residuals	0.847405 E-02	Durbin-Watson	1.01128

QFI(2) model

Dependent variable: p_L			
Mean of dep. var.	1.07105	Std. error of regression	0.777691
Std. dev. of dep. var.	0.702944	R-squared	0.085848
Sum of squared residuals	419.734	LM het. test	9.26978 [.002]
Variance of residuals	0.604804	Durbin-Watson	1.18327
Dependent variable: $\frac{v_S}{Y}$			
Mean of dep. var.	1.26042	Std. error of regression	3.24183
Std. dev. of dep. var.	4.4179	R-squared	0.513907
Sum of squared residuals	7293.56	LM het. test	22.5817 [.000]
Variance of residuals	10.5095	Durbin-Watson	0.687794
Dependent variable: $\frac{v_I}{Y}$			
Mean of dep. var.	2.71918	Std. error of regression	4.71488
Std. dev. of dep. var.	9.4487	R-squared	0.751411
Sum of squared residuals	15427.7	LM het. test	119.375 [.000]
Variance of residuals	22.2301	Durbin-Watson	0.656393
Dependent variable: p_K			
Mean of dep. var.	0.993294	Std. error of regression	0.019092
Std. dev. of dep. var.	0.041722	R-squared	0.884992
Sum of squared residuals	0.252957	LM het. test	91.8647 [.000]
Variance of residuals	3.64E-04	Durbin-Watson	1.19063

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