Pharmaceutical Price Controls and Minimum Efficacy Regulation: Evidence from the United States and Italy

Vincenzo Atella, Jay Bhattacharya, and Lorenzo Carbonari

Objective. This article examines the relationship between drug price and drug quality and how it varies across two of the most common regulatory regimes in the pharmaceutical market: minimum efficacy standards (MES) and a mix of MES and price control mechanisms (MES + PC).

Data Sources. Our primary data source is the Tufts-New England Medical Center-Cost Effectiveness Analysis Registry which have been merged with price data taken from MEPS (for the United States) and AIFA (for Italy).

Study Design. Through a simple model of adverse selection we model the interaction between firms, heterogeneous buyers, and the regulator.

Principal Findings. The theoretical analysis provides two results. First, an MES regime provides greater incentives to produce high-quality drugs. Second, an MES + PC mix reduces the difference in price between the highest and lowest quality drugs on the market.

Conclusion. The empirical analysis based on United States and Italian data corroborates these results.

Key Words. Pharmaceutical market, regulation, innovation

Regulation plays a crucial role in the pharmaceutical market. The rationale behind regulation is dual: to guarantee and improve patient health and safety and to limit expenditures (especially public expenditures) 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 (e.g., Italy, France, Spain). In such an environment, regulatory agencies generally articulate three objectives, though authorities rarely explicitly define acceptable trade-offs among them: drug quality, access, and expenditure control (Maynard and Bloor 2003). In the United States, without

national health insurance, this interaction is limited to ensuring patient health and safety.

Our goal is to investigate how regulatory schemes affect the relationship between price and quality in the pharmaceutical market. We develop a simple model in which pharmaceutical companies charge different prices to heterogeneous consumers for innovative drugs. Buyers differ in their *willingness-to-pay* for quality (efficacy). We then derive equilibria under two regulatory regimes: (1) a regime with minimum efficacy standards (MES) and (2) a MES regime combined with a drug price controls (MES + PC). The first regime models the regulatory structure of the pharmaceutical market in the United States, while the second models the structure in many other countries, including specifically 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. This article thus presents a unified model of drug regulation, drug prices, and drug quality applicable to multiple countries. We test some of our theoretical predictions using drug market data from United States and Italy. To do so, we develop a novel method for measuring drug quality from a database of randomized clinical trials. Our findings have important implications for drug regulation policy, which we explore in the final section of the article.

BACKGROUND

Minimum quality standards are among the regulator's most important tools. When an innovative compound is developed, the pharmaceutical firm submits an application for marketing authorization. The firm is then required to extensively evaluate the safety and efficacy of the new compound. Only a small fraction of the compounds tested in laboratories will end up in human trials, and only a fraction of those will be approved by European Medicines Agency (EMA), in the EU, or by the Food and Drug Administration (FDA), in the United States. Both the FDA and the EMA require companies to establish safety, efficacy, and sound manufacturing of new products for licens-

Address correspondence to Vincenzo Atella, MSc, Associate Professor, University of Rome "Tor Vergata," Via Columbia 2, Rome 00133, Italy; e-mail: atella@uniroma2.it. Jay Bhattacharya, Ph.D., is Associate Professor at the Center for Primary Care and Outcomes Research (PCOR), Stanford University School of Medicine, Encina Commons, CA. Lorenzo Carbonari, Ph.D., is Assistant Professor at the University of Rome, Rome, Italy.

ing. 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 MES efficacy.

Once the product is marketed, several other requirements are imposed to allow for reimbursement by public programs. Several forms of price controls (e.g., price ceilings, reference pricing, rate of return, and so on) can be imposed together with positive and negative lists.² Therefore, regulation can have a substantial impact on the portfolio of drugs available in a market as well as on drug prices. On the most innovative drugs, the regulatory environment can have substantial upstream effects by altering incentives for drug development (Peltzman 1973).

The extent of price controls on drugs also differs considerably across countries.³ Countries such as Germany allow price freedom only for innovative drugs. In the United States prices are free, but Health Maintenance Organizations (HMOs) and other Pharmacy Benefit Managers (PBMs) create formularies of “preferred” drugs that physicians and patients are encouraged to use via price incentives.⁴ Countries such as Italy, France, and Spain provide examples of regulatory frameworks that deter pharmaceutical companies from charging high prices. Drug prices are set through negotiation between the government and industry; firms must agree to the final price to obtain reimbursement from public health insurance.

THE MODEL

In this section, we provide a description of our approach to modeling regulation of the market for pharmaceutical products.⁵ Our approach is an application of the Rothschild and Stiglitz (1976) model of asymmetric information to the pharmaceutical market. Here, we are interested in how regulation affects the quality of drugs that ultimately end up on the market and how regulation affects the prices of those drugs. Throughout, we maintain the assumption that firms have some degree of control over the quality (measured here by efficacy) of the drugs they produce, and that greater investments in research produce higher quality drugs. While the model makes simplifications for analytic convenience (e.g., the model only allows two drugs on the market), it has observable implications for what we should expect to find in real world markets. After

developing the model, we consider how the introduction of price controls and MES changes the model outcomes.

There is a third possible regulatory structure in which purchasers negotiate with pharmaceutical companies over prices. This structure is intermediate between the two cases that we consider. In the MES alone setting, firms decide prices without any direct regulatory oversight, while in the price control plus MES setting, purchasers determine prices via regulators. Since a structure that features negotiation is intermediate between the cases we do consider, we do not discuss this regulatory setting further.

A Model of Limited Information

The first key idea is that buyers differ in their demand for drug efficacy. For reasons having to do with analytic and expositional simplicity, we model this idea by allowing two types of buyers: a high type who is willing to pay a lot for a drug with a fixed level of efficacy, and a low type who is willing to pay less for the same drug. Buyers, regardless of type, choose drugs to maximize their own utility, subject to a budget constraint and to the drugs actually on offer in the market. The latter, we will see, depends on both information constraints facing drug sellers and on the regulatory regime.

The second key idea is that firms cannot distinguish between high and low-type buyers when they offer a drug for sale on the market. If firms could perfectly discriminate, it would extract the entire surplus from each group of buyers. It would offer a highly efficacious drug and sell it at a very high price, which low-type buyers would eschew. It would also offer a less efficacious drug at a low price that would attract low-type buyers. Socially optimal efficacy levels that equate (private) marginal benefits from drug consumption with the marginal costs (which includes R&D costs) of producing a drug at a given efficacy level would ensue.

However, because firms cannot distinguish between buyer types when selling drugs, this first-best optimum is impossible. The problem is that high-type buyers will “masquerade” as low-type buyers and purchase low efficacy drugs rather than the high efficacy drugs that are aimed at them. At equilibrium prices, low efficacy drugs will be priced so low and high efficacy drugs so high, that high-type buyers will prefer the former to the latter. Firms that follow this strategy will lose money.

What is possible, instead, is a separating equilibrium in which firms still offer a high efficacy drug and a low efficacy drug. In this equilibrium, the high efficacy drug is still offered at the same price and efficacy level as in the full

information case, but the low efficacy drug is at a lower efficacy level than the full information case. This is an equilibrium because the high types do not prefer the worse low efficacy drug over the high efficacy drug at equilibrium prices, while the low types still prefer the low efficacy over the high efficacy drug. In effect, the high types impose a negative externality on the low types in this model; if there were no high types on the market, the low types would have access to a better low efficacy drug at the same price.

The Effects of Regulation

A bit of notation will be useful for the remainder of the discussion in this section. Let $\{e_L^{SB}, p_L^{SB}\}$ be the efficacy level and price of the low (L) efficacy drug in the separating equilibrium and let $\{e_H^{SB}, p_H^{SB}\}$ be the efficacy level and price of the high (H) efficacy drug. “ SB ” here stands for second-best, since the first-best equilibrium is impossible due to information constraints.

Different regulatory schemes alter equilibrium drug quality and prices. We analyze two regulatory approaches: minimum drug efficacy standards and price control regulation. We start with a market where regulation requires minimum drug efficacy, but no pure price controls, such as in the United States. 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 *MES* scheme.

Suppose that the government fixes the efficacy requirement $\underline{e}$ such that: e_L^{SB} . That is, the MES binds on the low efficacy drug, but not the high efficacy drug. In this regulatory setting, there is still a separating equilibrium, with a high efficacy— $\{\tilde{e}_H, \tilde{p}_H\}$ —and a low efficacy drug— $\{\tilde{e}_L, \tilde{p}_L\}$. Perhaps unsurprisingly, the regulation does not affect the efficacy level of the high-type drug relative to the unregulated limited information market, $\tilde{e}_H = e_H^{SB}$. However, the efficacy of the low efficacy drug is increased to meet the MES, $\tilde{e}_L = \underline{e} > e_L^{SB}$. The price of the low efficacy drug similarly must rise to cover the marginal costs of production, $\tilde{p}_L > p_L^{SB}$. Finally, the price of the high efficacy drug must decrease in equilibrium, or else the high efficacy drug would no longer be attractive to the high-type buyers, $\tilde{p}_H < p_H^{SB}$.

The imposition of a just-binding MES increases the welfare of the low-type buyers, since they would prefer a better low efficacy drug than is available in the unregulated market. And it certainly will not harm the high-type buyers since it does not change the efficacy of the high-type drug and may lower its price somewhat. However, a sufficiently restrictive MES may reduce welfare

because it imposes higher costs on research and development. At an extreme, if regulation imposes too high standards, prices could rise to a point where L -type buyers are excluded from the market. There exists a minimum efficacy threshold that optimally balances the higher R&D costs with the higher efficacy drugs delivered to low-type buyers. This optimal level is just below the level that excludes low-type buyer from the market.

We turn next to the effect of a regulatory scheme that includes MES and price controls (MES + PC). We model a price control as a fixed price level, $\hat{p}$, imposed exogenously by the government, above which it is illegal to sell drugs. We consider a price control that binds on the high-type drug, but not on the low-type drug— $\hat{p}_L^{SB}$. This is similar in spirit to many price control regimes in Europe, and in particular it captures the form of price controls in place in Italy. Let $\{\hat{e}_L, \hat{p}_L\}$ be the efficacy-price pair for the low-type drug and let $\{\hat{e}_H, \hat{p}_H\}$ be the efficacy-price pair for the high-type drug in the separating equilibrium that occurs under MES + PC regulation.

Firms respond to the price control by producing high-type drugs that are lower in quality than they would be without any regulation or with just MES regulation— $\hat{e}_H$. The price of the high-type drug is correspondingly lower. The quality of the low-type drug will improve in this equilibrium to meet the MES, while the price of the low-type drug will increase to the level that would obtain under the MES alone regime. The welfare effects of the regulation are more complicated than in the MES alone case. Whether net welfare increases depends upon how binding is the price control and on the relative size of the two groups of buyers.⁶

Testable Implications of the Model

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

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

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

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

If we use the difference $(p_H - p_L)$ as a measure of price dispersion from our discussion above, it should be clear that the price difference between the highest and lowest quality drugs are greater under the MES regime than under the MES + PC regime. This is true because the binding price control in the MES + PC regime forces the high-type drug to be sold at a lower price (and of course to have a lower quality), while the binding efficacy control increases the price and quality of the low-type drug: $(\tilde{p}_H - \tilde{p}_L) > (\hat{p}_H - \hat{p}_L)$.

Testable prediction 3: Correlation between price and quality. There is a higher correlation between price and efficacy expected for low efficacy drugs under an MES regime than under an MES + PC regime. Moreover, if the difference in price between the high-type drug under the MES and MES + PC regimes is sufficiently high— $(\tilde{p}_H - \hat{p}) > (\tilde{e}_H - \hat{e}_H)$ —then the MES scheme provides also a higher correlation for the high efficacy drugs compared to MES + PC.

In general, the model predicts that the correlation between drug price and drug quality will be lower under an MES + PC regime than under an MES alone regime. This decreased correlation between price and quality is not only unambiguous for lower quality drugs but also pertains for higher quality drugs if the price control binds sufficiently tightly. From a policy perspective, this prediction of a diminished correlation between quality and price under an MES + PC regime is important because it suggests that price controls in the drug market would reduce the returns to firms from investing in research that produces higher quality in the first place.

EMPIRICAL ANALYSIS

The aim of this section is to test the predictions developed in the previous one. We have collected data on Italian and U.S. pharmaceutical markets, which represent two good examples of the regulatory regimes that we have discussed in our theoretical framework. In fact, while in both markets we observe a MES regime, only in United States prices are free to fluctuate. In Italy, several forms of price regulation apply.⁷

Unfortunately, no test of prediction 1 is possible in principle. Prediction 1 is about which sorts of drugs would be developed under different regulatory conditions in markets that never interact with each other. Of course, in reality, drugs developed under American regulation by an American firm are often sold in Italy and elsewhere around the world. Though Italy and United States represent two polar regulatory schemes, they effectively share the same fruits of research in drug development.

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, Wang, and Wang 2005). Mitchell (2007) reports that, between 2000 and 2005, 73 percent (52 drugs) of the new medicines approved in both the EU and the United States 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.⁸

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

Data

Our primary data source is the *Tufts—New England Medical Center—Cost Effectiveness Analysis Registry* which allows us to compare the cost-effectiveness of a broad range of interventions (among which drugs are the most studied) using standardized cost-utility ratios (see <https://research.tufts-nemc.org/cear/default.aspx>). The collection consists of detailed abstracted information on published cost-effectiveness studies from a wide range of fields, including *infectious diseases*, *cardiovascular diseases*, *muscular and rheumatological diseases*, *malignant neoplasms*, 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 U.S.\$) divided by the incremental health benefits quantified in terms of quality adjusted life years (QALYs).

Though there are important caveats to the QALY as a measure, it enables a standardized comparison of the benefits from different drugs, thus allowing us to measure the social value of an innovation in treatment.⁹ When the cost-effectiveness ratio is lower, more QALYs can be accrued per dollar spent: treatments with low levels of \$/QALY are preferred. Interventions that simultaneously reduce cost and improve health are defined as *cost-saving*. Poorly performing interventions that raise costs while causing harm to health status are defined as *dominated*. In our regressions, our key drug quality indicator (QI) is defined as one over the \$/QALY measure in the Tufts data. We have assigned the value zero to all *dominated* drugs, while the maximum value in the class has been given to the drugs defined as *cost-saving*. Inverting eases interpretation—a higher value of QI indicates a better drug.

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*. The size of our dataset equals the number of comparisons selected (132) times the number of products (brand names) available for each active ingredient in Italy (98 brand names) and United States (83 brand names). The final sample from this procedure contains 500 observations, of which 310 belong to the Italian market and 190 to the U.S. market. For each brand name we merge in the Italian and U.S. drug prices.¹⁰

We extracted the information on U.S. drugs' brand names from the FDA and Merck Manuals On Line Digital Library. We estimated U.S. prices using information from the Medical Expenditure Panel Survey (MEPS), which is a nationally representative dataset of Americans (<http://www.merck.com/mmhe/index.html>). 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 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 U.S.\$ per mg.¹¹ Finally, we collapse the dataset at the brand-name level. Summary statistics are reported in Table 1.

Testing Prediction 2: Price Variability

According to our theoretical model, we expect a lower price variability in Italy (a PC regime) than in the United States (a relatively free-price regime). We test

Table 1: Summary Statistics

<i>Variable</i>	<i>Mean</i>	<i>SD</i>	<i>Min</i>	<i>Max</i>
p	6.336	41.327	0.0002	445.6
$\log(p)$	-2.912	2.854	-8.517	6.1
\$/QALY	66,157	98,334	0	700,000
QI	0.014	0.031	1.43E-06	0.09
Generics	0.213	0.409	0	1

Notes. $N = 181$; each observation represents a molecule sold in the either the United States or Italy. That is, each molecule can generate either one or two observations.

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 used in outpatient settings only, obtained using data on prices and brand names provided by AIFA for Italy and by MEPS for United States.¹² Given that the types of active ingredients included in the AIFA and MEPS database are different, our first step was to obtain a common basket of active ingredients across the two countries.¹³ We then identified a list of common active ingredients in both databases and then selected all brand names within that list. Finally, we computed average price per milligram by brand name.

We find that U.S. drug prices have a higher variance in drug prices than Italian drug prices, independently of the dataset we use, thus confirming our theoretical prediction. In particular, the statistical analysis shows that the difference in price variances across the two countries is statistically significant at 1 percent level and that price variance in Italy is lower than price variance in United States (see Figures 1 and 2). Furthermore, in both samples, the United States has a higher average price per milligram than does Italy: 3.17 versus 1.30, in the Tuft sample, and 0.051 versus 0.026, in the larger sample.

Figure 1: Densities Plots of Price Distributions: Tufts Sample

Figure 2: Densities Plots of Price Distributions: MEPS-AIFA Sample

Testing Prediction 3: Correlation Between Efficacy and Price

To test the correlation between the log of price and QI we run the following OLS regression¹⁴:

$$\log(p_i) = \gamma_0 + \gamma_1 QI_i + \gamma_2 US_i + \gamma_3 USQI_i + \varepsilon_i, \quad (1)$$

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

The interpretation of equation (1) is straightforward. The value $(\gamma_1 + \gamma_3)$ measures the effect that quality has on drug price in United States. 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 United States.

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

Our main regression results are shown in Table 2. In the regression using the whole sample, we find that a positive relationship between quality

and price emerges in the United States ($(\gamma_1 + \gamma_3) > 0$ and statistically significant), with United States showing a stronger relationship than Italy ($\gamma_3 > 0$ and significant at .05). There is actually a negative relationship between drug price and drug quality in Italy, which suggests that price regulations there have created perverse incentives.

Similar results hold when we split the sample into *low* and *high* quality drugs, although some differences emerge depending on how we select the threshold to construct the subgroups. In particular, quality exerts a positive and statistically significant impact on price for *low* quality drugs in both the United States and Italy, but there is no statistically significant difference between the United States and Italy. For *high* quality drugs, there is a positive relationship between price and quality in the United States, but not in Italy. The difference in response for low quality drugs is only statistically significant when we set the high-low quality threshold at the median. Overall, we can conclude that in Italy price level seems to be less responsive to quality than it is in the United States. This is exactly what our model predicts.

As robustness check, we run a version of the model in which we include additional controls for the presence of *generic* versus *branded* drugs in the two markets. It is at least theoretically possible that the results in Table 2 are an artifact of differences between the two countries in sales of lower priced generic versions of the drugs. However, in practice we find that including drug-specific controls for generic market share in the regression does not qualitatively change our results. In these regressions, there is still a strong positive relationship between price and quality in the United States, but not in Italy,

Table 2: Regression Results and Tests

Variable	Overall Sample	Low Efficacy		High Efficacy	
		Below the Median	Below 75th Percentile	Over the Median	Over 75th Percentile
<i>QI</i>	−20.634*	16,800**	3,318**	−23.4**	−30.3**
<i>US</i>	−0.232	0.579	0.423	−0.034	0.017
<i>USQI</i>	27.878*	7,510.355	442.628	23.44**	23.370
Test H_0 : $QI + USQI = 0$	$F = 3.04$	$F = 4.43$	$F = 6.24$	$F = 2.59$	$F = 2.37$
	$p = .05$	$p = .014$	$p = .003$	$p = .08$	$p = .10$
<i>N</i>	175	80	121	86	43
Prediction 3	Corroborated	Partially corroborated		Corroborated	

Notes. Our calculation based on AIFA and MEPS data.

* $p < .1$,
** $p < .05$.

and for low quality drugs, there is a negative relationship in Italy. To save space do not include a table with these results, but it is available upon request from the authors.

CONCLUDING REMARKS

In this article, we have developed a framework to evaluate the welfare effects of two different types of drug regulation: MES and a mix of MES and price control scheme (MES + PS). Two main theoretical prediction stem from this model. First, the average drug quality delivered should be higher under the MES regime than in a regime that includes price controls. Second, MES + PC regulation reduces the difference in prices between high and low quality drug. Despite its simplicity, the model's predictions are confirmed in United States and Italian drug price and quality data.

We find that (1) there is more price variability in the United States (where drug prices are not controlled) than in Italy; and (2) there is a tighter correlation between drug prices and quality in the United States than there is in Italy. In fact, we find that the correlation between price and quality, as measured by standard measures of cost-effectiveness, is negative for drugs with the highest levels of cost-effectiveness in Italy, while the same correlation for the same set of drugs is positive in the United States.

Our results have implications for the proper regulation of pharmaceutical markets. Price controls deliver a mix of costs and benefits. On the benefit side of the ledger (apart from lower prices, which, all else equal, benefits patients) is a lower variance for any given set of drugs in the price of drugs. Most people favor social welfare functions that place a positive value on reducing the financial uncertainty associated with getting sick. Price controls deliver such reduced uncertainty by decreasing the variance in the price of drugs.

On the cost side of the ledger, price controls reduce the availability of the highest quality drugs. In addition, they limit the close link between drug quality and price that is present in a market without price controls. To the extent that developing high-quality drugs is more expensive than developing lower quality drugs, this reduced correlation further undercuts the incentives that pharmaceutical companies face to produce high-quality drugs.

While some aspects of the debate over price controls discussed in this paragraph are well known, an important contribution of this article is to highlight the reduction in the variance of drug prices and the reduction in the cor-

relation between price and quality of drugs caused by price controls. How policy makers and the population at large should value these costs and benefits is of course beyond our scope herein.

ACKNOWLEDGMENTS

Joint Acknowledgment/Disclosure Statement: The authors thank William Vogt, Rusty Tchernis, Alan Garber, and session participants at the American Economic Association meeting in 2010 and the Italian Economic Association meeting in 2010 for their helpful comments. Bhattacharya thanks the National Institute on Aging for partly funding his work on this project. The authors received no funding from any pharmaceutical company or any other agent with a financial interest in the findings of this study.

Disclosures: None.

Disclaimers: None.

NOTES

1. Pharmaceutical expenditures represent a substantial component of total health expenditures in all Organization for Economic Cooperation and Development (OECD) countries.
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 (2003).
4. Such price incentives for one or two preferred products within a group of therapeutic substitutes have increased the price elasticity of demand for drugs in the managed care sector in the United States. 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 United States) has required that drug manufacturers provide drugs at a 15 percent discount off the list price or the “best price” given to any private purchaser, whichever is less (Danzon and Chao 2000).
5. The Appendix S1 provides a formal description of our model, along with proofs of the key propositions. The interested reader can refer also to Atella, Bhattacharya, and Carbonari (2008).
6. Please see the Appendix S1 for details on this welfare calculation.
7. In Italy two different PC schemes coexist: the Average European Price (AEP)—for old products and *me-too* products—and a scheme based on price negotiation—for new medicines registered by EMEA or for all those drugs for which AEP cannot be implemented. A free price setting scheme exists in Italy for over-the-counter

- (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 2003).
8. 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 2007).
 9. See McGregor (2003) for a consideration of the strengths and methodological shortcomings of this measure.
 10. When the comparison involves a combination of active ingredients, we have computed the average price per milligram.
 11. The exchange rates used are from the Federal Reserve Bank of St. Louis.
 12. The use of this larger sample has been possible because the testing of this prediction does not involve information on drug quality (efficacy).
 13. Italian data concern all drugs belonging to classes A (fully reimbursed) and H (distributed through hospitals) and include 5,003 observations (brand names), while U.S. data concern all household prescription drugs and include 1,526 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, the MEPS dataset does not include vaccinations. On the contrary, the AIFA database collects all drugs available in the Italian market.
 14. We use the natural logarithm as a dependent variable to reduce the influence of outlier data points.

REFERENCES

- Atella, V., J. Bhattacharya, and L. Carbonari. 2008. "Pharmaceutical Industry, Drug Quality and Regulation: Evidence from US and Italy." National Bureau of Economic Research Working Paper 14567 [accessed October 4, 2010]. Available at: <http://www.nber.org/papers/w14567>.
- Danzon, P. M., and L. W. Chao. 2000. "Does Regulation Drive out Competition in Pharmaceutical Markets?" *Journal of Law and Economics* 43 (2): 311–57.
- Danzon, P. M., Y. R. Wang, and L. Wang. 2005. "The Impact of Price Regulation on the Launch Delay of New Drugs – Evidence from Twenty-Five Major Markets in the 1990s." *Journal of Health Economics* 14 (3): 269–92.
- Kanavos, P. 2003. "Overview of Pharmaceutical Pricing and Reimbursement Regulation in Europe." *Japanese Pharmacology and Therapeutics* 31 (10): 819–36.
- Maynard, A., and K. Bloor. 2003. "Dilemmas in Regulation of the Market for Pharmaceuticals." *Health Affairs* 22 (3): 31–41.
- McGregor, M. 2003. "Cost-Utility Analysis: Use QALYs Only with Great Caution." *Canadian Medical Association Journal* 168 (4): 433–4.
- Mitchell, P. 2007. "Price Controls Seen as Key to Europe's Drug Innovation Lag." *Nature Reviews Drug Discovery* 6: 257–8.

- Peltzman, S. 1973. "An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments." *Journal of Political Economy* 81 (5): 1049–91.
- Rothschild, M., and J. Stiglitz. 1976. "Equilibrium in Competitive Insurance Markets: An Essay on the Economics of Imperfect Information." *Quarterly Journal of Economics* 90 (4): 629–49.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Appendix SA1: Author Matrix.

Appendix S1: Consider a Market Where a Monopolistic Firm Sells Its Drugs to a Set of Heterogeneous Insurers and Providers.

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.