5880

THE PHARMACEUTICAL INDUSTRY

Patricia M. Danzon
The Wharton School - University of Pennsylvania
© Copyright 1999 Patricia M. Danzon

Abstract

The pharmaceutical industry raises unique economic questions because of three related features. First, the high rate of R&D, technical change and importance of patent protection raise important positive and normative questions related to industry structure, prices, profits and public policy. Second, the industry is heavily regulated in all major functions. Early regulatory requirements focused on safety and efficacy. More recently, prices, promotion and expenditures are increasingly regulated, arising out of policy concerns to control spending under social insurance programs. Optimal policies must consider trade-offs between control of moral hazard, assuring access to medical care and preserving incentives for innovation. Third, major drugs are global products and the costs of R&D are global joint costs. This creates incentives for national free-rider strategies, whereas socially optimal policies should consider cross-national spillovers and optimal price differentials. Existing literature provides a framework and some empirical evidence on some of these issues, but many questions remain unanswered.
JEL classification: L1, L4, L5, I11, L65, K32
Keywords: Pharmaceutical Industry, Regulation, Anti-trust, Health Care, R&D, Insurance

1. Introduction

The pharmaceutical industry is of interest to the field of law and economics for two, related, reasons. First, the usual issues of structure, conduct and performance when applied to the pharmaceutical industry must take into account its unusually high rate of R&D, which implies a high rate of technical change, critical importance of patent protection, potential for market power and novel price and product competitive strategies. This raises interesting positive and normative issues related to prices, profits and public policy.

Second, the industry is heavily regulated in all major functions. Much of the early regulation and early economic literature focused on regulation related to safety and efficacy. Because pharmaceuticals may entail

significant risks to health as well as potential benefits, all industrialized countries require that new drugs meet certain safety standards as a condition of market access. Since the 1960s some countries, including the US and the UK, also require evidence of efficacy; regulate the conduct of R&D; monitor manufacturing processes for quality; and restrict promotion and advertising, both to physicians and to consumers.

In the 1980s and 1990s, the focus of most new regulation in most countries has been related to control of costs, through regulation of manufacturer prices, insurance reimbursement, and/or total expenditures. These policies arise out of concern to constrain health spending under public insurance schemes which pay for a large fraction of pharmaceutical expenditures. Insurance coverage tends to make demand less price-elastic, increasing consumption volume and use of more costly drugs. The controls adopted by public and private insurers have significant effects on both the demand and supply sides of the market and on the nature of competition. This in turn affects returns to and incentives for R&D and consumer welfare. A growing literature examines both positive and normative issues raised by these cost control regulations. This literature has certainly increased our understanding of these regulations but many questions remain unanswered. The effects of such regulation are profound and multi-dimensional even within a single country, affecting consumption patterns, productivity, R&D and hence the supply of future technologies.

Moreover, research-based pharmaceuticals are global products that are diffused worldwide through licensing arrangements or, increasingly, through local subsidiaries of multinational corporations. The profitability of pharmaceutical R&D thus depends on worldwide sales and on policies adopted in many national markets. Each country faces an incentive to adopt the regulatory policies that best control its pharmaceutical budget in the short run, free-riding on others to pay for the joint costs of R&D, and ignoring cross-national spillovers of national regulatory policies through parallel trade and international price comparisons. But although policies remain national, the industry is global and market segmentation is breaking down. This requires a global perspective on both positive and normative analysis.

The future structure of the industry, as it adapts to changing technology and regulation, is another interesting question with no certain answers. The emerging technologies of biotechnology and genomics are transforming the nature of R&D and comparative advantage within the industry. Small firms play an increasingly important role in the development of new drugs and new R&D technologies. Biotechnology and gene therapy have raised important safety and ethical issues for regulation. The alliances that link biotech firms with each other and with large pharmaceutical companies raise interesting questions related to agency and the nature of the firm.

The primary focus of this survey is the recent literature on measurement of prices, profits, and cost of R&D, and on these new regulatory initiatives. A previous survey article on the political economy of the pharmaceutical industry (Comanor, 1986) reviewed the early literature on industry structure, pricing and effects of regulation, focusing almost exclusively on US regulations governing safety and efficacy in the 1960s and 1970s and related literature. Scherer (1993) focuses on issues related to pricing, profits and technical progress. Material covered in these earlier reviews is briefly reviewed here. The focus here is inevitably on US issues and evidence, given the dominance of US-based literature and firms in this industry. However, regulatory issues and evidence from other countries are included where possible. The focus on issues raised by regulation and policy is made without apology (for a contrary view, see Comanor, 1986). Regulation of safety, efficacy and quality fundamentally affect the industry's cost structure and the nature of competition, while regulation of price, reimbursement and promotion affect demand and profitability. By any measure, regulation has been and remains a critical factor that shapes this industry and must be central to any realistic analysis of the industry.

2. Safety and Efficacy Regulation: Costs and Benefits

Much of the early literature on the pharmaceutical industry grew out of the major regulatory initiatives adopted in the US in 1962. Under the 1938 Food, Drug and Cosmetics Act, any firm seeking to market a new chemical entity (NCE) was required to file a new drug application (NDA) to demonstrate that the drug was safe for use as suggested in proposed labeling. The Food and Drug Administration (FDA) had 180 days to reject the NDA. Congressional hearings on the industry were initiated in the late 1950s, arising out of concerns about prices, excess profits and promotion. Legislation was precipitated by the thalidomide tragedy. The drug thalidomide was still under review in the US but had been marketed in several countries of Europe, causing birth defects in hundreds of babies. The 1962 Kefauver-Harris Amendments to the 1938 Act strengthened safety requirements, extending FDA regulation to cover clinical testing and manufacturing facilities. More controversial, the Amendments also added the requirement that drugs show proof of efficacy, which usually requires double blind, randomized controlled trials of the drug relative to placebo; removed the time limit (previously 180 days) within which the FDA could reject an NDA; restricted manufacturers' promotion to approved indications; and required that all promotional material must include a summary of side-effects and contraindications. The UK tightened safety regulations in 1964 and added efficacy requirements in 1971; some other countries

followed suit. However others, such as France and Japan, retained much looser efficacy requirements (Thomas, 1996).

The presumption underlying the requirements for proof of efficacy was that asymmetric information prevented physicians and consumers from making accurate evaluations, leading to wasted expenditures on ineffective drugs and enabling companies to use product innovation as an obstacle to price competition. However, the extent of the market failure was a matter of assumption, not evidence, and the added requirements clearly entailed additional costs. These costs include the real resource costs of larger and longer clinical trials and increased delay in bringing new drugs to market, which entail foregone benefits to consumers and foregone revenue to manufacturers. Higher fixed costs of R&D raise the threshold of the expected revenue needed to break even on developing a new drug, leading to higher break-even prices, *ceteris paribus*. Some drugs would be totally eliminated by the new, higher threshold, including some with potential positive net benefits to consumers (assuming some Type II errors by regulatory bodies), particularly for relatively rare diseases with small potential market size. The Orphan Drug Act of 1982 attempts to remedy the latter problem; however, this addresses only the smallest markets and by the imperfect means of granting market exclusivity.

2.1 Costs of Regulation
An extensive literature has attempted to quantify the social and private costs and benefits of regulatory requirements for proof of efficacy, in particular, the 1962 US Amendments. Most research has focused on costs, in particular, the decline in the number of new drug introductions, longer delays for NCEs that ultimately do reach the market, higher input cost and capitalization cost per successful NCE due to larger and longer clinical trials, and shortened period of patent life - all of which coincided with the 1962 Amendments. Measurement of benefits has been even more elusive, because it requires comparing the actual rate of new drug introductions to the counterfactual rate that would have occurred, had the Amendments not been passed.

Grabowski, Vernon and Thomas (1978) report that the number of NCEs fell from 233 in the five-year period 1957-1961 to 93 in 1962-1966 and 76 in 1967-1971. Some decline would be consistent with the intent of the legislation, if some of the prior introductions were ineffective. However, the percentage of total ethical drug sales accounted for by new NCEs declined roughly in proportion to the number of drugs, from 20.0 percentage in 1957-1961 to 5.5 percent in 1967-1971. This tends to refute the argument that only the most insignificant drugs were eliminated.

Several studies (Baily, 1972; Peltzman, 1973; Wiggins, 1981) have attempted to estimate the contribution of the Amendments to this dramatic

decline in new drug introductions. Bailey (1972) estimates a production function of new drugs and concludes that input costs per NCE increased more than three-fold after 1962. Peltzman estimates a demand pull model to predict new drugs for the post-1962 period based on pre-1962 relationships. He attributes all the difference between predicted and actual number of NCEs to regulation. However, this is an assumption rather than a tested proposition since he does not explicitly control for other possible contributing factors.

Grabowski, Vernon and Thomas (1978) attempt to identify the marginal contribution of regulation, controlling for other possible contributing factors, including the depletion of new product opportunities; the thalidomide tragedy that may have made manufacturers and physicians more risk averse, hence reduced demand for new drugs; and pharmacological advances that may have raised R&D costs independent of regulation. Their strategy is to compare trends in NCE discoveries in the US relative to the UK, an appropriate comparator country because of its strong and successful research-based pharmaceutical industry. This provides a quasi-natural experiment because the UK did not adopt efficacy requirements until 1971 and its 1963 safety requirements were statistically unrelated to the flow of new discoveries. Grabowski et al. find that research productivity, defined as number of NCEs per (lagged) R&D expenditure, declined sixfold between 1960-61 and 1966-1970 in the US, compared to a threefold decline in the UK, and that the 1962 US Amendments increased the cost per new NCE by a factor of 2.3. They conclude that these differentials are plausibly attributable to regulation, since the UK would have been equally affected by exogenous changes in scientific opportunities and testing norms and by any thalidomide-related change in demand. Using the UK as a benchmark provides a conservative estimate because changes in the US, as the largest single pharmaceutical market, would influence incentives for innovative R&D for all firms, regardless of country of domicile, and hence could have contributed to the decline in discovery rates in the UK.

Several studies have examined the role of regulation in increasing delay for drugs that ultimately do reach the market. Dranove and Meltzer (1994) estimate that the average time from a drug's first worldwide patent application to its approval by the FDA rose from 3.5 years in the 1950s to almost 6 years in the 1960s and 14 years in the mid-1980. Wardell (1973) and Wardell and Lasagna (1975) report that the US lagged behind each major European country in new drug introductions for various new drugs sold in the US in the late 1960s. Comparing the US and Britain for the period 1962-1971, they find that more drugs were launched earlier in Britain than the US. The US had 59 product-years of prior availability compared to 120 in Britain. Of single country drugs, 77 were exclusive to Britain while

21 were confined to the US. The authors attributed these differences to the increased stringency of FDA regulations.

Other studies provide further support for the hypothesis that the 1962 Amendments delayed the introduction of new drugs into the US. Grabowski and Vernon (1978) compare introduction dates in the US and the UK for drugs discovered in the US between 1960 and 1974. The proportion of drugs introduced first in the US declined significantly between the periods 1960-1962 and 1972-1974, while the proportion introduced later in the US increasing significantly. The authors conclude that increased regulatory scrutiny in the US caused multinational companies to introduce new products abroad before their US launch. Similarly, Grabowski (1980) finds that many more drugs were introduced first in Europe despite most being discovered in US research laboratories or by US-based firms, with the lag increasing over time.

Wiggins (1981) extends the evidence by using differences in average FDA approval times across therapeutic categories. He finds large and significant effects of the 1962 Amendments, particularly on R&D cost per new product introduced, with some additional depressing effect on research expenditures and significant variation across therapeutic categories. However, in a study of new product introductions between 1956 and 1976, by therapeutic category, he finds that the overall decline is dominated by a few therapeutic classes for which regulatory stringency appears to be less important than other, non-regulatory factors in the decline in new product introductions.

The cost in foregone consumer welfare from delay or elimination of new drugs remains a current issue for different reasons in different countries. In the US, concern has focused on regulatory delay in approval of promising therapies for life-threatening diseases and other conditions that lack effective alternative therapies, such as AIDS. The economic argument is that the costs of delay are higher, hence the optimal risk-benefit trade-off is different if no alternative therapy exists. Since the mid-1970s the FDA has attempted to accelerate approval of such critical drugs, under pressure from Congress, consumer groups and the pharmaceutical industry. Early studies (by, for example, Wiggins, 1981) concluded that the drug lag for 'important therapeutic advances' was similar to that for all new chemical entities. More recently, Dranove and Meltzer (1994) conclude that, beginning in the 1950s, more important drugs - especially drugs that proved to be successful in the marketplace - have been developed and approved more rapidly than less important drugs. This differential appears to reflect actions of drug companies as much as regulatory priority setting. Moreover, for their period 1950-1986 the trend towards longer average development and approval times implied that even drugs two standard deviations above the mean level of importance took longer to reach the market. One interesting feature of the

Dranove and Meltzer study is the use of a comprehensive set of *ex post* measures of drug importance, including citations in medical textbooks, in medical journals, and in subsequent patent applications; the extent of worldwide introduction; and US sales. To the extent that these *ex post* measures of importance are noisy measures of *ex ante* forecasts of importance, their estimates of differential delay are understated.

These findings that, since the 1962 Amendments, delay in approval for important drugs has increased less than for more minor drugs, and that firm strategies can significantly influence delay, implies that estimates of the average drug lag due to the 1962 Amendments may overestimate the social costs of the regulation-induced delay. On the other hand, if it is costly for firms to accelerate approval, then the measure of total social costs should include these added expenditures as well as the pure delay-induced costs.

The fact that approval time continued to lengthen through the 1980s and that this is not confined to the US suggests either that other countries have experienced similar regulatory factors or that other factors such as common clinical factors may play an important role. Recent evidence suggests some convergence. Although Dranove and Meltzer (1994) find that approval times have lengthened in the US, their data indicate some narrowing of the gap between the US and other countries at the end of their period. Schweitzer, Schweitzer and Guellec (1996), using a sample of drugs approved in the US between 1970 and 1988, conclude that there were no significant differences in approval between the US and the G-7 countries, but that Switzerland was consistently quicker. These different findings may reflect differences in time period, methodology or sample. They may also reflect real changes in firms' optimal timing of launch in different countries. In particular, with increasing interdependence between markets, due to parallel trade and regulatory use of international price comparisons, the incentive of firms is to delay launch in countries with relatively low prices that may become a ceiling for prices in other countries. More on this below.

2.2 Benefits of Regulation

Of course, regulatory control may also benefit consumers, by reducing the risk that harmful or useless drugs are admitted to the market. The production of safety and efficacy information is a public good which may be underprovided by the market. For safety, liability may provide an alternative corrective to regulation. For efficacy, the market may acquire information over time, but learning by experience may entail a welfare loss. The optimal regulatory policy would set safety and efficacy standards to achieve the optimal balance between costs and benefits.

The only study that has attempted to estimate both the benefits and costs of efficacy regulation is Peltzman's (1973) study of the effects of the 1962

US Amendments. Peltzman attempts to estimate the benefits of regulation by examining the rate of growth of market shares of new drugs before and after the Amendments. He concludes that the benefits were minimal and were far outweighed by the costs, which he estimates as foregone consumer surplus due to the reduced flow of NCEs which he attributes entirely to regulation. These conclusions depend critically on the methods for estimating costs and benefits, which have been questioned (for example, Temin, 1980). In particular, if consumer learning is slower or less accurate than assumed, Peltzman's estimates understate the benefits of regulation. Conversely, Peltzman's estimates of costs may be overstated by ascribing the decline in NCEs solely to the regulation. Nevertheless, this is an important study because it offers a theoretical and empirical framework for evaluating the overall net benefits of efficacy requirements in a particular country.

The more numerous studies of cross-national differences in regulatory approval times and number of drugs admitted cannot provide the basis for policy implications because cross-national comparisons can only meaningfully be made for drugs that are approved in all comparison countries, which is a relatively small fraction of all drugs; because delay may reflect corporate strategies in additional to regulatory constraints; and because the delay may yield benefits in risk reduction or reduced wasteful expenditure on ineffective drugs. Thus delay and other regulatory costs cannot alone define the optimal extent and form of regulatory control, which remains an unresolved issue.

Nevertheless, recent efforts to harmonize regulatory requirements across countries should reduce the expense and delay of new drug approval and yield net social benefits. The information generated by conduct of clinical trials is a public good, as is regulatory review of the evidence assuming similar standards. In 1995 the European Union established the European Medicines Evaluation Agency (EMEA) as the required approval route for biotech products and as an optional route for other innovative products. The EMEA's goal is to review submissions within 365 days. An alternative is single country approval under the same rules, with reciprocity to other EU countries subject to objection. Competition between these alternative routes may stimulate efficiency. National systems remain for products that seek approval in only a single country. Harmonization between Europe, the US and Japan has been achieved on some issues but remaining differences still require country-specific trials and approval.

2.3 R&D Cost per New Chemical Entity
The research-based pharmaceutical industry invests a higher percentage of sales in R&D than most other industries (US CBO, 1994). The R&D/sales ratio for the US research-based industry has increased from 11.9 percent in

1980 to 21.2 percent in 1997 (PhRMA, 1997). However, because of the long lag between R&D and sales, a point-in-time R&D/sales ratio is downward biased as an estimate of the fraction of total costs that is accounted for by R&D. The sales in the denominator pertain to several cohorts of drugs currently on the market, whose R&D occurred many years earlier; conversely, the R&D expenditure in the numerator aggregates the one-year expenditures for several different cohorts that will generate sales over several future decades. To estimate R&D as a fraction of total cost, the stream of costs over the life cycle of a drug, from discovery through launch and sales, must be expressed in discounted present value at a common date. Applying this calculation to the date of launch, R&D accounts for roughly 30 percent of total costs (Danzon, 1997).

The appropriate methodology for measuring the R&D cost per new drug approved was pioneered by Hansen (1979), using company-specific data for a cohort of drugs. DiMasi et al. (1991) extend this approach to estimate R&D costs for drugs introduced from 1980 through 1984. The average successful NCE incurred $73m. of preclinical testing expense and $53m during clinical testing, excluding amortization of failures and cost of capital. These out-of-pocket expenses have increased over time, partly due to increasingly stringent regulation and increased targeting of chronic conditions that require longer trials. Since only 23 percent of the drugs entering human trials reached market launch, the costs of the failures ('dry holes') must be amortized across the successful compounds to yield the out-of-pocket cost per successful new drug. Grabowski, Vernon and Thomas (1978) report that the success rate of drugs entering clinical trials declined from one in three in the 1950s to less than one in ten after 1962. The final adjustment is to add the cost of foregone interest on capital between the time of investment outlay and market launch, which is approximately twelve years. This includes ten years from beginning trials to filing for an NDA and an additional two or more years for regulatory review. Assuming a 9 percent real cost of capital, this foregone interest accounts for roughly half of the total estimated pre-tax cost per successful NCE of $231m. in 1987 dollars (DiMasi et al.,1991). The US Congress OTA (1993) updated this to $359m before tax in 1993 dollars. Di Masi et al. (1991) estimate that a one year reduction in NDA review time would reduce the total cost by 19 percent. This large effect reflects the high capitalization cost of delay added after all investments has been incurred. Note that this measure of delay cost does not include the foregone revenue to the originator firm because delay shortens effective patent life.

An alternative, not mutually exclusive view of the rise in R&D cost per new drug is the dramatic decrease in productivity of R&D expenditures over time. Henderson and Cockburn (1996) report that in 1971, member firms of the US Pharmaceutical Manufacturers' Association spent about $360m on

R&D, compared to $8.9 billion in 1991, an increase of over 2300 percent in constant 1991 dollars. Over the same period, the output of important patents (those granted in two of the three major world markets, the US, Europe and Japan) fell, while the number of drugs discovered per year remained approximately constant. They conclude that this increase in cost cannot be explained by shifts in the distribution of R&D across therapeutic categories. The possibility of bias due to shifts in the location of R&D - as foreign firms shift a larger share of the R&D to the US - is not explored.

These estimates of costs per new drug and regulation-induced delay must be viewed as *ex post* averages that reflect the endogenous decisions made by firms, given the constraints imposed by regulation, technology and market opportunities. Firms can influence the out-of-pocket costs and duration of R&D by their selection of drug candidates, rejection rates on questionable leads, and development strategies. For example, pursuing certain trials simultaneously rather than in sequence saves time but entails out-of-pocket expense that could have been averted by a sequential strategy. Size of clinical trials may be influenced by the tolerance for risk of finding statistically insignificant effects. Thus the observed average cost per NCE presumably reflects the subset of drug candidates and strategies that were expected to yield revenues sufficient to cover costs. The striking rise in real R&D expenditures in the 1970s and 1980s is consistent with rational behavior in the face of rising out-of-pocket and delay costs only if technological and market opportunities were also expanding. More recently, manufacturers have become more aggressive at screening out less promising candidates early in the development process, as regulation and competition have reduced expected revenues in recent years and possibly reduced expected prices of late arrivals in a therapeutic class. Thus changes in cost per NCE reflect firms' optimizing responses to changes in market opportunities, as well as technological and regulatory shifts.

Henderson and Cockburn (1996) point out that if R&D entails wasteful, competitive investments as firms race against each other in substantially similar research, then the reported average cost per drug overstates the true R&D expense required in a more ideal competitive environment. On the other hand, if there are significant spillovers across projects within and between firms, then the average observed cost understates the resource requirement for a single firm to develop a new drug. Using detailed data from individual firms, they conclude that the evidence is more consistent with the spillover hypothesis and find no evidence to support the racing hypothesis. This is consistent with qualitative evidence that R&D spending and employment changes slowly, driven by heterogeneous firm capabilities and the evolution of scientific opportunities. However, as the authors note, these conclusions are tentative because they depend on the use of patents as

a measure of innovative output. Moreover, the assumed lag structure permits testing of only one specific model of racing behavior. On the other hand, their study makes no attempt to measure potential benefits to consumers that should be offset against any additional cost of duplicative R&D, if the existence of competing drugs on the market lowers prices. More on this below.

The evidence from Dranove and Meltzer (1994) provides further support for the proposition that R&D costs and delay are at least partly endogenous. Their conclusion that pharmaceutical manufacturers, rather than the FDA, are more responsible for relative acceleration of important drugs rests upon evidence that acceleration is observed during the 1950s, before the lengthy approval process was initiated and accelerated development is a worldwide phenomenon. Once market importance is controlled for, scientific importance does not appear to be associated with accelerated review, which might suggest no independent role for regulation, after controlling for the role of manufacturers. However, in reality, interaction of manufacturers and regulators is important but difficult to separate empirically. Future studies may find a greater contribution by the FDA, at least for drugs to treat highly visible, life-threatening diseases such as AIDs.

For countries other than the US there are no methodologically comparable estimates of R&D cost per successful NCE, correctly calculated to include the amortized cost of dry holes and capitalization cost. However, even if a cross-national comparison of R&D cost per NCE using comparable methodology were available, causal inference would be difficult for several reasons. First, with the harmonization of regulatory requirements firms increasingly conduct multi-national trials for global drugs. If country-specific studies reflect only the costs incurred in each country, all cost estimates are likely to be downward biased and relative costs will be upward biased in the countries where a disproportionate share of R&D is undertaken, particularly the US. Second, cross-national comparisons of R&D costs may be subject to sample selection bias because the mix of drugs that is approved differs greatly across countries. This reflects not only differences in regulatory stringency but also medical norms, local supply characteristics, pricing environments and other factors that affect costs and expected revenues and hence influence the portfolio of drugs that firms submit for approval. For example, a country with less stringent efficacy requirements might have a lower ratio of dry holes to successful NCEs, *ceteris paribus,* hence lower total cost per new drug approved. However, this would reflect differences in drug characteristics, in addition to the pure differential cost for a standardized cohort of drugs.

2.4 Cost of Capital

Several studies have attempted to estimate the pharmaceutical industry's cost of capital, as a critical input in estimates of the cost and profitability of R&D. The cost of capital determines the interest cost on R&D funds invested and the discounted present value of life-time revenue flows. Using standard finance models such as the capital asset pricing model (CAPM), the conclusion is generally that the pharmaceutical industry is of average risk, with a beta approximately equal to one, a nominal cost of capital of roughly 15 percent or 10 percent in real terms in 1990 (for example, Grabowski and Vernon, 1993; Myers and Shyam-Sunder, 1996 and references cited therein). Although the industry is often perceived as highly risky because the success of any individual drug candidate is highly uncertain, such risks are readily diversifiable. However, Myers and Shyam-Sundar (1996) point out the sequential nature of investment in R&D amplifies risk. Investing in R&D is equivalent to investing in compound lotteries and compound call options. Both beta and the opportunity cost of capital are higher for early stage R&D projects than for later stages. By implication, the average cost of capital is higher for small companies, that have several early-stage projects but no final products, than for large companies that have a diversified portfolio of products at various stages of the life cycle of development and commercialization.

3. Patents

The purpose of patent protection is to grant the originator firm a period market exclusivity that provides an opportunity to charge a price above marginal cost in order to recover the investment in R&D. In theory, the socially optimal patent term is defined by trading off the marginal utility gain from stimulating the development of innovative products against the loss from suboptimal consumption that results if patents lead to prices in excess of marginal cost. The optimal patent term may thus differ between countries. In pharmaceuticals, as in other industries, the period of effective market exclusivity may be much less than the nominal patent term because of entry of slightly differentiated products that are close substitutes. However, patent protection does block entry of generically equivalent imitator versions of the same compound until patent expiration.

For pharmaceuticals, the value of patent protection is further constrained by two factors. First, the effective patent life is truncated by the delay between patent filing and product launch, which is particularly long for pharmaceuticals due to the lengthy process of drug development and regulatory approval described earlier. For example, with a nominal patent

term of 20 years, the mean duration of 12 years from discovery research to product launch would leave an effective patent life of only eight years.

In the US, the 1984 Patent Term Restoration and Competition Act grants to innovator firms an extension of patent term for up to five years, to offset the loss due to regulatory delay. However, as a quid pro quo, the 1984 Act expedited post-patent entry by generic manufacturers, by granting them access to the active ingredient before the actual patent expiry, and by regulating market access with an Accelerated New Drug Application (ANDA) that requires only a showing of bioequivalence to the originator product, without new trials. This 1984 Act has greatly accelerated generic entry after patent expiry in the US. Similar measures have been proposed for the EU but so far have not been adopted. The extent of generic penetration and the speed of generic erosion of originator market share differ significantly across countries and over time, depending on policies adopted by regulators and third party payers. Studies of generic penetration and effects on brand pricing strategies are discussed below.

Second, in most countries drugs are reimbursed by publicly financed health or social insurance schemes. Insurance coverage tends to reduce demand elasticity, which could increase market power, *ceteris paribus.* Offsetting this, most public and private insurers have adopted controls on price, reimbursement, volume or total expenditures on drugs, in order to constrain manufacturers' exploitation of this inelastic demand and to constrain insurance-induced overuse (moral hazard) on the part of patients and of providers, who may use prescription drugs to enhance demand for their own services (Danzon and Liu, 1996). Regulation designed to control costs can significantly limit and even nullify the value of patents to originator firms.

Weak patent protection and associated copying of innovator drugs by local firms, particularly in developing countries, has been an important issue in international trade negotiations. In the Uruguay round of GATT, participating countries agreed to a 20 year patent life from date of application. However, because drugs already in the pipeline were exempted from the new rules, this provision would not grant patent protection to new drugs reaching the market for several years in countries that newly granted intellectual property protection.

Differences between countries in patent protection would matter less if markets were fully separable, such that the effect of weak patent protection in one country affected only that country. However for pharmaceuticals there are important market spillovers for two reasons. First, pharmaceutical R&D is a global joint cost of serving all countries in which a drug is marketed. The incentives for investment in global products thus depends on total global revenues. This gives each country an incentive to free-ride, waiting

for others to pay the joint costs. Second, the ability of producers of global drugs to segment markets along national lines and charge different prices, is breaking down as a result of parallel trade and regulatory use of foreign prices to set domestic prices. The EU Court of Justice, in *Merck v. PrimeCrown* (1996) upheld the right of parallel importers to import pharmaceuticals from one EU member state in which a product had no patent protection to another EU country in which the product was under patent protection. With parallel trade, the weak patent protection in one country effectively spills over to other countries, undermining the ability of the manufacturer to realize the value of the patent in countries that respect patents. The same effect occurs if the government in a country with patents regulates domestic prices based on prices in other countries that do not recognize intellectual property.

The theory of Ramsey pricing (Ramsey, 1927) provides the theoretically optimal set of price differentials for pricing to cover joint costs when consumers differ in their ability or willingness to pay. The use of Ramsey pricing to set optimal cross-national differences in prices is discussed in (Danzon, 1997a, 1997b). However, Ramsey pricing sets optimal price differentials, taking demand elasticities as given. But demand elasticities for individual products depend on patent structure. Thus in a full social optimum, the differentials in both patent terms and prices would be simultaneously determined. This simultaneous determination of cross-national differences in patent terms and prices for global products such as pharmaceuticals is an interesting issue for future work.

4. Pricing: Competition and Regulation

The pharmaceutical industry is structurally competitive, with low overall concentration. Although concentration within specific therapeutic categories is greater, the market is contestable in the long run, however, since there are no barriers to entering the process of research and discovery by established or new firms, as evidenced by the large number and high rate of turnover of start-up companies. It is incorrect to infer that entry would take 12 years (the mean time from discovery to approval for new drugs). Competitive entry is initiated long before a promising innovative compound for a new indication or with a new mode action reaches the market. Competitor firms can obtain information on the drug candidates under development by other firms in the industry, from patent filings and regulatory filings with the FDA. The techniques of rational drug design make it increasingly easy for competitors to develop similar but chemically distinct compounds to a promising new compound under development. Thus the pioneer may not necessarily be the first to reach the market and even if it is, follower compounds that are close

therapeutic substitutes now enter the market within months. The SSRIs (selective seratonin reuptake inhibitors) and statins (HMG CoAse Reductase inhibitors) illustrate the rapid speed of imitative entry.

To the extent that market power exists, it results largely from legal restrictions and other institutional factors. The role of patents in intentionally restricting competition has already been described. In addition, in most industrialized countries the demand for ethical drugs is channeled by legislation through physicians and other licensed professionals who are authorized to prescribe drugs. This separation of decision maker from payer makes demand less elastic, if physicians are uninformed about drug prices or, even if informed, are imperfect agents for patients. Insurance coverage further reduces price sensitivity. Traditional insurance that reimburses for the price of the drug, net of a fixed co-payment fee per script or a small co-insurance percentage, reduces demand elasticity in familiar ways. To offset this, both private and public insurers increasingly use strategies designed to make physicians more cost-conscious with respect to price and volume of prescriptions. Since most insurers outside the US are public or quasi-public bodies, these cost control strategies have the effect of regulation. An important consequence of this vital role of physicians and insurance coverage in influencing demand for drugs is that demand conditions differ across countries and over time, as medical reimbursement and insurance systems change. Thus any analysis of the form and extent of competition in the pharmaceutical industry is context-dependent and must take into account institutional arrangements in the local medical and insurance markets.

4.1 Pricing and Competition in Unregulated Markets

The early literature provides interesting evidence on competition in relatively free markets because insurance coverage and regulatory controls were less widespread. In the 1960s and 1970s, US patients paid directly out-of-pocket for most outpatient drugs, with minimal insurance coverage. Nevertheless, opinion in the economic and policy literature was divided on the competitive effect of closely substitutable drugs and hence on the effects of the 1962 Amendments. Some view the development of closely substitutable 'me-too' products as waste that is costly to consumers, on the theory that the rapid introduction of new products, protected by patents, leads to increased product differentiation and higher prices (see, for example, Comanor, 1964 and Temin, 1980). This theory predicts that the 1962 Amendments, by requiring proof of efficacy and restricting drug advertising, should increase price competition. The alternative view is that the extent of price competition depends positively on the number of close therapeutic substitutes, in which case the existence of close substitutes may benefit consumers. To assess the impact of the 1962 US Amendments on prices, Peltzman (1973) examines average price changes in a time series

analysis from 1952 to 1962 and a cross sectional analysis for the three years preceding the 1962 regulations. He finds no evidence that the number of NCEs had any net inflationary impact on drug prices, even under the strong assumption that innovation offers no net therapeutic benefit. He concludes that, if anything, the 1962 Amendments accelerated the rate of drug price inflation and added to the annual cost of drugs to consumers.

Several subsequent studies tend to confirm that the development of new, closely substitutable drugs does not limit price competition. In a study of launch prices of new drugs introduced between 1958 and 1975, Reekie (1978) found that new drugs that offer significant therapeutic advance were priced above existing drugs but tended to lower price over time, whereas imitators were priced lower initially but tended to increase prices. This pattern, of a skimming strategy for innovative drugs and a penetration strategy for imitators was confirmed by Lu and Comanor (1998) using data for 144 new drugs launched in the US between 1978 and 1987. The penetration strategy is consistent with a multiperiod model with interrelated demand and imperfectly informed buyers, in which sellers offer a low initial price to encourage use and build reputation. Imitative products optimally set even lower initial launch prices and raise prices over time (Schmalensee, 1982).

Most of these studies predate the application of managed care principles to pharmacy benefits in the US in the 1980s and 1990s, which has significantly affected demand for pharmaceuticals. Pharmacy benefit managers (PBMs) typically establish formularies of preferred drugs, which are selected on the basis of price and cost-effectiveness. Incentives and other inducements are offered to patients, physicians and pharmacists to use preferred drugs. Such strategies increase the cross-price elasticity of demand between therapeutic substitutes and are particularly powerful between generic equivalents (see below).

For therapeutic substitutes, the use of formularies, physician monitoring and other strategies enables PBMs to shift market share between therapeutically similar, single source drugs, thereby increasing the demand elasticity facing manufacturers of on-patent drugs. Because of their ability to shift market share and hence make demand more elastic, PBMs have been able to negotiate discounts averaging 20-25 percent off the list price that is charged to the unmanaged, retail pharmacy sector (Boston Consulting Group, 1993). Evidence that new drugs are being launched at lower list prices than established drugs in the same product class and that the discount is greater, the greater the number of existing drugs in the product class (Boston Consulting Group, 1993) suggests that price sensitivity is spilling over to the unmanaged market.

The future form of discounting and related competitive strategies in the US is uncertain because of litigation and growing legislative constraints initiated by retail pharmacists, who have not been offered discounts for patented drugs on the same terms as PBMs because individual retail pharmacists cannot - and arguably should not attempt to - shift market share between therapeutic substitutes (Danzon, 1997a). Pharmacists countrywide filed a massive series of antitrust claims against drug manufacturers, alleging collusive pricing and price discrimination (Scherer, 1996). This litigation explicitly excluded off-patent, multisource drugs, for which pharmacists do receive discounts because their legal authorization to substitute generic equivalents enables them to shift market share between multisource drugs. The recent partial settlement of this litigation and the pharmacists' success in obtaining passage of anti-discount pricing legislation in several states, may reduce the practice of discounting and possibly reduce price competition more generally. The effect on profitability is theoretically ambiguous: while individual firms presumably perceived discounting to be in their short-run interests, the long-run effects, once discounting became an industry-wide strategy, could have been negative. However, since managed care has irreversibly changed the price-sensitivity and sophistication of purchasers, legal impediments to discounting will not simply return the status quo ante. Drug manufacturers are developing innovative competitive strategies, including risk-sharing contracts, but it is too soon to predict future developments.

4.2 Generics
Generic substitution programs are used by HMOs and most pharmacy benefit managers in the US and in some other countries, notably the UK, Canada, Germany and other countries that use reference price reimbursement (see below). The main strategy is to limit reimbursement for multisource drugs to the price of a low or moderately priced generic. The patient must pay the difference if a higher priced drug, usually the originator brand, is dispensed. In the US most states have overturned their anti-substitution legislation and now authorize pharmacists to dispense a generic of their choice unless the physician explicitly notes that the brand is required. Since pharmacists capture the difference between the reimbursement price and the acquisition cost, pharmacists have strong incentives to select a relatively cheap generic, rather than a more expensive generic or brand. Thus for the manufacturer of multisource products, the primary customer is the pharmacist whose demand is highly price elastic. The cost and delay for generics entering the market was greatly reduced in the US by the 1984 Drug Price Competition and Patent Term Restoration Act, which reduced testing requirements and granted earlier access to essential data for generics, in return for extended patent life of originator drugs to compensate for time lost due to regulatory approval requirements.

Several studies have examined the effects of the 1984 Act on generic entry and, more generally, the effect of generics on prices, promotional activity and market shares of brand drugs. The differences between the studies probably reflects changes in market conditions, as more states relaxed their anti-substitution laws in the 1970s and 1980s, the 1984 Act, and the growth of managed care in the 1980s and 1990s. Frank and Salkever (1992) provide a formal derivation of the conditions under which generic entry can lead to price increases for brand name drugs. Drawing on the observation made in several studies, that the prescription drug market consists of at least two segments, price-sensitive consumers and brand loyal consumers who are less price sensitive, they show that one plausible condition under which entry may increase brand prices is that entry makes the reduced form demand for the originator (after taking into account response of generics) less elastic. Viewing promotion and price as simultaneous choice variables, they also develop the conditions under which brand advertising may decrease while brand prices increase.

Caves, Whinston and Hurwitz (1991) analyze post-patent pricing and promotion for 30 drugs whose patents expired between 1976 and 1987. They find small decreases in brand price following generic entry, with slightly greater effects in the hospital market than in the retail sector, as expected given the wider prevalence of formularies in hospitals at that time. However, their empirical specification includes therapeutic class-specific time effects, in addition to linear and quadratic time variables, which may capture some of the patent expiration effects. Caves, Whinston and Hurwitz (1991) also find significant reduction in brand promotion even before patent expiration. The net effect of less promotion and lower generic prices is that quantity sold does not increase significantly after patent expiration, implying ambiguous welfare effects. They conclude that a significant component of promotion of branded drugs is of the 'market expansion' variety, which reduces the extent to which these activities can be viewed as limiting generic competitors.

Grabowski and Vernon (1992), using data on patent expirations that spanned the 1984 Act, find that some brand prices increased after generic entry and that generic prices were significantly inversely related to number of generic competitors. A safe conclusion is that none of these studies find strong brand price reductions following generic entry, whereas number of generic entrants has strong downward pressure on generic price.

All of these studies underestimate generic penetration in the 1990s, which has greatly accelerated due to the growth of managed care and, possibly, patent expirations for more significant drugs with larger potential markets. For recent patent expirations, the brand drug typically loses over

half the market in less than a year, compared to five years or more found in previous studies. Thus the ability of brand advertising to build brand loyalty (for example, Caves, Whinston and Hurwitz, 1991) has apparently diminished significantly. This experience underscores the point that conclusions on competition are context-specific, depending on the time period, insurance arrangements and resulting incentives for physicians, pharmacists and patients, which interact to determine demand elasticities and hence optimal manufacturer pricing strategies.

None of these studies formally examine the role of pharmacists in drug demand and generic switching. Masson and Steiner (1985) show that for a sample of 37 multisource drugs in 1980, pharmacists obtained the generic at an average price 45 percent lower than the brand, but the difference at retail was only 24.3 percent, because the pharmacist retained a higher average absolute margin on the generics. Similarly, Grabowski and Vernon (1996) show that for 15 drugs whose patents expired between 1984 and 1987, the average absolute margin was roughly 40 percent higher on the generic. Caves, Whinston and Hurwitz (1991) find that pharmacists were quite conservative in exercising their right to substitute a generic, even where authorized. However, the recent gain in market share of generics suggests that this has changed as a result of the growth of managed pharmacy benefits and the associated pressure on pharmacy margins and reimbursement incentives that are designed to make pharmacists highly price sensitive in their choice between drugs.

Alexander, Flynn and Linkins (1994) attempt to estimate aggregate demand elasticities using country-level data for seven countries pooled over the period 1980-1987. They use a two-stage procedure. Price is treated as endogenous and estimated in the first stage, with a labor cost index included as an identifying variable. The second stage equation regresses Quantity on this predicted price variable and measures of income, physicians per capita, fixed country effects and a time trend. The resulting elasticity estimate of !2.8 is implausibly large, since it implies even higher product-specific elasticities. It is probably upward biased (in absolute value) due to spurious negative correlation induced by imputing quantity by dividing total expenditures by an estimate of average price that is at best very rough. Since labor cost is presumably highly correlated with income per capita, it is unclear whether the system is identified. Finally, since prices were regulated in five of the seven countries, the assumption that prices are endogenously determined by manufacturers is questionable. Other studies have generally estimated much lower aggregate demand elasticities (less than !1.0 in absolute value). These studies are reviewed in Anessi (1997).

4.3 Price Change
The pharmaceutical industry has been under considerable attack in the US for rates of price increase in the late 1980s that appeared to exceed general inflation. Accurate measurement of price levels and intertemporal price change is particularly problematic, however, in industries with rapid technological change, including pharmaceuticals. Suslow (1996) uses hedonic methods to estimate a quality-adjusted measure of price change for anti-ulcerants. She concludes that unadjusted price indexes that fail to adjust for quality improvements are upward biased. Griliches and Cockburn (1994) demonstrate the upward bias in the official US producer price index for pharmaceuticals that results from treating generics as new drugs, rather than as new versions of old drugs. Berndt, Griliches and Rosett (1993) show that lags in updating the market basket used in official price indexes led to official estimates of price growth being upward biased by as much as 50 percent in the US. Danzon and Kim (1996), using data from seven countries for the period 1981-1992, show that biases differ across countries, depending on the form and effects of regulation, the role of generics and the structure of the official index (fixed or chained weights). For example, the upward bias from treating generics as new drugs rather than modifications of old drugs is greatest in the US, where generics have a relatively large market share, relatively low prices and negative price change over time.

4.4 Regulation of Prices, Reimbursement and Expenditures
As noted earlier, to the extent that market power exists in the pharmaceutical industry, it derives partly from the legal grant of monopoly through patent protection. The inelastic nature of demand may be exacerbated by comprehensive insurance coverage, which has provided a rationale for regulation of prices, volumes and/or expenditures in most countries with public and social insurance systems.

An extensive literature has addressed the general question of optimal insurance coverage under conditions of moral hazard. Because insurance tends to undermine cost-consciousness of patients and providers in their use of medical services, including drugs, optimal insurance policies include some contractual terms to control insurance-induced overuse (moral hazard). Although early insurance theory typically focuses on consumer co-payment (for example, Pauly, 1968; Zeckhauser, 1971), in the case of medical insurance the optimal trade-off between control of moral hazard and financial protection may yield co-payments that are optimally too low to provide much incentive. Forms of provider cost-sharing may therefore be preferred (Ellis and McGuire, 1991). In the case of drugs, optimal insurance coverage should also take into account the effects of current prices and volumes on incentives for R&D.

In practice, the cost control strategies applied to drugs by private and public insurers differ across countries and continually evolve over time. A limited literature addresses the positive issue of measuring the effects of different insurance and regulatory structures on prices, drug expenditures and drug use. Harder to measure - and an important topic for future research - are effects of regulatory strategies on health benefits for current patients, on manufacturers' incentives to invest in innovative R&D, and hence effects on future patients.

Under direct price regulatory schemes, such as France and Italy, the manufacturer must obtain approval of the price of a new drug before it can be reimbursed by the social insurance system. Subsequent price changes must also be approved and price decreases may be mandated. The criteria used for setting prices include cost, comparison with existing drugs and international price comparisons. The 1989 EU Transparency Directive requires that such criteria be 'transparent' and neutral with respect to country of origin, but interpretation inevitably permits significant discretion. In practice, such systems are widely alleged to be used to pursue industrial policy goals, granting higher prices for products that are locally produced. Danzon and Percy (1996) develop a model showing that such biased regulation creates incentives for manufacturers to distort production efficiency and incur excessively high costs - for example, construction of an excessive number of production plants - in order to obtain higher prices.

Other countries, including Germany, the Netherlands and New Zealand have established reference price systems that limit the reimbursement price for drugs in designated groups. Manufacturers remain free to charge more than the reference price; however, since the patient must pay the difference, demand is highly elastic above the reference price, leading most manufacturers to drop their prices to the reference price. Zweifel and Crivelli (1996) analyse reference pricing using a duopoly model; Danzon and Liu (1996) develop a model with physicians as imperfect agents and monopolistic competition between suppliers. The empirical analysis shows that reference pricing significantly reduced price levels and the rate of price increase, which is consistent with independent rather than collusive pricing by manufacturers. Branded drugs suffered a loss in market share despite a reduction in relative price under reference pricing. Prices of non-reference priced drugs increased, as predicted by an optimal life-cycle pricing strategy with reduced economic life and possibly with market segmentation (Danzon and Liu, 1996).

The effect of reference price systems on the quality of care for patients and on R&D incentives for manufacturers depends critically on the criteria used to cluster drugs, since reference pricing induces competition primarily between drugs in the same cluster. In particular, if on-patent drugs are

clustered with older drugs for which patents have expired, reference pricing tends to undermine the ability of innovator firms to recoup the costs of R&D while under patent protection. At the limit, if a new drug is reimbursed at a reference price rate determined by the supply price of a generic version of an old molecule and this price reflects the marginal cost of production, the incentive for innovative R&D would be seriously undermined. In theory, of course, since reference price limits apply only to reimbursement, patients should be willing to pay the differential if the new drug truly offers greater therapeutic benefits. However, physicians may be reluctant to take the time to explain the options, risks and benefits. In the case of Germany, the legal requirement that physicians explain to the patient why a more expensive drug is needed would impose a time cost on physicians that is not reimbursable but has a significant opportunity cost. Thus physician response plausibly contributes to the observed high demand elasticity at prices above the reference price.

Price controls alone do not control drug expenditure growth, which is driven largely by the introduction of new, higher priced drugs that are or are perceived to be more effective. In 1993, therefore, Germany adopted a global limit on drug spending, with physicians at risk for the first DM280m of any overrun and the pharmaceutical industry at risk for the next DM280m overrun. This strategy dramatically reduced expenditures (Munnich and Sullivan, 1994). Danzon and Liu (1996) provide a theoretical and empirical analysis that distinguishes effects of reference pricing and drug budgets, using data from the period 1986-1994. They show that if physicians were perfect agents for patients, drug budgets should have no effect. In fact, the sharp spending cut reflected a reduction in number of prescriptions and substitution of older, cheaper drugs for newer, more expensive drugs that can only be plausibly explained by physicians' concern for their own income. In response to the 1993 drug budgets, manufacturers cut prices of on-patent drugs by more than the mandatory 5 percent price roll-back, consistent with a significant drop in demand and increase in demand elasticity. Schulenburg et al. (1994) report that the referrals to specialists and hospitals increased in response to the drug budgets, plausibly because inpatient drugs were not included. Thus the net budget saving was much less than the saving in outpatient drug costs.

Under the UK Prescription Price Regulation Scheme (PPRS), manufacturers are permitted to set prices of patented drugs, subject to the constraint that the rate of return on capital invested in the UK fall within a range, currently 17-21 percent. Each company negotiates with the government for a company-specific return of rate that depends on such factors as contribution to the economy. Prices of off-patent drugs are regulated. Standard theory predicts that pure rate of return regulation induces excessive capital investments and lower productivity (Averch and

Johnson, 1962). However, in an empirical study of the effects of such biased regulatory schemes in the UK, France and Italy on labor and total factor productivity, Danzon and Percy (1996) find that although the rate of growth of capital and labor in the UK pharmaceutical industry has been high, relative to other UK industry and relative to pharmaceuticals in other countries, it has not been biased towards capital relative to labor, possibly because the permitted rate of return may depend on employment growth. Moreover, the UK has experience relatively high productivity growth, compared to other regulated and unregulated countries.

Price regulation in most countries has been effective in controlling prices but not expenditures. Several cross-national price comparisons show that drug prices are significantly lower in France and Italy, which have strict price regulation, than in the US or Germany (for example, BEUC, 1989; Farmindustria, 1993). However, Danzon and Kim (1998) show that the measured differentials can vary significantly, depending on the sample of drugs used, the index number methodology used, including unit for measuring price and weights. Most international comparisons have been undertaken for regulatory purposes, have been biased by use of very small, non-random samples including only branded drugs, and have not adhered to standard index number methods (for example, GAO, 1992, 1994). For example, the exclusive focus on branded drugs tends to bias comparisons in favor of countries with strict price regulation. Regulation and competition are to some degree substitutes: less regulated markets tend to have higher brand prices but larger generic market shares and lower priced generics, plausibly because substantial brand mark-ups and cross-price elasticity of demand are necessary conditions to attract significant generic entry. The increasing use of international price comparisons, particularly for comparing prices across countries of the EU, imply that these methodological issues are of prime policy importance.

The failure of price controls to constrain expenditure growth has prompted several countries to adopt controls on volume or expenditures. Germany's national drug budget, described above, has evolved in 1997 into physician-specific drug spending targets with financial penalties for significant overruns. The UK has indicative drug budgets for general practitioners that, so far, are merely advisory and lack direct financial consequences (except for fundholding physicians who voluntarily assume financial risk for a broad range of services including drugs). France negotiates revenue caps with individual companies; prices are rolled back if volume and hence total revenue exceed the target level.

Many issues related to costs and benefits of these evolving regulatory strategies require further analysis. The evidence from Germany shows that placing physicians at financial risk is a potent weapon to limit drug

spending. However, it is a blunt weapon because physician budgets cannot be perfectly risk-adjusted to reflect differences in patient characteristics. Such caps therefore create incentives for cream skimming and/or service restrictions for sick patients. Limits confined to drug spending create no incentive for efficient substitution between drugs and other medical services, outpatient versus inpatient care, and so on. Cost-effective substitution between services is essential to achieve the maximum value from total health expenditures, but physicians cannot be expected to have the information or time required to evaluate alternative treatment regimens for specific patient conditions. In addition, in the longer run, regulatory systems that penalize physicians for prescribing costly new drugs could significantly reduce incentives for R&D.

In response to the cost-increasing effects of new technologies, there is a growing interest by governments and other payers in the use of technology assessment, including cost-effectiveness analysis, to evaluate new drugs. Although so far no country requires evidence of cost-effectiveness for registration, an increasing number of countries consider economic factors as a condition of reimbursement. Australia and the province of Ontario in Canada were the first require data on cost-effectiveness in reimbursement decisions. France and the UK encourage the provisions of such data, as do many private insurers in the US (Elixhauser, Luce and Steiner, 1995). Since the conclusions from a cost-effectiveness study are highly sensitive to - and only as good as - the methodology and data employed in the study, there have been several attempts to establish guidelines for such studies (Drummond, 1994, 1996).

Thus whereas the key research issue of the 1960s and 1970s was the design of market access controls, to appropriately balance reduction in risks to health and safety against delay in market access, the key issue in the 1990s is the design of price regulatory strategies that provide an optimal trade-off between control of drug spending, access for patients to new, more advanced therapies, incentives for optimal use of drugs relative to other medical services and long-run incentives for manufacturers to develop new drugs for the future.

5. Profitability and Rates of Return

The pharmaceutical industry has been under frequent attack for apparently high profits. (The term 'profit' is used to denote a return in excess of a normal return on capital invested.) Accurate measurement of profits is not easy in any industry. It is particularly problematic in the case of pharmaceuticals because of the length of product life and because of the importance of investments in intangible R&D and promotional capital. Both

of these investment flows are expensed on accounting statements but, from an economic perspective, are more correctly viewed as investments with a multi-year payout over the market life of a drug.

Several approaches have been used to measure profitability. The Lerner index of price relative to marginal production cost suggests high profitability. The ratio of the price of originator drugs relative to generic price several years after patent expiration (a rough measure of marginal cost) is roughly 5 (Caves, Whinston and Hurwitz, 1991). However, this probably overstated the Lerner index at earlier points of the life cycle for this cohort of drugs, since the price of originator drugs tended to rise in real terms with age in the US in the 1980s (Danzon and Kim, 1996). More fundamentally, a Lerner index based on short-run marginal production cost at a single point in time in one country is not a good indicator of the conceptually correct measure, which compares the discounted present value of global revenues over the full life cycle, relative to total costs including investments in R&D and promotion.

A second approach to profitability measurement attempts to adjust reported rates of return on book value of capital to take account of intangible capital of R&D and promotion. Standard accounting practices treat investments in R&D and promotion as current expenses rather than as investments in intangible capital, leading to systematic upward bias in accounting rates of return for industries with relatively high intangible investments. Clarkson (1996) illustrates the effects of these adjustments for firms in fourteen industries for the period 1980-1993. Before adjustment, the average accounting rate of return on equity for the fourteen industries is 12.3 percent; the pharmaceutical industry has the highest return of 24.4 percent. After adjustment for intangible capital, the average is 10.2 percent compared to 13.3 percent for pharmaceuticals, which is less than the adjusted return for petroleum, computer software and foods.

The most reliable approach to measuring the rate of return to investment in a cohort of drugs uses discounted cash flow estimates of the costs and returns for that cohort. Grabowski and Vernon (1990, 1996) estimate the returns on R&D for new drugs introduced in the 1970s and in 1980-1984, respectively. The cost estimates include dry holes and interest cost of funds, based on data gathered from individual firms. Market sales data for the US are used to project a sales profile over an economic life of over 20 years. Foreign sales are estimated using a foreign sales multiplier. Applying a contribution margin to net out direct costs then yields a life-cycle profile for net revenue, which is discounted to present value using a 10.0-10.5 percent real cost of capital. Grabowski and Vernon conclude that drug introductions in the 1970s on average earned a return roughly equal to their cost of capital. The later cohort on average yielded a positive net present value of $22.2m, or an internal rate of return of 11.1 percent, compared to the 10.5

percent cost of capital. Given the margin of error in estimating several of the key parameters, the hypothesis of a normal rate of return cannot be rejected.

The returns distribution across drugs is highly skewed, such that only the top 30 percent of drugs cover the average R&D cost. Grabowski and Vernon (1996) use simulation analysis to show that an important implication of this skewed distribution of returns is that regulatory strategies that target these 'blockbuster' drugs could significantly reduce expected average returns and hence reduce incentives for R&D. By contrast, a competitive strategy that permits high prices for patented drugs but then promotes generic competition after patent expiry has a much less negative effect on incentives for R&D, because a given loss in sales revenue is more heavily discounted if it occurs late rather than early in the product life cycle. While the basic point is important and correct, the magnitude of the revenue loss from targeting blockbuster drugs may be sensitive to the assumption that R&D cost per drugs is uniform whereas the distribution of revenues is highly skewed. To the extent that firms can anticipate the different market potential of different drugs and incur higher R&D costs for drug candidates with potentially greater returns, the cost distribution may roughly mirror the returns distribution, such that the distribution of net revenues is less skewed than the distribution of gross revenues.

Using similar methodology, a smaller sample (1981-1983 drug introductions) and different parameter values, the US OTA (1993) concluded that the average NCE in this period earned excess returns of $36m over the average R&D cost. Again, no confidence interval is reported and conclusions are sensitive to several important assumptions. Moreover, even if the drugs introduced in the 1980s did earn abnormal returns, the experience of the 1990s cohort of drugs is likely to be less favorable, because of the growth of managed care in the US, increased regulatory stringency in many foreign markets, and more rapid generic erosion of post-patent market shares in several major markets, including the US, Germany and the UK. Although the rapid growth in R&D investment - indeed any investment - by the pharmaceutical industry in the 1980s implies that at least normal and possibly above-normal returns were anticipated, such growth would also be consistent with expanding technological possibilities.

Although this cohort rate-of-return approach is the only valid approach to measuring profitability, it is vulnerable to the fundamental objection that, if estimated returns either exceed or fall short of normal levels, this reflects either measurement error on the part of researchers or market disequilibrium that is probably already being corrected by competitive entry, such that the analyst's estimate is obsolete before it is made. Since there are no significant barriers to entry to research activities, if pharmaceutical R&D were to generate persistently excessive returns, competitive entry would occur as

long as expected profits exceed the cost of capital. Dissipation of excess profits could take the form of price competition but could also include undertaking more or riskier R&D that targets new therapeutic areas with little prior experience. This competitive adjustment process may not be smooth or instantaneous, because market and regulatory conditions, including insurance reimbursement systems, are continually changing; market entry through new R&D may take time and the actual realization of returns may be different from that anticipated when an R&D investment is initiated.

In general, a reasonable assumption is that competitive entry to exploit R&D opportunities will tend to restore expected profitability to normal levels if anticipated profits are above normal. The more important policy question is whether the resulting rate of introduction of new drugs and mix of innovative vs. imitative drugs is socially optimal. In other words, changes in the regulatory and reimbursement environment may affect profitability in the short run. But in the long run, the rate and mix of R&D adjusts such that normal returns are realized on average. Whether the resulting R&D expenditures entail significant duplicative investment is an important issue. Henderson and Cockburn (1996) provide some evidence against this idea, but not a definitive rejection. The current trend of payers to demand evidence of cost-effectiveness relative to existing drugs as a condition for reimbursement above existing drugs, reinforces incentives for manufacturers to target R&D towards innovative therapies and away from imitative drugs. Of course, the great uncertainty *ex ante* as to the ultimate therapeutic value of new drugs and the speed of approval implies that *ex post* realizations may still yield some me-too drugs. Even the optimal number of me-toos is uncertain, given their value as a competitive constraint and sometimes as a source of significant improvements for some subsets of patients.

6. Industry Structure and Productivity: Regulation or Technology?

Government regulation has had a significant impact on industry structure. In the US, the 1938 Federal Food, Drug, and Cosmetic Act restricted the sale of some drugs to prescription, leaving only less potent drugs available for direct over-the-counter (OTC) demand by consumers. The fact that insurance coverage is restricted in many countries to prescription drugs and that physician agency is an issue only for prescription drugs has distinguished the prescription sector from the OTC sector. The 1962 Amendments, enacted to promote safety and efficacy, further differentiated the research-based industry.

Several studies have examined the effects of regulation and other factors on industry structure and economies of scale in R&D. Temin (1980)

examines the impact of regulatory and technological change on the structure of the US pharmaceutical industry using firm level data from 1948 to 1973. Major technological advances in the postwar period dramatically increased the number and therapeutic potential of new drugs. Temin finds that the size of drug firms increased dramatically during this period with much of the growth concentrated in large rather than small firms.

Grabowski and Vernon (1976, 1977) suggest that regulation-induced increases in cost and risks of R&D create scale economies that result in the concentration of innovation in large firms. They also hypothesize that this concentration would lead to higher market shares and higher prices for drugs that do obtain FDA approval, due to the reduction in the number of close competitors. Their empirical findings support the first hypothesis, showing an increasing proportion of innovations concentrated in large firms and increasing concentration ratios of innovational output. However, they find no evidence to support the second hypothesis: concentration of sales in the industry did not increase and competition from generic and non-patented products prevented prices from rising.

The relationship between research productivity and firm size is further examined by Thomas (1990). Despite the decline in the annual number of NCE introductions following the 1962 Amendments, levels of real R&D expenditures rose each year from 1960 to 1980. Thomas shows that the decline in NCE introductions around 1962 was concentrated in the smallest firms, many of which dropped out of innovation. Using productivity trends in the UK as a control to isolate the effects of regulation in the US, Thomas estimates the 'direct effects' of regulation on individual firms and the 'indirect effects' resulting from the asymmetric impact of the regulation on small and large firms. In contrast to Grabowski and Vernon, he concludes that the sales gains due to reduced competition from smaller firms more than offset the reduction in research productivity for large firms.

Thomas (1996) extends the argument that strict safety and efficacy regulation in the US and UK led to a shakeout of smaller, less innovative firms and concentration of innovative effort in larger firms. This, together with relatively free pricing policies, may have contributed to the preeminence of these two countries in developing innovative products, by forcing the development of the necessary skills. Thomas argues that the much less stringent efficacy regulation in France and Japan has sheltered weak domestic firms and hence contributed to the failure of these countries to develop skills necessary to compete in the global pharmaceutical marketplace. The price regulatory systems in these two countries, which depress prices over the life of a drug, create incentives for firms to focus R&D efforts on a large number of new drugs in order to get frequent price increases, rather than invest in fewer, truly innovative drugs that achieve global penetration (Danzon, 1997).

More recently, the structure of the pharmaceutical industry has been undergoing fundamental change. Horizontal mergers have combined some of the largest firms, ostensibly to further exploit potential economies of scale, scope and risk-pooling. Other large firms have integrated forward into distribution, with the acquisition of pharmacy benefit management companies. The stated rationale for this strategy is to gain access to information and possibly leverage to gain sales advantage. The long-term value of both the horizontal and vertical integration strategies remains to be determined, compared to the alternative of devoting the same resources to R&D. It is also plausible that the optimal strategy is different for different firms, depending on their other assets and capabilities.

At the same time, the biotechnology revolution has dramatically increased the importance of small firms in discovery research and related development of new tools for enhancing R&D productivity, for example, through rational drug design. In the 1980s a very small number of successful biotech firms developed their functional scope to become fully integrated pharmaceutical companies, similar in structure to the traditional chemical-based firms. However, theory and evidence for the 1990s indicate a higher degree of specialization and mutual dependence between small and large firms. Most small firms now specialize in discovery, relying on large firms for development and marketing expertise where regulatory interactions and economies of scale play a greater role. Conversely, although large firms still have in-house R&D activities, they also draw extensively on discoveries - tools and target compounds - that are in-licensed from smaller firms. The extent and form of alliances between small firms, particularly biotech, and large firms varies, in part reflecting the particular expertise of large firms. However there is virtually universal recognition that small firms have a key role to play and that most large firms cannot compete effectively in the R&D race without taking advantage of the developments offered by small firms.

An important implication of this mutual dependence is that it is now almost impossible - and perhaps a meaningless task - to attempt to estimate returns to scale in R&D productivity. Since all firms draw on technologies developed by other firms through licensure and other sharing arrangements, any attempt to allocate specific new drugs to specific firms in order to count the number of new drugs per firm is at risk of error because most drug innovation employs inputs developed by several other firms, in addition to the firm that ultimately takes it through the regulatory process.

7. Promotion and Advertising

7.1 Information or Persuasion?

The pharmaceutical industry's large expenditures on advertising and promotion have been controversial in both the economic literature and the policy debate, with concern over both magnitude and form. Critics question the social value of these large promotional expenditures and charge that they lead to increased market power and higher prices. The alternative view is that promotion provides information to physicians and consumers which is necessary for the effective use of the products. Considerable research has focused on determining the competitive effect of promotional expenditures in the pharmaceutical industry.

An early proponent of the anti-competitive hypothesis, Walker (1971) argues that large promotion expenditures raise entry barriers and increase market power, by requiring new entrants to make large outlays in order to attract attention to new products. The alternative view is that advertising may enhance competition by facilitating the introduction of new products and new firms. Schwartzman (1975) finds that more innovative firms spend larger sums on promotion. Telser (1975) finds that the extent of new entry into a therapeutic class is positively related to promotional intensity. However, this positive correlation between research and selling intensity, at the level of either the firm or the therapeutic class, does not prove that the effect of advertising is to enhance competition. Clearly the two may be simultaneously determined and both causally related to such unobservable factors as technological advance and market potential.

Leffler (1981) estimates a model across therapeutic categories with selling effort as the dependent variable and the number of new products introduced as the primary explanatory variable. He finds a significant positive effect which he interprets as suggesting that informative advertising of pharmaceuticals may be substantial. He also finds evidence, however, that advertising of established pharmaceutical products accomplishes 'reminder' and 'habit-formation' purposes by finding significant coefficients on variables which indicate therapeutic categories in which he hypothesizes that the returns from noninformative, repetitive advertising are relatively high. These results suggest that the impact of advertising is multidimensional and that the net effect on competition may differ, depending on the circumstances.

The distinction drawn by Leffler between the 'persuasion' and 'information' roles of pharmaceutical promotion is extended by Hurwitz and Caves (1988) in a study of promotional expenditures for a sample of drugs that went off-patent and their generic competitors. Their interest is in the scope of rent-seeking in manufacturers' promotion outlays. They note that

the social costs generated by rent-seeking behavior must be weighed against the efficiency advantages of sellers as suppliers of product information demanded by buyers. Their results indicate that the leader's (the original patent holder) market share increases significantly with its own sales promotion, independent of the amount of goodwill generated before it went off-patent, although these past investments are also important. In addition, the leader's share diminishes with generic outlays. The leader's price premium significantly increases the generics' share of advertising, although the implied sensitivity is small in the short run. They conclude that there are both information and rent-seeking functions of pharmaceutical promotion.

Beales (1996) uses the FDA policy restricting manufacturer advertising of unapproved indications as a natural experiment to test the importance of pharmaceutical marketing as a source of information for physicians. He analyzes the impact of promotional activity following FDA approval of second indications for existing drugs on the share of patients treated with the newly approved product, the total fraction of patients treated with drug therapy, and the average price level. He finds some evidence that seller-provided information after approval results in increased market share for the new indication as well as lower average price per prescription of other products in the market, suggesting an increase in consumer benefits from increased manufacturer-provided information. However, it is difficult to differentiate between the impact of FDA approval itself and the impact of promotional expenditures in this study.

7.2 Regulation of Promotion and Advertising

Several countries have adopted regulations designed to discourage promotion. The UK PPRS limits the promotional expenditure that can be deducted as a cost in calculating the net rate of return. The provisions of the German global drug budgets, that place the pharmaceutical industry at financial risk for budget overruns (after the share paid by physicians), are designed to discourage promotional effort. Similarly, the French revenue caps for individual pharmaceutical firms severely reduce the incentive for incremental promotional effort that would lead to a budget overrun for the firm.

In the US, since 1962 the FDA has imposed strict limits on content of promotional material to physicians and consumers. More recently, the growth of managed care has fundamentally changed the nature of marketing of pharmaceuticals. The autonomy of the physician has been reduced, with power shifting to payers or their agents, in the form of pharmacy benefit managers or pharmaceutical and therapeutics committees that make formulary decisions. This shift in the primary 'customer' from the physician to a cost-conscious decision maker has been accompanied by a dramatic

increase in the importance of cost-effectiveness analysis, to demonstrate that a particular drug is more cost-effective than the alternatives. The available evidence on use of cost-effectiveness analysis by managed care organizations is summarized in Elixhauser, Luce and Steiner (1995).

In response to this trend, the FDA has proposed regulations that would require that a pharmaceutical firm's cost-effectiveness claims be supported by 'sound' analysis. If this requirement is defined as requiring a double blind, randomized clinical trial between the two drugs under comparison, it raises many of the same issues that were debated at the time of the 1962 efficacy requirements. In particular, are the gains from reducing the risk of misleading claims outweighed by the costs of the added regulatory requirements? These costs would include higher out-of-pocket costs for firms that would ultimately be passed on to consumers; delay and foregone benefits to consumers if the diffusion of new drugs is delayed; and a reduction in the number of drugs that are worth developing. Again, some might argue that elimination of me-too drugs would, on balance, benefit consumers but, as discussed earlier, both theory and evidence on this point remain inconclusive. However, it seems likely that as purchasers are increasingly either a managed care regime in the US or sophisticated, cost-conscious institutional buyers in other countries, that firms will face strong incentives to eliminate drugs that are clearly going to be pure me-toos at an early stage in the R&D process.

The case for a regulatory requirement for randomized controlled trials (RCTs) before cost-effectiveness claims can be made seems weaker than the case for RCTs for efficacy. The information on both costs and effects produced from RCTs is of dubious value as evidence of cost-effectiveness in practice because trials do not mirror actual practice. Strict protocols are applied to the selection of participating patients, to assure compliance and follow up all questionable outcomes. The result is that neither costs nor effects of controlled trials reflect those that would be realized in actual practice by a particular patient, group of patients or health plan. Moreover, the evidence (Elixhauser, Luce and Steiner, 1995) suggests that managed care plans are quite skeptical of cost-effectiveness claims made by manufacturers. Similar conclusions surely apply to government regulators that review such claims for public insurances. Nevertheless, there appears to be a strong case for encouraging competition in the provision of information on cost-effectiveness of pharmaceuticals, including the development of guidelines for the conduct of such studies.

8. Conclusions

The economics literature on the pharmaceutical industry has made many valuable contributions, in framing some of the important issues and providing useful - although rarely definitive - empirical evidence. Nevertheless, we still lack complete answers to some of the basic questions raised by policymakers and academics. If the moral hazard effects of insurance justify some forms of control, which forms provide the best trade-offs between reasonable control of costs, access for patients, incentives for efficient mix of medical services and incentives for innovative R&D? Is there a case for separate regulation of promotional activity for pharmaceuticals, distinct from that applied to other consumer products? If so, what forms of regulation of promotional activities yield the greatest net social benefits, and how does this differ between prescription and over-the-counter medications? These are only some of the interesting questions that remain to be explored.

Bibliography on The Pharmaceutical Industry (5880)

Alexander, Donald, Flynn, Joseph E. and Linkins, Linda A. (1994), 'Estimates of the Demand for Ethical Pharmaceutical Drugs Across Countries and Time', **26** *Applied Economics*, 821-826.

Anessi Pessina, Eugenio (1997), *The Effect of User Charges on the Utilization of Prescription Medicines in the Italian National Health Service*, Unpublished Doctoral Dissertation, Philadelphia, The Wharton School, University of Pennsylvania.

Averch, Harvey and Johnson, Leyland (1962), 'Behavior of the Firm under Regulatory Constraint', **52** *American Economic Review*, 1052-1069

Baily, Martin N. (1972), 'Research and Development Costs and Returns: The U.S. Pharmaceutical Industry', **80** *Journal of Political Economy*, 70-85.

Beales, J. Howard, III (1996), 'New Uses for Old Drugs', in Helms, Robert B. (ed.), *Competitive Strategies in the Pharmaceutical Industry*, Washington, DC, The American Enterprise Institute Press 281-305.

Berndt, Ernst R. and Greenberg, Paul (1996), 'Price Growth of Prescription Pharmaceutical Preparations: An Update and Explanation', in Helms, Robert B. (ed.), *Competitive Strategies in the Pharmaceutical Industry*, Washington, DC, The American Enterprise Institute Press, 35-48.

Berndt, Ernst R., Griliches, Zvi and Rosett, Joshua G. (1993), 'Auditing the Producer Price Index: Micro Evidence from Prescription Pharmaceutical Preparations', **11** *Journal of Business and Economic Statistics*, 251-264.

BEUC (1989), *Drug Prices and Drug Legislation in Europe*, Brussels.

Boston Consulting Group (1993), *The Changing Environment for U.S. Pharmaceuticals.*

Caves, Richard E., Whinston, Michael D. and Hurwitz, Mark A. (1991), 'Patent Expiration, Entry, and Competition in the U.S. Pharmaceutical Industry', *Brookings Papers on Economic Activity: Microeconomics,* 1-66.

Clarkson, Kenneth W. (1996), 'The Effects of Research and Promotion on Rates of Return', in Helms, Robert B. (ed.), *Competitive Strategies in the Pharmaceutical Industry*, Washington, DC, American Enterprise Institute Press, 238-268.

Comanor, William S. (1964), 'Research and Competitive Product Differentiation in the Pharmaceutical Industry in the United States', **31** *Economica*, 372-384.

Comanor, William S. (1986), 'The Political Economy of the Pharmaceutical Industry', **24** *Journal of Economic Literature*, 1178-1217.

Danzon, Patricia M. (1996), 'The Uses and Abuses of International Price Comparisons', in Robert B. (ed.), *Competitive Strategies in the Pharmaceutical Industry*, Washington, DC, The American Enterprise Institute Press, 85-106.

Danzon, Patricia M. (1997a), *Price Regulation in the Pharmaceutical Industry: National vs. Global Interests*, Washington, DC, The American Enterprise Institute Press.

Danzon, Patricia M. (1997b), 'Price Discrimination for Pharmaceuticals: Welfare Effects in the US and the EU', **4** *International Journal of the Economics of Business*, 301-322.

Danzon, Patricia M. (1998), 'The Economics of Parallel Trade', **13(3)** *PharmacoEconomics*, 1-12.

Danzon, Patricia M. and Kim, Jeong (1996), 'International Price Comparisons for Pharmaceuticals', Working Paper, Philadelphia, University of Pennsylvania, The Wharton School.

Danzon, Patricia M. and Liu, Hong (1996), 'Reference Pricing and Physician Drug Budgets: The German Experience in Controlling Pharmaceutical Expenditures', Working Paper, Philadelphia, University of Pennsylvania, The Wharton School.

Danzon, Patricia M. and Percy, Allison (1996), 'The Effects of Price Regulation on Productivity in Pharmaceuticals', in Robert Lipsey (ed.), *Studies in Income and Wealth,* National Bureau of Economic Research, forthcoming.

DiMasi, Joseph A., Bryant, N.R. and Lasagna, Louis (1991), 'New Drug Development in the United States from 1963 to 1990', **50(5)** *Clinical Pharmacology and Therapeutics*.

DiMasi, Joseph A., Hansen, Ronald W., Grabowski, Henry G. and Lasagna, Louis (1991), 'The Cost of Innovation in the Pharmaceutical Industry', **10** *Journal of Health Economics*, 107-142.

Dranove, David and Meltzer, David (1994), 'Do Important Drugs Reach the Market Sooner?' **25** *Rand Journal of Economics*, 402-423.

Drummond, Michael F. (1994), 'Guidelines for Pharmaoeconomic Studies: The Way Forward', **6** *Pharmacoeconomics*, 493-497.

Drummond, Michael F. (1996), *Experimental versus Observational Data in the Economic Evaluation of Health Care Technologies*, University of North Carolina.

Elixhauser, Anne, Luce, Bryan R. and Steiner, Claudia A. (1995), *Cost Effectiveness Analysis, Medical Technology Assessment, and Managed Care Organizations*, Bethesda, MD, MEDTAP International Inc..

Ellis, Randall and McGuire, Thomas (1991), 'Optimal Payment Systems for Health Services', **10** *Journal of Health Economics.*

Farmindustria (1993), *Indicatori Farmaceutici*, Rome, Farmindustria.

Frank, Richard G. and Salkever, David S. (1992), 'Pricing, Patent Loss and the Market for Pharmaceuticals', *Southern Economic Journal*, 165-79.

Grabowski, Henry G. (1980), *Drug Regulation and Innovation.*

Grabowski, Henry G., Vernon, John M. and Thomas, Lacy G., II (1978), 'Estimating the Effects of Regulation on Innovation: An International Comparative Analysis of the Pharmaceutical Industry', **21** *Journal of Law and Economics*, 133-163.

Grabowski, Henry G. and Vernon, John M. (1976). 'Structural Effects of Regulation on Innovation in the Ethical Drug Industry', in Masson, R.T. and Qualls, P.D. (eds), *Essays on Industrial Organization in Honor of Joe S. Bain*, Cambridge, MA, Lippincott, Ballinger 181-205.

Grabowski, Henry G. and Vernon, John M. (1977). 'Consumer Protection Regulation in Ethical Drugs', **67** *American Economic Review*, 359-64.

Grabowski, Henry G., Vernon, John M. and Thomas, Lacy Glenn (1978), 'Estimating the Effects of Regulation on Innovation: An International Comparative Analysis of the Pharmaceutical Industry', **21** *Journal of Law and Economics*, 133-163.

Grabowski, Henry G. and Vernon, John M. (1990), 'A New Look at the Returns and Risks to Pharmaceutical R&D', **36** *Management Science*, 804-821.

Grabowski, Henry G. and Vernon, John M. (1992), 'Brand Loyalty, Entry and Price Competition in Pharmaceuticals after the 1984 Act', **35** *Journal of Law and Economics*, 331-350.

Grabowski, Henry G. and Vernon, John M. (1993), 'Returns to R&D on New Drug Introductions in the 1980's', in Helms, Robert B. (ed.), *Conference on Competitive Strategies in the Pharmaceutical Industry*, Washington, DC, The American Enterprise Institute Press.

Grabowski, Henry G. and Vernon, John M. (1996), 'Prospects for Returns to Pharmaceutical R&D under Health Care Reform', in Helms, Robert B. (ed.), *Competitive Strategies in the Pharmaceutical Industry*, Washington, DC, The American Enterprise Institute Press194-207.

Griliches, Zvi and Cockburn, Iain (1994), 'Generics and New Goods in Pharmaceutical Price Indexes', **84** *American Economic Review*, 1213-1232.

Hansen, Ronald W. (1979), 'The Pharmaceutical Development Process: Estimates of Current Development Costs and Times and the Effects of Regulatory Changes', in Chien, R.I. (ed.), *Issues in Pharmaceutical Economics,* Lexington, MA, Lexington Books. 151-187.

Henderson, Rebecca and Cockburn, Iain (1996), 'The Determinants of Research Productivity in Ethical Drug Discovery', in Helms, Robert B. (ed.), *Competitive Strategies in the Pharmaceutical Industry*, Washington, DC, The American Enterprise Institute Press, 167-193.

Hurwitz, Mark A. and Caves, Richard E. (1988), 'Persuasion or Information? Promotion and the Shares of Brand Name and Generic Pharmaceuticals', **31** *Journal of Law and Economics*, 299-320.

Leffler, Keith B. (1981), 'Persuasion or Information? The Economics of Prescription Drug Advertising', **24** *Journal of Law and Economics*, 45-74.

Lu, John and Comanor, William (1998), 'Strategic Pricing of Pharmaceuticals', *Review of Economics and Statistics*, forthcoming.

Masson, Alison and Steiner, Robert L. (1985), *Generic Substitution and Prescription Drug Prices: Economic Effects of State Drug Product Selection Laws,* Washington, DC, Bureau of Economics, Federal Trade Commission.

Munnich, Frank E. and Sullivan, K. (1994), 'The Impact of Recent Legislative Change on Germany', **6(Suppl.1)** *PharmacoEconomics*, 11-16.

Myers, Steward C. and Shyam-Sunder, Lakshmi (1996), 'Measuring Pharmaceutical Industry Risk and the Cost of Capital', in Helms, Robert B. (ed.), *Competitive Strategies in the Pharmaceutical Industry,* Washington, DC, The American Enterprise Institute Press, 208-237.

Pauly, Mark V. (1968). 'The Economics of Moral Hazard', **58** *American Economic Review*, 231-237.

Peltzman, Sam (1973), 'An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments', **8** *Journal of Political Economy*, 1049-1091.

Pharmaceutical Research and Manufacturers of America (PhRMA) (1997), *1997 Industry Profile,* Washington, DC.

Ramsey, Frank P. (1927), 'A Contribution to the Theory of Taxation', **37** *Economic Journal*', 47-61.

Reekie, W. Duncan (1978), 'Price and Quality Competition in the United States Drug Industry', **26** *Journal of Industrial Economics*, 223-237.

Scherer, Frederic M. (1993), 'Pricing, Profits and Technological Progress in the Pharmaceutical Industry', **7** *Journal of Economic Perspectives*, 97-115.

Scherer, Frederic M. (1996), 'How U.S. Antitrust Can Go Astray: The Brand Name Prescription Drug Litigation', **4** *International Journal of the Economics of Business*, 239-256.

Schmalensee, Richard (1982), 'Product Differentiation Advantages of Pioneering Brands', **72** *American Economic Review,* 349-365.

Schulenburg, Mathias V.D. and Schöffski, O. (1993), *Implications of the Structural Reform of Healthcare Act on the Referral and Hospital Admission Practices of Primary Care Physicians*, Hanover, University of Hanover, Institute of Insurance Science.

Schulenburg, J. Matthias Graf Von Der and Schöffski, Oliver (1994), 'Transformation des Gesundheitswesens im Spannungsfeld zwischen Kostendämpfung und Freiheit, Eine ökonomische Analyse des veränderten Überweisungs- und Einweisungsverhaltens nach den Arzneimittelregulierungen des GSG (Transformation of the Health Care System, An Economic Analysis of the Changes in Referrals and Hospital Admissions after the Drug Budget of the Health Care Reform Act of 1992)', in Oberender, P. (ed.), *Probleme der Transformation im Gesundheitswesen*, Baden-Baden, Nomos, 45-81.

Schwartzman, David (1975), *The Expected Return from Pharmaceutical Research*, Washington, DC, The American Enterprise Institute Press.

Schweitzer, Stuart O., Schweitzer, Maurice E. and Guellec, Marie S. (1996), 'Is There a U.S. Drug Lag? The Timing of New Pharmaceutical Approvals in the G-7 Countries and Switzerland', **53** *Medical Care Research and Review*, 162-178.

Suslow, Valerie Y. (1996), 'Measuring Quality Change in the Market for Anti-Ulcer Drugs', in Helms, Robert B. (ed.), *Competitive Strategies in the Pharmaceutical Industry*, Washington, DC, The American Enterprise Institute Press, 49-72.

Telser, Lester (1975), 'The Theory of Supply with Applications to the Ethical Pharmaceutical Industry', **18** *Journal of Law and Economics*, 449-478.

Temin, Peter (1980), *Taking Your Medicine: Drug Regulation in the United States*, Cambridge, MA, Harvard University Press.

Thomas, Lacy Glenn, II (1990), 'Regulation and Firm Size: FDA Impacts on Innovation', **21** *RAND Journal of Economics*, 497-517.

Thomas, Lacy Glenn, II (1996), 'Industrial Policy and International Competitiveness in the Pharmaceutical Industry', in Robert B. Helms (ed.), *Competitive Strategies in the Pharmaceutical Industry,* Washington, DC, The American Enterprise Institute Press, 107-129.

US Congress, Office of Technology Assessment (OTA) (1993), *Pharmaceutical R&D: Costs, Risks and Rewards*, Washington, DC, Government Printing Office.

US Congressional Budget Office (CBO) (1994), *An Analysis of the Administration's Health Proposal,* Washington, DC, Government Printing Office.

US General Accounting Office (GAO) (1992), *Prescription Drugs: Companies Typically Charge More in the United States than in Canada*, Washington, DC, Government Printing Office.

US General Accounting Office (GAO) (1994), *Prescription Drugs: Companies Typically Charge More in the United States than in the UK*, Washington, DC, Government Printing Office.

Walker, Hugh E. (1971), *Market Power and Price Levels in the Ethical Drug Industry,* Bloomington, University of Indiana Press.

Wardell, William M. (1973), 'Introduction of New Therapeutic Drugs in the United States and Great Britain: An International Comparison', **14** *Clinical Pharmacology Therapeutics*, 773-790.

Wardell, William M. and Lasagna, Louis (1975), *Regulation and Drug Development*, Washington, DC, American Enterprise Institute Press.

Wiggins, Steven N. (1981), 'Product Quality Regulation and New Drug Introductions: Some New Evidence from the 1970s', **63** *Review of Economics and Statistics*, 615-619.

Zeckhauser, Richard (1971), 'Medical Insurance: A Case Study of the Trade-Off Between Risk Spreading and Appropriate Incentives', **2** *JET*, 10-26.

Zweifel, Peter and Crivelli, Lucien (1996), 'Price Regulation: Lessons from Germany', **9** *Journal of Regulatory Economics.*