

INDUSTRIAL POLICY AND THE PHARMACEUTICAL INDUSTRY

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'Price and Profit Control, New Competitive Dynamics and the Economics of Innovation in the Pharmaceutical Industry'

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Introduction

The focus of this paper is the economics of the pharmaceutical R&D process. Major developments currently impacting the industry include the fact that R&D costs for new drugs are rising very rapidly. Product life cycles are also shortening, which means that there is less time to recover R&D costs and other investment expenditures. Firms are increasingly dependent on a small number of products — they are often referred to as blockbuster products — to finance the future R&D for new drug introductions.

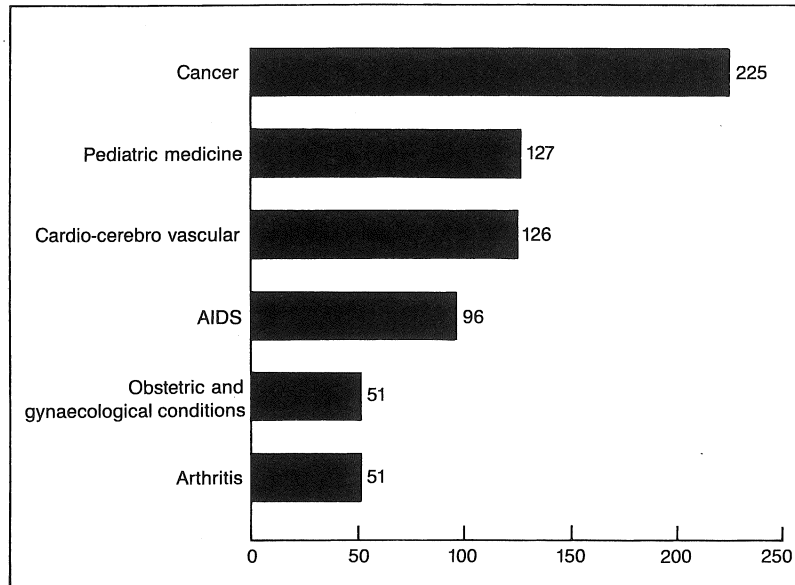
In terms of public policy, pharmaceuticals are also the focus of vigorous cost containment efforts in virtually all major countries. Price regulators tend to be driven by short-term budgetary considerations. The extreme skewness in new drug sales and returns make the blockbuster or top decile of drugs the special targets of these regulators. They try to obtain these big-selling drugs at 'breakeven' prices, while letting other countries bear the high fixed costs of R&D. Of course the more countries which try to behave in this manner, the more negative the consequences for R&D incentives.

This paper provides an overview of several factors influencing the current and future environment for pharmaceutical R&D. The following section examines current economics of the R&D investment process, including the trends in R&D costs and product life-cycles. The second section discusses some of the main results from my ongoing work on the returns to R&D for new drug introductions. The final section considers the consequences of price and profit controls for R&D incentives.

The R&D Investment Process

This is a time of exploding opportunities for pharmaceutical advances. Increased knowledge of physiological processes at the molecular level enable researchers to develop more selective and potent pharmaceutical targets. New research tools, such as electron microscopy and X-ray crystallography, and new research techniques associated with biotechnology, have helped enhance the search for significant new compounds. Because of these advancements, pharmaceutical industry R&D now can be cat-

FIGURE 1 Number of Clinical Research Projects (1991)



Sources: PMA

egorised more as a 'discovery by design' approach, as opposed to the random screening of compounds that was once prevalent.

Pharmaceutical firms are currently pursuing numerous research projects in the areas of critical medical need. Figure 1 shows the number of clinical research projects across several important therapeutic areas. Cancer had over 200 separate research projects in 1991. This reflects the growth of biotechnology which has been focused on new cancer treatments. Pediatric medicine and cardiovascular therapies each had more than 100 clinical research projects, while AIDS had close to 100 projects in that year.

Although there is great optimism about the scientific potential for important new drug discoveries, there is also mounting evidence that the R&D process from an economic perspective is becoming longer and costlier. Figure 2 shows a plot of the average duration of the investigational New Drug (IND) and New Drug Application (NDA) phases for annual US new drug approvals between 1964 and 1991. By the early 1990s, the IND or clinical investigational phase averaged over 5 years and the NDA or regulatory review phase was about 2½ years. If we add to this a pre-clinical phase of 2 to 4 years, we obtain a mean total R&D time of almost 12 years.

FIGURE 2 Duration of IND and NDA Phases for Self-originated NCEs of US firms

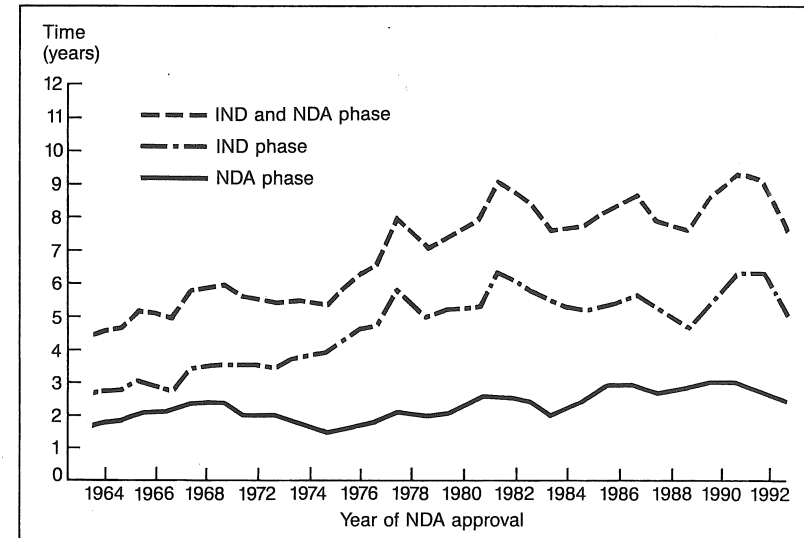
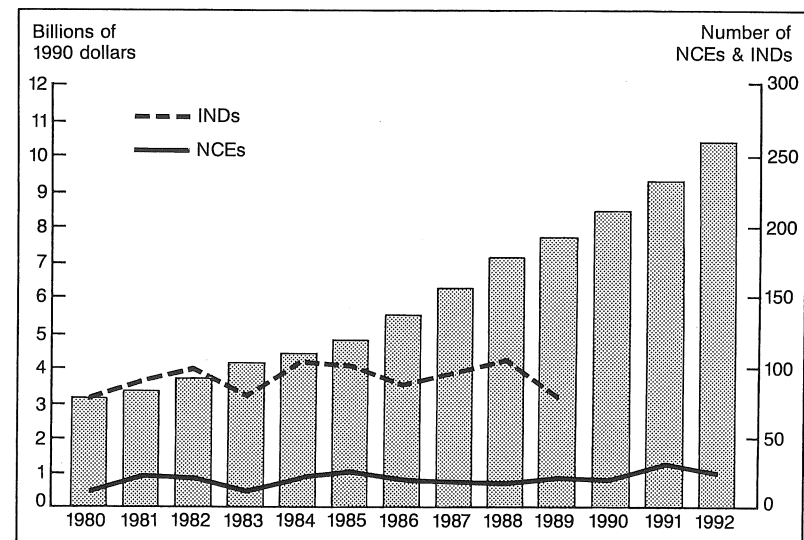


FIGURE 3 R&D expenditures, NCEs and INDs



The bar graph in Figure 3 shows annual industry R&D expenditures, expressed in constant dollars. The spaced and solid lines show the annual number of INDs filed and new chemical entities (NCEs) approved by the FDA. This figure indicates that R&D expenditures have increased several fold, even after adjustment for economy-wide inflation. At the same time, the annual number of INDs and NCEs has changed only moderately. While the issue of R&D costs is best analysed at the level of individual drugs, the aggregate data series in Figure 3 suggest that R&D investment costs per new drug introduction have been increasing significantly in real terms.

The Center for the Study of Drug Development at Tufts University has completed a microeconomic study of R&D costs (DiMasi, 1991). The principal investigators in this study are Joe DiMasi, Ron Hansen, Lou Lasagna and myself. This analysis is designed to estimate the average R&D cost for NCEs discovered and developed by US-owned firms (i.e. their self-originated NCEs). Data were obtained on a random sample of 93 drugs first tested in humans between 1970 and 1982. In this analysis the costs of drug candidates that fail in pre-clinical and clinical trials are incorporated into the average costs of the new drug introduction. R&D expenditures also are capitalised to the date of marketing introduction to reflect the time costs associated with an investment in pharmaceutical R&D.¹

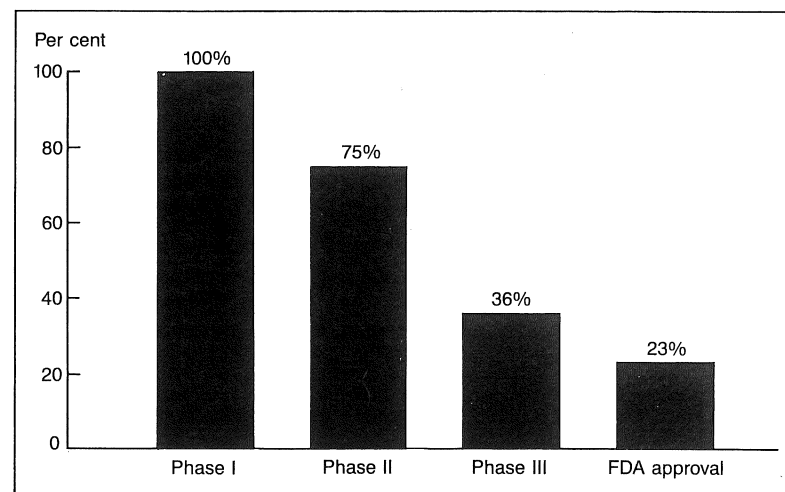
Our best estimate is that it takes an average of \$231 million (in 1987 dollars) and 12 years to discover and develop a new drug. Of this total, \$114 million is the out-of-pocket R&D costs and \$117 million is the time cost associated with the 12-year average investment period. In addition, we find substantial variability around this mean cost estimate. Research is continuing with respect to how R&D costs vary by therapeutic category and other characteristics.

Figure 4 shows the average attrition rate of a representative new drug compound in our sample as it goes through each development phase toward FDA approval. Of the full cohort of drugs beginning clinical testing, 75 per cent enter Phase II and 36 per cent survive to Phase III. Furthermore, 23 per cent of the clinically tested compounds for our sample firms eventually obtain FDA approval. While this success rate has been increasing over time, 4 to 5 compounds must still be taken into man for each one that obtains approval. This is an important factor which caused R&D costs in pharmaceuticals to multiply in value as one proceeds through the different testing phases.

Our findings also imply that average R&D costs per new drug intro-

1 Time costs measure the income foregone from investing in development for the period before returns are earned. Time costs are measured at the pharmaceutical industry's cost of capital. The sum of out-of-pocket cost and time cost is the capitalised cost of new drug development.

FIGURE 4 Probability of clinically tested NCEs entering various phases and gaining FDA approval



duction have been increasing significantly. An earlier analysis by Hansen (1979) using the same general methodology found an average R&D cost of \$54 million (in 1976 dollars). Hansen's R&D cost estimate is \$100.7 million expressed in 1987 dollars. Hence in real terms total capitalised costs are about 2.3 times larger in our study than in the earlier period analysed by Hansen.

What factors account for this increase in real R&D costs per new drug introduction? This is clearly an important issue for further research. Some key factors can be highlighted on the basis of our present knowledge. First, pharmaceutical R&D now entails significantly greater expenditures in the discovery phase. A second factor associated with longer R&D times and higher costs per new drug introduction is the shift in research focus toward therapeutics to treat chronic clinical conditions such as cardiovascular disease and cancer. Chronic disease drugs require more long-term testing and greater overall resource investments prior to commercial introduction. A third factor accounting for higher R&D costs is the rapid escalation in the out-of-pocket costs for clinical trials and the greater capital equipment requirements associated with current R&D activities in the pharmaceutical industry.² There are strik-

2 There is preliminary evidence that the increase in out-of-pocket expenditures for clinical trials is due both to an increase in the number of trials performed and the cost per trial (OTA, 1993; Boston Consulting Group, 1993).

ing changes in this regard emerging from our analysis compared to the situation of a decade ago. Understanding the forces underlying this rapid increase in out-of-pocket costs is an important topic for future research.

In our R&D cost study, we also simulated the effect on total R&D costs of a one year reduction in regulatory approval time. The regulatory approval phase in the United States has averaged approximately 2¹/₂ years over the past decade. If this could be reduced by one year, we estimate that it would decrease R&D costs by \$19 million. This is roughly 8 per cent of our overall estimate.

A reduction in regulatory review time, of course, may require more resources at the FDA. However, the aggregate R&D cost saving for the industry of a one year reduction in review times would be substantial. In particular, a saving of \$19 million per approved NCE multiplied by an average of 19 approved NCEs per year, yields an aggregate annual potential savings in industry R&D costs of \$361 million. To put this in perspective, this is roughly half the FDA's total annual budget in recent fiscal years. Furthermore, it significantly exceeds the annual budget for the new drug division of FDA. Hence, there are strong potential benefits to be obtained from a faster and more efficient FDA review process if this can be done without compromising patient safety. In September 1992, the US Congress instituted user fees on new drug applications (HR 6181). The user fee will be dedicated to the hiring of additional FDA reviewers with the objective of eventually reducing the average review times to one year. If successful in this objective, this could have significant positive incentive effects on R&D (Grabowski and Vernon, 1994).

Product Life Cycles

Whereas R&D investment costs have been increasing, product life cycles have been getting shorter. This is the result of faster follow-on from competing new drugs and increased generic competition when patents expire. The fast followers have occurred in many competitively active therapeutic classes like the ace inhibitors cardiovascular drugs, the newer non-tricyclic antidepressants and the cholesterol-lowering agents. Within a few years after the pioneering product is introduced, there are follow-on competitive products coming into the market. In addition, these products are now typically introduced at significant discounts to the market leader and also frequently offer aggressive discounts to managed care organisations to gain access to their formularies. The changes in the case of the United States are driven by the growth of managed care and are sometimes referred to as the new competitive dynamics.

The fast follower phenomenon is illustrated by the experiences in the United States of the cholesterol-reducing therapeutic group. The breakthrough product introduction was Mevacor in 1987. The second and

third entrants, Provachol and Zocor, were introduced in the next year and priced below Mevacor. More recently Sandoz has announced that its 1994 competitive entrant in this class will be priced at a discount of 50 per cent below Mevacor. Similar competitive experiences have occurred in ACE inhibitor and nontricyclic anti-depressant therapeutic class (Grabowski, 1994).

Another major change in the product life cycles over the last decade is due to increased competition from generics. Several years ago, when a patent expired, a manufacturer would lose part of the market share to generics, but at a fairly slow pace (Statman, 1982). This situation changed dramatically in the wake of the 1984 Drug Price Competition and Patent Restoration Act and demand side developments on the 1984 Act shortened and simplified the regulatory process for generic drugs by allowing the submission of an abbreviated new drug application (ANDA). This allowed generics an easier and faster entry into the market. At the same time, the growth of managed care organisation on the demand side has accelerated the utilisation of generics in the United States.

John Vernon and I have examined the experiences of 18 economically significant drug products whose initial generic competition occurred in the 1984 to 1987 period (Grabowski and Vernon, 1992). For these drug compounds, the average product was subject to 25 generic competitors and lost approximately half its market share within 2 years. An examination of drugs coming off patents during the 1990s in the United States indicates the rate of sales erosion after patent expiration is accelerating. For example, two recent expirations, Xanax and Naprosyn, lost much more than 50 per cent of their sales volume in the first several months after initial generic entry, despite a marketing strategy of offering their own generic products.³

In many European countries, similar sales losses are occurring under reference pricing schemes. There is evidence that product life cycles are shortening on a global basis due to intensified competition among brand name products and an increased availability and willingness to utilise generic substitutes. While legislation has also been passed in the United States and Europe to stabilise effective patent terms and restore patent time lost during the clinical regulatory review periods, these efforts have so far had minimal positive effects on innovation incentives (Grabowski, 1991a).

³ In the case of Xanax, Upjohn has seen its \$500 million annual sales shrink to \$42 million during the first year of generic competition. Although Upjohn managed to maintain a large market share with its own generic formulation of alprazolam, the generic price fell to \$4 for 100 tablets, compared to \$52 for 100 tablets of Xanax. Similarly, Syntex's generic naproxen took 64 per cent of new prescriptions in January 1994, the first full month after patent expiration. However, the generic price fell to \$12 per 100 tablets compared to a price of \$65 for 100 tablets of the brand name product, Naprosyn. As a consequence, Syntex's overall revenues from this product dropped more than 50 per cent in the first month of generic competition. 'Effects of US Generic Price Cuts', Scrip, April 12, 1994, p19.

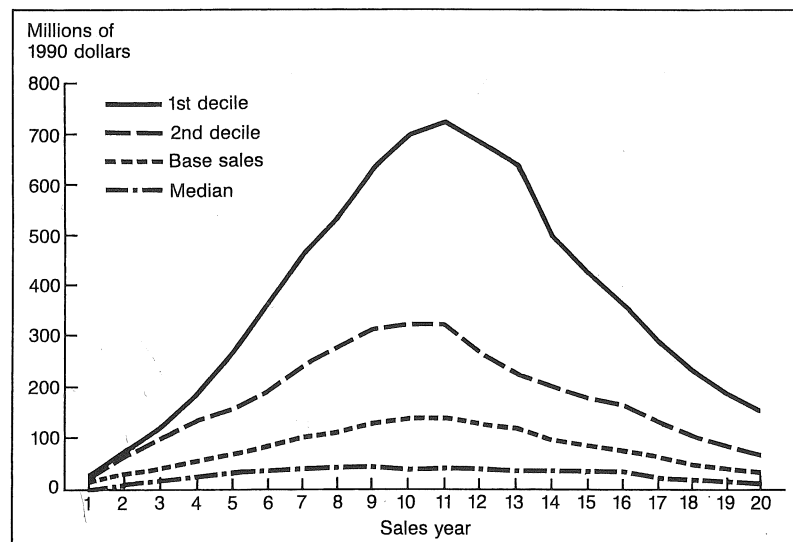
Returns to Pharmaceutical R&D

John Vernon and I have been engaged in an ongoing long-term study of the returns to US new drug introductions. We have completed our analysis of the returns on new drugs introduced during the 1970s, and we are currently analysing the returns to the new drug introduction of the 1980s utilising a comparable methodology. This section discusses the nature of the analysis and some of the major findings from this on-going work (Grabowski, 1994).

A key question which we address in this work is whether the average US NCE earns a rate of return on R&D investment that is commensurate with the pharmaceutical industry's cost of capital. We also examine the distribution of returns and the breakeven time for the average NCE to cover its R&D costs. Our analysis is based on a comprehensive sample of US NCE introductions and is performed on a real after-tax basis.

Figure 5 shows some aggregated sales profiles for the US market for 1980-1984 introductions. In particular, it shows annual sales estimates for the mean, median and top few deciles of our sample. These curves exhibit the classical life cycle pattern of rapid sales growth, maturity, and sales decline. This figure also illustrates the highly skewed nature of the sales distribution for new drug introductions. The sales peak of the top decile drugs are several times greater than the sales peak for the second decile. Furthermore, the mean sales curve is much higher than the

FIGURE 5 US sales profiles of 1980-84 NCEs



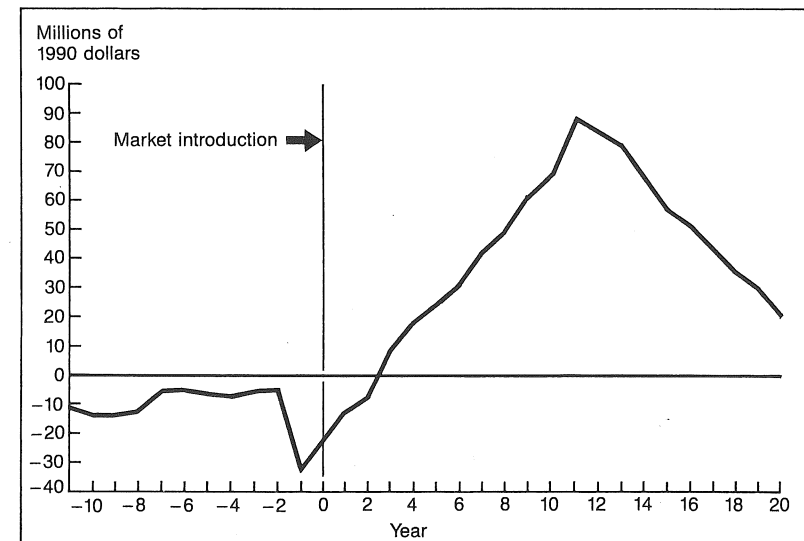
median one. This is a very important point in terms of understanding the pharmaceutical industry economics. A few top-selling drugs are really key in terms of economic success in providing the funds for future research.

Rates of return are estimated from the series of annual net cash flows starting at the beginning of the R&D investment period and going to the end of the product's life cycle. A life cycle profile of the cash flows for the average new drug introduction in our 1980-84 sample is presented in Figure 6. Cash flows are negative over the pre-clinical and clinical R&D period and become increasingly so in the years prior to initial marketing due to the addition of heavy launch and capital investment outlays. By year 3 after product launch, cash flows generally become positive. They then escalate rapidly, reach a peak in year 11 after marketing, and then begin a period of sharp decline. We assumed 20 years as the expected product lifetime for this sample cohort.

The baseline values in Figure 6 provide the basis for computing the internal rate of return (IRR) and the net present value (NPV) for the mean 1980-84 NCE.

A basic finding of the analysis is that the IRR for the mean NCE is 11.1 per cent. This is only slightly above the industry's 10.5 per cent cost of capital over this period (Myers and Shyam-Sunder, 1994). The capitalised value of R&D investment costs for the representative 1980-1984

FIGURE 6 Cash flows for mean 1980-84 NCE

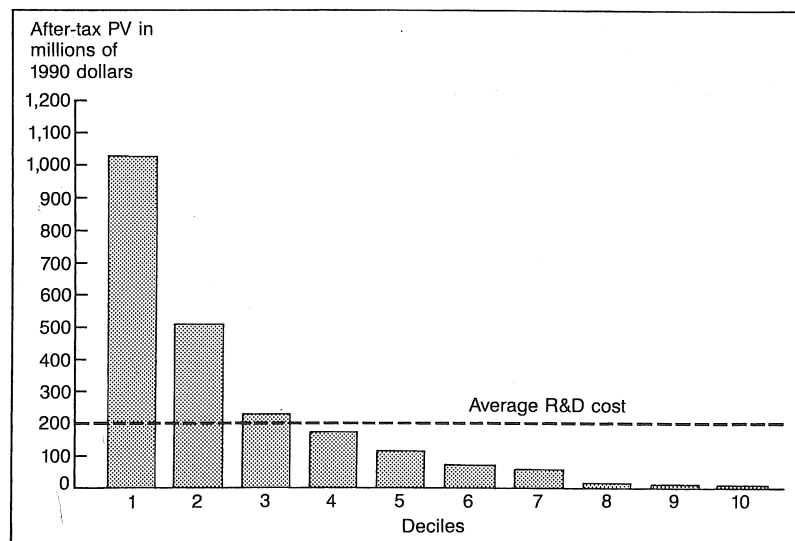


NCE is \$201.9 million after tax (in 1990 dollars). The discounted value of net cash returns resulting from this R&D investment is \$224.1 million. Hence, the net present value (NPV) for the mean 1980-1984 NCE is \$22.1 million.

Although the average NCE's returns on R&D are moderately higher than the cost of capital, there are larger variations in present values and returns across NCEs. As in our earlier work on 1970s NCE introductions, we found that the distribution of present values is highly skewed. Figure 7 shows the present value by deciles for the 67 NCEs in our sample. The top decile of NCE has an estimated present value of cash flows after launch that is more than five times the capitalised value of average R&D costs. In addition, only the top three deciles have present values that exceed average R&D costs.

The above analysis confirms the fact that the search for blockbuster drugs is what motivates the pharmaceutical R&D process. Many of smaller, niche-type products are useful therapies in the physician's arsenal. Furthermore, a great many of these products also contribute to the firm economically in terms of covering their direct R&D investment expenditures. However, the products below the third decile will not typically cover any of the common discovery costs or costs of large numbers of the products that fail in the development process. Hence, a firm must occasionally obtain a drug in the top few deciles, if it is to earn positive long-run returns on its total portfolio of projects.

FIGURE 7 **Present values by decile: 1980-84 NCEs**



This extreme skewness of returns to pharmaceutical R&D also has an important implication for the profit and price controls. That is, when price regulation develops that focuses on the big selling drugs — the top few deciles — then the returns to overall new drug innovation will be reduced significantly, and it will be difficult to sustain a high rate of technological advance. This is a key issue that is addressed further below.

Public Policy

In the scientifically promising but fragile economic environment that currently exists with respect to pharmaceutical R&D, public policy-makers will have considerable influence on the future level and sources of drug innovation. R&D investment outlays are inevitably influenced positively and negatively by a host of government policies.

I have already discussed the significance of regulatory policies for the incentives for pharmaceutical innovation at earlier places in this paper. Recent attempts in American and Europe to make the registration process more efficient and less cumbersome could have an important positive effect on research incentives. The movement toward a European registration process for new drugs is also a positive development.

The support of basic biomedical research is another government policy that can dramatically influence the incentives for new drug innovation over the long run. Recently the growth of government-supported research in the United States has been lagging industry-funded R&D efforts (Grabowski, 1991b). This reflects a tighter environment for government expenditures in all areas.

Government reimbursement policies toward new drug introductions will undoubtedly have a crucial impact on the returns to new drug R&D in the 1990s. As health care cost escalates, more countries are turning to stringent price and profit controls to hold down the growth in costs. The most successful new drugs from a commercial perspective are generally those drugs which provide significant therapeutic advances over established medicines. Reekie (1978), Lu (1993) and others have shown that such innovative drugs are typically launched at a premium price relative to substitutes, whereas the majority of imitative drugs are introduced at a price discount. Government price regulators charged with holding down the growth of pharmaceutical expenditures naturally focus, therefore, on the subset of the most innovative new therapies, especially those expected to expand existing markets or achieve large market size. These are also the therapies most likely to be in the top decile of new drug introduction in terms of expected sales revenues.

In some recent model simulations, John Vernon and I have shown the highly adverse effects on the incentives for pharmaceutical R&D of price controls that focus on innovative new products with large expected sales. These simulations were motivated by some of the proposed US.

health care changes and a desire to analyse the consequences of these changes for the pharmaceutical innovation process. Of course very restrictive systems of price controls on pharmaceuticals are already in effect in several other countries that encompass this kind of regulatory behaviour.

In particular, we assume in our simulations that regulators focus their attention on the top decile of products and impose breakeven pricing criteria for these drugs. We utilise our distribution of 1980–84 US NCE introductions in this analysis. The best way to describe this scenario is to refer to Figure 7 again, which shows the present value by decile for the 67 NCEs for our 1980–84 sample. We assume that regulators constrain the price so that the IRR for these top decile drugs are just equal to the overall cost of capital for the industry in our model (i.e. 10.5 per cent). In this case, the present value of cash flows for the top decile drugs is just equal to the present value of R&D costs. In other words, the large 'excess' profit for this top decile of products is completely eliminated.

Our simulation analysis examines the effect on average returns to R&D when this 'breakeven' pricing constraint is imposed on the top decile of products. The effect for the average NCEs is a negative change in the expected NPV from \$22.2 million to -\$60.2 million. This is more than 30 per cent of the total present value of the average NCE (-\$82.4 million/\$24.1 million). With such large expected losses for the representative new drug, firms would be expected to respond by curtailing expenditures on future R&D projects until expected returns again become positive.

In interpreting these results, it must be remembered that the search for blockbuster drugs is what motivates pharmaceutical R&D. However, government price regulators typically have a myopic bias. They are unlikely to allow for the fact that probability of commercial success for any given R&D project is very low and that the returns to blockbuster drugs must compensate for low or negative returns on most other new drug introductions.

The type of price regulation can be expected to have an especially chilling effect on the most long-term risky R&D projects. If one regards R&D investment as somewhat like a lottery — with low probabilities of achieving high returns — price regulation clearly changes the attractiveness of the 'R&D lottery'. Winning the lottery now provides the likelihood of only a break-even return. As a consequence, firms would be expected to devote more of their R&D and marketing activities to certain incremental or 'niche' type advances that entail less technological and regulatory risks. To the extent that prospective social gains are positively correlated with risk bearing in pharmaceutical R&D, these are precisely the wrong signals to create in the US market.

The type of new drugs that are most negatively impacted by a myopic top-down system of price controls are those that increase current bud-

geted health care expenditures. This would include, for example, maintenance therapies directed to improvements in quality of life. Another negatively impacted class of drugs involve therapies where the patient benefits are long term in character. Even drugs that can demonstrate that they are cost reducing to the health care system in current periods may not be encouraged in the environment if they raise the pharmaceutical budgets of government entities. This is because expenditure decisions in government bureaucracies are often made on an individual component basis. Savings to other health care expenditure budgets receive lesser weight and can go unrewarded.⁴

Price controls on innovative new drugs have extremely negative consequences for smaller firms exploring new technologies, such as those in the emerging biotech sector. Biotech firms concentrate their R&D activity on long-term discovery research and are highly dependent on venture capital and external investment sources. It is no accident that these firms are primarily a US phenomena, where the market for pharmaceutical products has not been subject to extensive government price controls, and the venture capital market is most highly developed.

The biotech segment of firms are especially vulnerable to price controls because they are typically too small to pool R&D successes and failures in any meaningful way. Second, their external sources of R&D funding are likely to respond to the price regulation provisions and enhanced commercial uncertainties by sharply raising the price and availability of R&D investment funds. Currently, all but the very largest biotech firms operate with cash surpluses for R&D (denoted in the trade as 'burn rates') of only a few years. Many biotech firms would not survive a system of controls that are targeted to the most important new commercial medicines.

An alternative cost containment approach would be for the government to improve market information and encourage the adoption of cost-efficient new products as well as the usage of low-price generic products as they become available after patent expiration.

This has been recommended by several economists examining the options in the case of US health care reform (Scherer, 1993; Grabowski, 1994). There are several reasons why this is a more preferable direction to build on compared to the price regulation of important drugs. First

⁴ The administration of drug budgets by the Medicaid Program in several US states offers a number of illustrative samples. Moore and Newman (1992) recently found that restrictive Medicaid formularies resulted in prescription drug savings, but substitution of other medical services caused expenditures to rise elsewhere in the Medicaid system. Similar results were observed in a study by Soumerai and Avorn, which found drug payment limits for Medicaid recipients caused admissions to hospitals and nursing homes to increase. My analysis of state Medicaid programmes also found that enrollees experienced delays in the availability of important new drugs in several states due to formulary restrictions (Grabowski, 1988).

of all, the market is evolving strongly in this direction, and the government would be reinforcing rather than retarding market forces. At the present time, firms in the pharmaceutical industry are adapting to very fundamental changes on the demand side of the market. At the centre of these changes are the growing managed care plans of the private sector. To an increasing degree over time, these organisations have employed strategies such as drug formularies, generic prescribing and drug utilisation reviews to achieve substantial savings in their pharmaceutical expenditures. Looking to the future, a large number of the current top-selling drugs will experience patent expiration over the next several years, thereby providing opportunities for large cost savings from the market-oriented approach. Finally, a market-oriented strategy provides a more promising industrial policy approach for encouraging technological advances in pharmaceuticals,⁵ while price controls have been consistently shown to have a strong negative impact on the incentives for pharmaceutical innovation (Thomas, 1992a; 1992b).

Conclusions

The economic trends indicate that pharmaceutical R&D activity is becoming longer, costlier and riskier in nature, and product life cycles are contracting under increased competition on the demand and supply side of the market. It is fortunate that, to date, this has not caused a serious negative global impact on R&D investments of the pharmaceutical industry. The strong prospects for scientific advance and the ability to make strategic responses to the changing economics of R&D in some countries have kept global pharmaceutical R&D investments growing at a strong pace. Whether this will continue in the future is highly debatable. All countries are facing pressures to contain health care costs. Pharmaceuticals are a frequent target for this cost containment despite their cost-effective nature and their relatively small share in overall health care costs.

I think there is the risk that as health care costs escalate, virtually all countries will try to obtain the most innovative new pharmaceuticals at break-even prices and try to leave the payments for drug R&D to other countries. So we have what is a free rider problem evolving in the phar-

maceutical industry, as policymakers deal with the immediate stresses of today's health care costs. Left unchecked, these developments could result in a drastic curtailment of global R&D investment for new medicines, despite the exciting potential for scientific advances which now exist. I think it is very important that as strong a case as possible be made to prevent this undesirable scenario from occurring. Pharmaceutical discoveries have a major role to play in improving the quality of treatment and in providing cost-efficient options to the health care delivery systems of the future.

REFERENCES

- Boston Consulting Group (1993). *The changing environment for US pharmaceuticals*, New York.
- Dimasi, J, Hansen, R, Grabowski, H, and Lasagna, L (1991). The cost of innovation in the pharmaceutical industry. *J Health Econom.* 10: 107-142.
- Grabowski, H (1988). Medicaid patients' access to new drugs. *Health Affairs*, Winter, 102-114.
- Grabowski, H (1989). An analysis of US international competitiveness in pharmaceuticals. *Manag. Decision. Econom.* Special Issue: 27-33.
- Grabowski, H (1991a). *Pharmaceutical Research and Development: Returns and Risk*. Centre for Medicines Research Annual Lecture, Surrey, England.
- Grabowski, H (1991b). *The Changing Economics of Pharmaceutical Research and Development*. In: *The Changing Economics of Medical Technology* (Annetine C Gelijns and Ethan A Halm, eds.), pp35-52. National Academy Press, Washington, D.C.
- Grabowski, H (1994). *Health Reform and Pharmaceutical Innovation*. American Enterprise, Washington, D.C.
- Grabowski, H and Vernon, J (1990). A new look at the returns and risks to pharmaceutical R&D. *Management Science* 36: 804-821.
- Grabowski, H and Vernon, J (1992). Brand loyalty, entry and price competition in pharmaceuticals after the 1984 drug act. *J Law and Econom* 35: 331-350.
- Grabowski, H and Vernon, J (1994). Returns on new drug introductions in the 1980s. *J Health Econom*, 13: 383-406.
- Hansen, R (1979). *The Pharmaceutical Development Process: Estimates of Current Development Costs and Times and the Effects of Regulatory Changes*. In: *Issues in Pharmaceutical Economics* (R I Chien, ed.), pp151-187. Lexington Books, Lexington, Mass.
- Lu, J (1993). *Strategic Pricing of Patented New Drugs*, Unpublished doctoral dissertation, University of California at Santa Barbara, August.
- Moore, W and Newman, R (1992). US Medicaid drug formularies: Do they work, *PharmacoEconomics*, 28 (Supp. 92).
- Myers, S and Shyam-Sunder, L (1994). Cost-of-capital estimates for investment in pharmaceutical research and development. Forthcoming in: *Competitive Strategies in the Pharmaceutical Industry* (R Helms, ed.), American Enterprise Institute, Washington, D.C.
- Office of Technology Assessment (1993). *Pharmaceutical R&D: Costs, risks, and rewards*, US Government Printing Office, Washington, D.C.
- Reekie, W (1978). Price and quality competition in the United States drug industry. *Journal of Industrial Economics*, 26, No. 3, March, pp223-237.
- Scherer, F (1993). Pricing, profits and technological progress in the pharmaceutical industry. *Journal of Economic Perspectives*, 7, No. 3, pp97-116.
- Soumerai, S and Avorn, J (1991). Effects of Medicaid drug-payment limits on admission to hospitals and nursing homes, *New England Journal of Medicine*, October, pp1072-1077.
- Statman, M (1982). The Effect of Patent Expiration on the Market Position of Drugs. In: *Drugs and Health* (R Helms, ed.), pp. 140-151. American Enterprise Institute, Washington, D.C.
- Thomas, L G (1992a). Price regulation, industry structure and innovation: An international comparison of pharmaceutical industries. *Pharmacoeconomics* 1, Supplement, 9-12.
- Thomas, L G (1992b). Trends of innovation in the world pharmaceutical industry. *Rivista internazionale di Scienze sociali* 3 : 333-346.

5 The encouragement of generics can be expected to have less adverse consequences for innovation incentives compared to a price regulation approach. This reflects the fact that generic competition generally takes effect only after an effective patent life of approximately 10 to 12 years, and sales losses which occur later in the product life cycle are heavily discounted in an NPV analysis. To illustrate this latter point, John Vernon and I have examined the effects of two very severe generic competition scenarios using our 1980-84 sample of NCE introductions. In particular, in these scenarios, we assume that firms expect sales to fall 70 per cent and 90 per cent in the year after patent expiration. The observed change in NPV for the mean NCE under the most severe generic erosion scenario is observed to be much less than the change which occurs when the top decile drugs are constrained to a zero NPV (-\$29.9 million versus -\$82.4 million) (Grabowski, 1994).