The Effects of Pharmaceutical Price Controls on the Cost and Quality of Medical Care: A Review of the Empirical Literature

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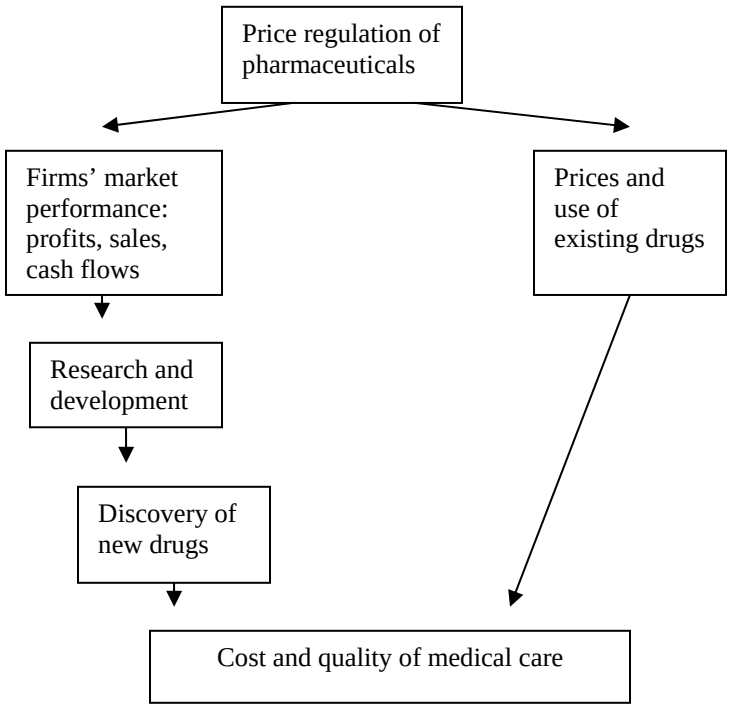
Introduction

In this essay, I review existing empirical studies of the effects government price regulation of pharmaceuticals on the cost and quality of medical care. As Figure 1 suggests, price regulation can affect cost and quality through two channels. It can affect cost and quality indirectly, by altering the incentives for pharmaceutical firms to engage in research and development (R&D) of new drugs. It can also affect cost and quality directly, by affecting the prices and use of existing drugs.

Figure 1: The Effects of Government Price Regulation of Pharmaceuticals on Cost and Quality



In summary, empirical research finds that price regulation has adverse effects on the cost and quality of medical care. This paper proceeds in five parts. Part I outlines the theoretical bases for the two key effects of price regulation. Part II reviews empirical research on the links between regulation, market performance, R&D, and the discovery of new drugs. Part III reviews empirical research on link between new drugs and the cost

and quality of medical care. Part IV reviews empirical research on the links between regulation, prices and use of existing drugs, and cost and quality. Part V concludes.

I. The two key effects of price regulation on the cost and quality of care

The primary goal of drug price regulation is to reduce expenditures by cutting prices. This may affect the cost and quality of care, and thus patient well-being, through two channels. In each case, the effects of price regulation on well-being are theoretically ambiguous.

First, regulation may affect cost and quality through its effects on R&D. Regulation-induced reductions in pharmaceutical expenditures mean lower profits and lower cash flows for pharmaceutical firms. Lower expected profits translate into a reduced supply of external capital, which translates into reduced investment. Holding profits constant, lower expected cash flows translate into a reduced supply of internal relative to external capital, which may independently reduce investment, to the extent that external capital markets are imperfect (Vernon 2004).

Reduced investment in R&D, in turn, may translate into fewer or less innovative new products. As Danzon (1997, Chapter 5) points out, the implementation of most forms of price regulation tends to intensify this effect. Regulators whose aim is to reduce drug expenditures focus disproportionately on products with high prices and/or volumes, but these targets also tend to be the most innovative. Furthermore, "reference pricing" systems also tend to be biased against innovative drugs, to the extent that the unregulated price of drugs within a reference group is positively correlated with their innovativeness.

If reduced R&D investment leads to fewer or different types of drug discoveries, there are two possible effects for society. On one hand, reduced R&D may lead to less cost-effective care. In this case, the costs imposed by regulation-induced reductions in R&D, in the form of higher mortality, morbidity, and/or expenditures on other forms of health care, would exceed the savings in R&D expenditures. On the other hand, reduced R&D may lead to more cost-effective care, if the savings in R&D expenditures exceeded the associated costs.

Second, regulation may affect cost and quality through prices and use of existing products. On one hand, lower regulated prices may lead to lower costs per use and therefore greater use, which may in turn lead to higher quality and lower overall costs of care. On the other hand, regulation may have unintended consequences for prices and use that mitigate or outweigh its intended benefits. Regulation may actually lead to increases in the prices of some products, which in turn may lead to lower quality and higher costs of care. In addition, lower regulated prices may reduce access to new drugs by leading firms to launch products later in regulated markets than they otherwise would, which would have similar adverse effects. As Danzon, Wang, and Wang (2003) explain, because low prices in one market may "spillover" to others, through parallel trade and external referencing, firms may prefer longer delay or non-launch to accepting a regulated price.

Because the magnitudes of these competing effects of regulation on patients' well-being are theoretically indeterminate, the effects of pharmaceutical price regulation have been studied extensively and are the subject of important policy debates. In the following sections, I summarize existing empirical research on this topic.

II. The links between price regulation, market performance, and innovation

An extensive empirical literature has examined the links in the pharmaceutical industry between regulation, market performance, R&D, and discovery of new drugs.[1] Studies examining the link between regulation and market performance find that regulation reduces the incentives for R&D. Ellison and Mullin (2001) assess the effect of regulation on pharmaceutical firms' market values with event studies of the effects of the evolution of President Clinton's health care reform proposal. They identify a 52.3 percent decline in market-adjusted pharmaceutical stock prices over the January 1992-October 1993 period, much of which occurred as the Clinton plan implicitly endorsed price regulation.

Vernon (2003) examines the relationship between price regulation and profit margins. Based on data on the world's 20 largest pharmaceutical firms from 1994-99, he finds a significant negative correlation between the proportion of a firm's sales subjected to price regulation, as measured by the proportion of sales from outside the US, and its pre-tax profit margins. In particular, he finds that a 10 percentage point increase in the proportion of sales from outside the US leads to a 2.7 to 3.5 percentage point decline (depending on specification) in profit margin. Vernon (2004) extends this analysis to show, in turn, that declines in a firm's profit margin from a high proportion of outside-the-US sales lead to declines in its R&D. He then simulates how global pharmaceutical R&D would respond to a new regulatory regime in which pharmaceutical prices in the US were regulated as they are currently regulated, on average, outside the US. He concludes that this regime would lead to a decline in industry R&D of between 23.4 and 32.7 percent.

[1] See Comanor (1986) for a review of older work.

In addition to reducing incentives for R&D through aggregate firm performance, regulation also reduces incentives for R&D by disproportionately affecting the prices of more innovative drugs (e.g., Danzon 1997, Chapter 5). Danzon and Chao (2000a) estimate the responsiveness of prices to two measures of innovativeness or therapeutic value -- the number of countries in which a molecule has been approved and molecule age. They classify countries as having more versus less stringent price regulation, based on the regulatory regime in effect in 1991-92. Based on IMS data on sales through retail pharmacies from 1991-92, they find that countries with more stringent price regulation have systematically lower prices for widely-approved molecules, holding constant molecule age; however, these countries also have systematically lower prices for older molecules, holding constant the number of countries in which the molecule has been approved. Danzon and Ketcham (2003) study the related question of the effects of more versus less stringent reference pricing systems on the prices of new drugs. They analyze data from Germany, the Netherlands, and New Zealand on the reference price and patient copayment at country-specific product launch date for all products with sales in the first half of 1998 in five major therapeutic categories (antiulcerants, hypoglycemics, antihyperlipidemics, antidepressants, and antihypertensives), for a total of 200 molecules. They find that the reference price of expensive versus inexpensive drugs in more stringent reference pricing systems is disproportionately lower than the analogous relative reference price in less stringent systems.

Changes in incentives for R&D, in turn, have a significant effect on firms' R&D investment decisions. Based on data on 14 firms from 1959-91, Gambardella (1995, Chapter 6) finds a significant positive effect of a firm's past sales on R&D. Scherer

(2001) finds a significant contemporaneous correlation between aggregate pharmaceutical margins and industry-level R&D from 1962-96. Based on aggregate data for major US pharmaceutical companies from 1952-2001, Giacotto, Santerre, and Vernon (2003) find that increases in real drug prices lead to increases in industry R&D, holding all else constant. They conduct simulations that indicate that the capitalized value of pharmaceutical R&D spending would have been about 30 percent lower if price regulation had limited the rate of growth of drug prices to the rate of overall price inflation, which would have resulted in 330 to 365 fewer new drugs discovered over that time period.

Grabowski and Vernon (2000) and Lichtenberg (2004c) use data on 11 firms from 1974-1994 and 55 firms from 1953-1996,[2] respectively, to isolate the independent effects of expected future profits and cash flows on R&D. Grabowski and Vernon measure expected future profits by industry-level sales of new chemical entities (NCEs) divided by real R&D expenditures and by industry-level profit margins; Lichtenberg measures expected future profits by firm-level market values. These two studies find that R&D responds positively to both factors, but that the effects of expected future profits are greater than the effects of cash flows.

Finally, R&D expenditures affect the rate of discovery of new drugs. Based on data on 28 firms from 1969-79, Jensen (1987) shows that R&D expenditures have a significant, positive effect on the number of NCEs discovered. In addition to affecting innovation through the *level* of R&D, regulation also affects innovation through the *return* to R&D. Gambardella, Orsenigo, and Pammolli (2000, Table 7) show that output

[2] Not all firms in the analysis in Lichtenberg (2004c) report data for all years; the total number of firm/year observations in this analysis is 872.

growth responds less to pharmaceutical R&D investment in countries with price regulation than in the US.

In a series of studies, DiMasi et al. (1991, 2003) quantify the "price" of innovation by estimating the expected costs of developing a new drug. Their most recent work analyzes confidential data from 10 pharmaceutical firms that account for 42 percent of the industry's total R&D expenditures. This research estimates the average out-of-pocket cost per new compound discovered during the 1990s to be $403 million (2000 dollars); capitalizing out-of-pocket costs to the point of marketing approval at a discount rate of 11 percent yields a total pre-approval cost of $802 million (2000 dollars). By comparison, DiMasi et al. (1991) reports that the average out-of-pocket cost per new compound for a random sample of 93 new compounds developed from 1970 to 1982 was $231 million (1987 dollars, capitalized to the point of marketing approval at a discount rate of 9 percent).

A related set of empirical studies estimates the effects of intellectual property protection on pharmaceutical R&D. This work is relevant because weaker intellectual property protection decreases pharmaceutical firms' expected returns from innovation just as price regulation does (e.g., Kremer 2003). For this reason, empirical estimates of the effects of intellectual property protection on R&D are a good proxy for the effects of regulation.

Pazderka (1999) investigates the impact of the strengthening of intellectual property rights in Canada on R&D in the Canadian pharmaceutical industry. After almost two decades of compulsory licensing of prescription drugs, Canada restored full patent protection in two steps taken in 1987 and 1992. Based on interindustry

comparisons of R&D in Canada, comparisons of Canadian pharmaceutical R&D to OECD averages, and trends in Canada's share of foreign R&D by US pharmaceutical firms, he finds relative increases in Canadian pharmaceutical R&D spending after 1987. Lanjouw and Cockburn (2001) find that stronger intellectual property protection in developing countries stimulates R&D on drugs that address those countries' health needs. Specifically, they find that increases in intellectual property protection in the 1980s in countries with a high incidence of malaria were accompanied by increases in research related to that disease. Hughes, Moore, and Snyder (2002) simulate the effects of the policy of eliminating all patent protection on prescription drugs, and find that society would lose $3 in benefits of innovation for every dollar gained due to easier access.

III. The link between pharmaceutical innovation and cost and quality of care

Empirical evidence shows that both the discovery and use of pharmaceuticals – particularly new or novel compounds – lead to lower medical expenditures and improved health outcomes.[3] Lichtenberg (2004b) estimates the effect of the stock of drugs available to treat a disease on the death rate from that disease. He matches data from three sources on the treatments and outcomes for 100 diseases from 1979-98: data from First DataBank's National Drug Data File on the list of all drugs appropriate for treatment of each disease; data from the FDA on the year in which every compound available in the year 1998 was approved as a NME; and data on mean age at death by cause of death from the Compressed Mortality File from the National Center for Health Statistics. He finds that increases in the stock of available compounds to treat a disease lead to significant

[3] See Murphy and Topel (2003) for an analysis that quantifies the substantial potential gains to medical research more generally.

increases in the mean age at death and reduces the fraction of individuals dying before age 65 from a disease.

Lichtenberg concludes this study with a comparison of the total costs and benefits of pharmaceutical knowledge accumulation. He estimates that the increase in the stock of priority-review drugs from 1979-98 (on average, 6.0 drugs per illness) led to an increase in the mean age at death of 0.39 years (4.7 months) – or about 10 percent of the total increase in mean age at death during the period. Based on a value of a year of life of $150,000, the value of this knowledge is about $120 billion per year = 2,000,000 deaths per year * 0.39*150,000. Compared to the total estimated cost of $182 billion of all pharmaceutical expenditures on NME research and approval during the period, he estimates the rate-of-return on investment in pharmaceutical R&D to be 18 percent.

The *use* of drugs, particularly of novel or new drugs, also affects the cost and quality of care. Based on aggregate cross-sectional data from the early 1990s, Miller and Frech (2002) find a significant association between a country's expenditures on pharmaceuticals and quality and length of life. Lichtenberg (1996) estimates the effects of the growth in quantity and novelty of drugs used to treat a disease on the change in the number of days a patient with that disease spends in the hospital. He measures quantity growth with the total number of prescriptions written for patients with each of 93 diseases in the 1980 and 1991 National Ambulatory Medical Care Survey (NAMCS) Drug Mentions files. He measures novelty with an index that is increasing in the dissimilarity of the distribution of compounds prescribed for patients with each disease in 1980 versus 1991. He finds that both growth in quantity and novelty of pharmaceutical use lead to declines in the number of inpatient bed-days.

Lichtenberg (2000, 2001, 2002, 2003c) extends this research in important ways. Lichtenberg (2000) estimates the effect of the measures of growth in quantity and novelty above on mortality growth from each disease (both in- and out-of-hospital mortality) and on measures of growth in service utilization other than inpatient hospital bed-days. In this work, he finds that growth in quantity and novelty lead to reduced mortality, but to increased expenditures on ambulatory care. Lichtenberg (2003c) replicates the mortality results in Lichtenberg (2000), but extends the period of analysis to include 1970-1980 as well as 1980-1991/2, and substitutes the quantity of recently-approved drugs for the earlier quantity and novelty measures.

Lichtenberg (2001) makes a similar point with an analysis of data from the 1996 Medical Expenditure Panel Survey (MEPS) on 23,230 individuals and the 171,587 prescriptions they received. He estimates the effect of the age of each drug prescribed, as measured by the number of years since the drug's FDA approval, on individuals' subsequent medical spending, morbidity, and mortality, holding constant their other characteristics such as gender, age, education, race, income, insurance status, and medical condition. He finds that individuals consuming newer drugs had fewer hospital stays, lower nondrug medical spending of all types, fewer days of work lost, and lower rates of mortality than individuals consuming older drugs.

Lichtenberg (2002) replicates the spending results in Lichtenberg (2001) with newer MEPS data from 1996, 1997, and 1998 and several methodological advances. In this work, he finds that a reduction in the age of drugs utilized reduces non-drug expenditure 7.2 times as much as it increases drug expenditure. In particular, he estimates that reducing the mean age of drugs used to treat a condition from 15 years to

5.5 years increases prescription drug spending by $18, but reduces other medical spending by $129.

Results from these cross-illness studies are supported by results from studies of patients with specific illnesses.[4] Lichtenberg (2003a), for example, shows that deaths from HIV in the US declined in response to the one-year-lagged count of drugs approved by the FDA to treat HIV. Lichtenberg (2004a) assesses the contribution of pharmaceuticals to the increase in cancer survival rates using annual, cancer-site-level mortality rates for 1975-95. Controlling for site of cancer, year, incidence, stage distribution of diagnosed patients, age at diagnosis, and surgery and radiation treatment rates, he finds that cancers for which the stock of drugs increased most rapidly reported the greatest increases in survival rates.

Frank et al. (1999) quantify the costs and benefits of treatment for depression with selective serotonin reuptake inhibitors (SSRIs), a new class of drugs discovered in the 1980s. According to them, a standardized course of treatment with an SSRI costs $305 and yields a probability of being depression-free after 16 weeks of approximately 0.28, leading to a cost per depression-free case of $1,087 (= 305 / .2805). Because 15 percent of patients suffering from depression improve after 16 weeks with no intervention, this implies an incremental cost per depression-free case of $2,346 (= 305 / (0.28 - 0.15)). Although the benefits of freedom from depression are hard to quantify, based on standard assumptions, the benefits of SSRIs are more than worth the costs: every dollar spent on SSRIs generates a return of six to seven dollars.[5] Frank et al. (2003) undertake a similar analysis of treatment for schizophrenia. They show that the dramatic increase in the use

[4] See also Schoffski (2002) for a series of disease-specific case studies of the determinants of pharmaceutical use in Europe.
[5] See also Cutler (2004, Chapter 4) for an alternative analysis with similar conclusions.

of atypical antipsychotic drugs from 1994-95 to 1999-2000 (from 19% to 61% of individuals diagnosed with schizophrenia) was accompanied by a 22-25% decrease in the quality-adjusted cost of care. Gains of this magnitude are not limited to the use of new drugs: according to several studies catalogued in MEDTAP (2004), treatment of heart attack patients with statins and beta-blockers can create enormous improvements in the cost-effectiveness of care as well.

IV. The link between price regulation, use of existing products, and cost and quality of care

Empirical evidence on the link between regulation and access to and use of existing pharmaceuticals suggests that regulation reduces patients' well-being through this channel as well. This happens because the costs of price regulation, in the form of delayed access to drugs due to regulation-induced delays in new product launches, are unlikely to be outweighed by the benefits, in the form of increased use of drugs due to regulation-induced reductions in prices.

On one hand, price regulation leads to delays in new-product launches. Kyle (2003) matches data on all drugs developed and launched in the 28 largest pharmaceutical markets from 1980-2000 with OECD health data by country and year. She categorizes compounds into therapeutic classes using Medline data on citations to compounds by type of illness. She reports three key findings. First, holding other factors constant, drug launches into price-controlled markets are delayed. Second, drugs discovered by firms headquartered in countries with price controls reach fewer markets and take longer to diffuse than drugs from firms in countries without price controls.

Third, firms are less likely to introduce a drug in additional markets after entering a market with price controls.

Danzon, Wang, and Wang (2003) estimate the effect of country characteristics on the probability of launch for 85 NCEs that were launched in the UK or US between 1994 and 1998. They find that the probability of launch in one of 25 major pharmaceutical markets is positively related to expected price and volume, controlling for income per capita. They also find significant negative country-specific effects, holding all else constant, for countries that have stringent regulation and have been major parallel exporters (i.e., exporters of legitimately produced drugs into other countries without manufacturing firms' authorization). Similarly, Danzon and Ketcham (2003) find that launch lags are longer in countries with more versus less stringent reference pricing systems.

Launch delays, in turn, lead to reduced longevity. Lichtenberg (2003b) matches data from the World Health Organization on cause-specific mortality from 52 countries from 1982-2001 with information from the IMS Health Drug Launches database. He finds that launches of NCEs have a strong positive impact on the probability of survival, but that launches of drugs that are not NCEs do not. He concludes this study with calculations of the "mortality cost" of launch delays (p. 19). Based on his estimates, increasing a country's launch delay by 5 years would reduce life expectancy by 15 weeks.

On the other hand, the benefits from regulation-induced increased use of pharmaceuticals are unlikely to outweigh these costs. Danzon (1997, Chapter 4) presents evidence that confirms that stringent price regulation reduces the price of originator

prescription drugs and increases the overall volume of pharmaceutical consumption. However, she also shows that much of this higher volume is accounted for by molecules not sold in the US – a rough indicator of these molecules' lower therapeutic value.[6] Countries with the most stringent price regulation also have the lowest percentage among Danzon's study countries of sales of US-approved molecules. For example, in France, more than half of all sales of cardiovascular drugs in 1992 were of products that either could not meet FDA standards for safety and efficacy or would have sales insufficient to support launch in the US.

The potential benefits of price regulation are further mitigated by the fact that regulation may actually lead to price increases of some compounds. For the special case of Category 1 (line extension) new products in Canada, Anis and Wen (1998) show that the controls imposed by the Patented Medicines Prices Review Board led to price increases in some existing products during the 1987-95 period. Based on analysis of the IMS data from Danzon and Chao (2000a), Danzon and Chao (2000b) show that competition from generic drugs lowers prices less in countries with stringent price regulation.[7] They hypothesize that this is due to the fact that, in countries with stringent regulation, generic firms earn higher profits by becoming licensed co-marketers or introducing 'new' versions of compounds strategically to obtain higher regulated prices than they do by competing on the basis of price.

[6] According to Danzon (1997, p. 44), FDA standards of safety and efficacy are generally considered the most stringent of all major markets, and the US market is the most attractive market to enter.
[7] See Gambardella, Orsenigo, and Pammolla (2000, Figure 8) for analysis that reaches a similar conclusion.

V. Conclusion

How does government price regulation of pharmaceuticals affect the cost and quality of medical care? In theory, price regulation could improve patient well-being. Lower regulated prices could lead to lower costs per use and therefore greater use, which may in turn lead to higher quality and lower overall costs of care. But regulation may have a number of consequences that mitigate or outweigh this effect: reduced R&D, delays in the launch of new drugs even after they have already been discovered, and distortion of patients' and physicians' choices toward compounds with lower therapeutic value.

Because the magnitudes of the costs and benefits of price regulation are theoretically indeterminate, its effects have been studied empirically and the subject of considerable debate. In this essay, I review existing empirical research on the effects of price regulation of pharmaceuticals. In summary, empirical research finds that price regulation has adverse effects on the cost and quality of care.

The adverse effects of price regulation occur through two channels. First, price regulation depresses firms' market performance, thereby depressing R&D and the discovery of new drugs. Declines in the number and innovativeness of new drugs, in turn, lead to decreased longevity and higher expenditures on other forms of medical care. Second, price regulation delays drug launches, distorts consumers' choices toward less innovative drugs, and in some cases actually leads to increases in prices. These effects lead to decreased longevity as well.

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