INDUSTRIAL POLICY AND THE PHARMACEUTICAL INDUSTRY

The Proceedings of a Symposium held on 22nd June 1994, London

Edited by Adrian Towse

Office of Health Economics
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Foreword

Adrian Towse

This book contains the proceedings of a conference held by the Office of Health Economics in June 1994. The papers, by a number of distinguished contributors, explore the role industrial policy can play in providing an economic environment in which the pharmaceutical industry meets the needs of patients and health care purchasers, so providing an economic asset to those countries hosting its R&D and manufacturing activity.

Governments cannot avoid policy interaction with the pharmaceutical industry. They are responsible for both 'health and safety' and 'economic' regulation. The former primarily governs the licensing procedures before a new medicine can be put on the market. The latter has two key elements — intellectual property protection (the pharmaceutical industry is the most patent intensive of any industrial sector) — and, in most countries, government as a major purchaser of medicines. There is another key aspect of government policy that is of enormous importance to the industry — the funding of 'basic' science. Public funding of this research and of universities generates advance in 'basic' scientific knowledge and a supply of skilled scientists.

The first four papers in this book explore and contrast the approaches the European Community, and Japanese, US and UK governments have taken to industrial policy in this sector. Have they, intentionally or unintentionally, contributed to the relative success of the industry in their home bases? Those dealing with the European Community, Japan and the US are by Yarrow, and Professors Neary and Scherer, respectively. In the fourth paper Hale and Towse assess how valuable the UK-based pharmaceutical industry is to the UK economy. The fifth paper, by Professor Jones, then considers the scientific potential for medical breakthrough, trends in the costs of achieving these breakthroughs, and the importance of government science and education policy for the discovery and development process.

The seventh and eighth papers by Quam and Professor Grabowski respectively explore the role of government as purchaser and economic regulator. Quam discusses, from US experience, the relative merits of public versus private purchasing, and of centralised versus decentralised purchasing of medicines, for the long term health of patients and of the pharmaceutical industry, drawing lessons for Europe. Grabowski examines the potential impact of price control on innovation, drawing on a study of innovation in the USA. Finally Holmes and Professor Dunning explore the impact of government industrial policy on the location and investment decisions of the pharmaceutical industry.

I hope that the readers of this book will find the papers as stimulating

as did the audience in London in June 1994. The pharmaceutical industry has been a major contributor to health and to wealth creation, but is not without its critics. An understanding of the economic issues behind its relationship with governments is crucial to public policy making that ensures the industry continues to meet the needs of society.

CEC and EC Member State Industrial Policy and the Pharmaceutical Industry

George Yarrow

Introduction

My remarks are motivated chiefly by the publication of the European Community document on Industrial Policy, which most of you will know. It's called *Outlines of an Industrial Policy for the Pharmaceutical Sector in the European Community*. As the title suggests, particularly the word 'Outlines', it is in many respects a tentative document, which by no means confronts all the issues head on. Nevertheless it is an attempt to wrestle with some of the fundamental problems of the sector. In particular, how to maintain an innovative and internationally competitive industry in Europe, whilst simultaneously, of course, delivering value for money to the downstream health services. The document begins by expressing a general concern about the competitiveness of the European Industry and let me just quote from it:

> It says, and this is in the first paragraph, *'There are signs that the competitiveness in the Community Industry is yielding in comparison with its main competitors. Its ability to finance the research and development of new therapeutically innovative medicines, which is a condition for its long term competitiveness, in particular, seems to be relatively weak.'*

And that, I think, seems to be the motivating theme of the document.

The Inevitability of Industrial Policy

To some British ears the term 'industrial policy' itself, which is used in this context, is a rather awkward one. In particular, it has connotations of Governments trying to 'pick winners' among industrial sectors and also, to some extent, of discriminatory and somewhat ad hoc policies of intervention, many of which turn out at the bottom to be nothing more than delivery of favours to particular interest groups. So we can ask: isn't it the case that this type of policy was abandoned in many countries in the 1980s? And one might also ask whether, at the Community level, the founding Treaty regards such interventions as distortions of the market which are to be eliminated, rather than to be encouraged. Well I am going to deal with specific aspects of the European intervention later, but let me first deal with the question of the continuing relevance of industrial policy. I think it is the case that sectors such as pharmaceuticals inevitably are affected by a number of different Government policies. These might include in pharmaceuticals policies towards research support generally, research training, patent policy, drug licensing, as well

as, of course, a raft of policies to do with the organisation and operation of the National Health Service. These policies arise from fundamental economic problems which have to do with the nature of goods and services being supplied in various different markets. About which, more later. But the point that I want to make here is that this variety of policies inevitably has an impact on the supply side of industries such as pharmaceuticals, so that in effect, whatever the rhetoric is, governments do continue to conduct industrial policies in the sense of conducting policies which affect the supply sides of markets. Given that, I would argue that it is actually better to address the issue as a whole, to look at the overall impact of policies on the supply side of particular sectors of the economy, rather than to duck the issue and pretend that there isn't such a thing as an industrial policy.

Indeed, I would argue that to pretend that there isn't an industrial policy and to not look at the overall effect of various measures on a particular sector is to go back into the very ad hocery which is often the source of the criticisms of past industrial policies. So, my first point is simply that, whatever governments say, whatever the rhetoric is, industrial policies are conducted in the UK as much as anywhere else, and, given that, we might as well see if we can do it as efficiently as possible, rather than pretend that these things are non-existent.

Government intervention and regulation varies with the nature of goods concerned. Interventions take different forms and produce different effects depending on the fundamental underlying economic properties of the goods and services. There are many aspects of pharmaceuticals that might be mentioned but I am going to focus on two. First the importance of innovation in the industry and, secondly, the way in which purchasing decisions are made for pharmaceutical products. Both of these aspects have attracted a lot of discussion and are the points underlying much of the Community's document.

Innovative Competition and Price Competition

Taking the innovation issue first, my fundamental point is that competition is a multi-dimensional activity. When firms compete, they compete across many dimensions: it may be price, it may be marketing, it may be product quality, it may be quality of service, it may be research and development, it may be general forms of cost cutting. When we talk about competition we are not dealing with a simple text book case where firms have already got the best production techniques and all they're doing is competing on price; that is not the real world. Given that, the key point being made about this sector is that we can focus on two different dimensions in competition: price competition, and competition through R&D and innovation to introduce new and better quality products. For shorthand I am just going to call the latter 'innovative competition'.

There is a trade-off between those two types of competition, and this is a general point about competition. Sometimes you can target one dimension and make things more competitive in that dimension, but the consequence of that is that you get less competition in the other dimension. Or in fact, to put it more broadly in economic terms, there is, in these sectors where innovation is important, a trade-off between static efficiency and dynamic efficiency. Static efficiency being getting the best out of what you've got, dynamic efficiency relating to the production of new knowledge and techniques over time. That is a very important trade-off, because, where you have got a highly innovative sector, it's quite clear that over time, if you look at spans of decades, the real gains in consumer welfare come from the dynamic side. The real benefits and gains from competition, at least the great proportion of them, come from increases of knowledge over time rather than from better use of a particular stock of knowledge at a given point in time. That makes it very important to get this trade-off between price competition and innovative competition correct. This, in part, can be seen as a motivating factor behind the Community's industrial policy document. The best-known example of the trade-off and Government policy affecting the trade-off are patents where you deliberately create a monopoly right and therefore deliberately weaken price competition, precisely in order to stimulate innovative competition. I think everybody understands that. We weaken price competition in order to promote dynamic or innovative competition. However, what tends more frequently to be forgotten is that anything that strengthens price competition, and therefore reduces the returns from R&D, will also weaken innovative competition. It weakens the incentive to innovate, and will lead to less competitiveness in the dynamic race for new products.

I want to come back to that in a little while. Let me now go to a second quotation from the Community's Industrial Policy document which I think begins to betray some of the failures of analysis that often occur at this level, and these have been failures of analysis which I have also been critical of in European competition policy.

> *'The pharmaceutical market is not a normal market. Companies channel efforts into therapeutic innovation and continued improvements to existing products. Competition between companies focuses on therapeutic innovation. Promotion activities with health professionals play a keen role, enterprises are therefore often less concerned about competing on prices and rather concentrate on their costs, finances and sales volumes.'*

The first point I would make about that is that as a longtime student of markets I have yet to find anything that could reasonably be described as a normal market. Markets differ considerably. There may be common principles at work, but the characteristics of the goods and services makes market institutions vary quite a bit. I think the concept of a normal mar-

ket is a very dangerous one. It's one that economists are all too familiar with. The tendency to treat, let us say, the market for money or for labour or whatever as the same as for the market for apples and oranges, is a common problem in economic analysis. Having said that, in what sense can we say that this emphasis on dynamic competition, rather than price competition is abnormal? It is not at all unusual. There are other dynamic sectors of the economy where technological progress occurs very quickly and the pharmaceutical industry stands at a particular point in the spectrum of technological progressiveness, together with a number of other industries. Indeed, it is precisely because there are such substantial technological advances available and that such advance is not costless that in the interests of efficiency as a whole, balancing off long term dynamic factors and short term factors, this sector should have a high degree of innovative competition. I have said, over time, that is where the biggest gains can be reaped. So whereas I think we often find people looking at this tilt towards dynamic, innovative, competition and away from price competition as a problem, I would argue that it is actually the solution to a problem. It is a reasonably sensible balance of competition in a market where the biggest gains come over time from the increase of knowledge rather than from the better use of a given stock of knowledge. Now that is not to say, of course, that at any one point in time the balance is ideal, and governments can and do change the balance by a variety of devices. All I would argue for is when that's being done, the proper trade-off is recognised. As I say, when it's a question of patents, people do recognise the trade-off. Similarly, when arguing about national price controls I think it is generally accepted that if you squeeze prices through price controls you will weaken the incentive to innovate. But, there are other aspects too, like encouraging competition from generics and even things like encouraging transparency in purchasing decisions which, if they have the effect of reducing prices, and therefore reducing the returns to companies through innovative effort, will similarly affect the balance. All these measures to reduce prices will have a negative impact on dynamic competition. Now again, I wouldn't want to argue that greater transparency in purchasing is a bad thing. Generally speaking one would want people to be well informed and have a proper knowledge when they make purchasing decisions, and that's a positive point and one would argue for that. But, that's not to say one should ignore the fact that, if a policy like transparency does reduce prices, there is an inevitable cost to be borne and therefore that cost should be evaluated and put in the balance sheet. My criticism of many decision makers is that they simply don't recognise that, they want it all ways. They want to pretend that there are no costs. Of course, one of the things economists are always doing is trying to point out the costs of doing a and b and c to politicians and others.

Having said all that and noted that I think the Community document is not terribly explicit on these issues, nevertheless the underlying trade-off is recognised, and again I quote:

> *'The legitimate concern to limit public expenditures must not be allowed to jeopardise the future of pharmaceutical research in Europe.'*

So there is a general awareness, but I think a lack of attention to specific details throughout the document.

Let me go to the second point, the demand for pharmaceuticals, and note the points that are frequently made, that pharmaceutical sales are made most frequently on the basis of doctors' prescriptions, and that might lead to a situation where prices are not particularly important in the choice made. So the worry here is that the nature of demand and the insurance aspects of demand for pharmaceutical prices might lead to a situation of excessive pricing. There are a number of difficult problems at this point and I am just going to gloss over the issues and move straight on whilst acknowledging them. Prices are not the only problem here. It may not be a pricing problem, it may be much more a volume problem that arises from the nature of the demand system. But let's just take the pricing issue again. Once again, one has to be very careful about what you mean by the term 'excessive'. When we go back to the trade-off, if you say prices are excessive, then for a given trade-off between price competition and innovative competition, one is similarly saying that expenditures on R&D and the resources devoted to innovative effort are also excessive, because that's what happens with the balance. Prices go up, the rewards for innovation go up, more resources will be devoted to innovation. So to argue that prices are excessive has the implication that there is rather too much effort going into R&D. When you put it that way round it's not at all obvious that that's what the people want to say, and indeed going back to the Community's document it seems to be saying the opposite. It seems to be saying that there isn't enough resource going into R&D and the implication of that with the given trade-off is actually that the price is not excessive at all, prices are too low. So, once again, my general point is that there is a trade-off here, that the issues have to be faced and one has to be careful of cherry picking individual aspects of competition and treating them as things which can be varied in isolation. The number of mistakes in competition policy that are made by doing that is very large. Again, it comes back to looking at the market as a whole and the way competition as a whole works.

National versus European Union policy: The export of price control

Let me move on fairly smartly from that to the issue of National Policy vs Community Policy. I think one of the reasons why governments may tend to neglect the adverse effects of measures to reduce prices in their

home market on dynamic competition is that they may reason that whatever they do in their home market will in fact have relatively little impact on the global research effort in the pharmaceutical sector, which is determined by the returns across a whole range of different markets. In economic jargon this is what we call the 'free rider problem'. Another way of looking at it is to look at the problem of funding a given level of R&D activity. Individual customers will contribute to the funding of R&D according to the amount by which the prices they pay for pharmaceutical products exceed the production and other costs of those products, so there will be a margin made which contributes towards R&D and, secondly, total contribution varies according to the volumes that they consume. Of course each customer has incentives to minimise his own contribution to those collective overheads. We're dealing with something which is moving towards a public good and what everybody wants is for somebody else to pick up the tab and to pay for that particular good. So if it is believed that you can get lower prices on the national market without affecting the global R&D effort, of course that looks like an attractive strategy. But even accepting that lower prices would mean less resources being devoted to R&D, you can see that the trade-off is changed at the national level because you would get a biggish effect on prices coming through for a smallish cost on R&D on the assumption that everybody else maintained their existing contribution. So each nation state looking at this trade-off would see things in a distorted light from the point of view of welfare at the international level, and that is one of the rationales of the development of a Community-wide policy. Of course, Community-wide policy doesn't solve the problem, but at least it aggregates the national markets to some extent and one might argue that at the Community level as a whole there would be a greater sense of inter-dependence with the United States and Japanese markets and therefore perhaps less incentive at this level to try free-riding.

Subsidiarity notwithstanding I think there are very good arguments for the development of a Community interest in this area and of course that Community interest is already expressed in the documents published. However, given that, one would expect that the Community would be rather aggressive in trying to deal with national price controls where it was seen that such price controls were attempts of individual nations to bear less than a 'reasonable' share of the R&D burden. The document's treatment of price control and reimbursement is very circumspect indeed. It states, for example, that the Commission intends to monitor the impact on the functioning of the internal market of national pharmaceutical pricing and reimbursement measures in order to avoid any discrimination and to ensure transparency. It doesn't say that these price controls are going to be attacked. And that circumspect approach to national price controls appears even more anomalous when it is

recognised that as well as weakening innovative competition in the community, national systems of price controls tend in fact to distort price competition within the single market. So, to take an argument which I think many of you will be well familiar with, parallel trade if allowed to proceed unhindered will lead to a situation which drives prices towards the prices in the Member State with the tightest price controls. Effectively you get an export of the most stringent price controls from one country to the other. So, not only are the incentives to innovate weakened as a result, but arguably the pattern of trade flows is also distorted. For example, a pharmaceuticals export from one Member State to another might be affected because of the reduction in profitability that has occurred as a result of those price controls.

Now if we go to Community legislation on this point, it is certainly true that national regulations such as price controls are permissible under the Community Treaty. But they are severely constrained by the larger project of creating the European Single Market. I want to quote from a paper of which I am very fond. It was given at the first seminar of my own research institute in Oxford, a couple of years ago, by Michel Waelbroeck, a distinguished Belgian lawyer, whose paper is called *'Is the common market a free market?'* (Waelbroeck, 1992). He says the following:

> *'Member states no longer have unfettered discretion to resort to the many classic instruments of economic intervention such as state aids and the acquisition of shares in companies. The exclusive rights held by national monopolies are being submitted to the control of the Community and even their very existence is being called into question.'* Perhaps most importantly, *'The application of national regulation of trade and of price control measures is increasingly being challenged with success'.*

Waelbroeck notes that there's a trend, but I might just mention that he argues in his paper that the Community Treaty is not necessarily a neo-liberal document. What he argues is that the creation of the single market calls into question national industrial policies, but leaves open the issue of Community wide industrial policies, and that's the bottom line of the argument. There is this general trend to knock away individual state interventions at national level which do distort the market. That paper, of course, was pre-Maastricht, and one also wonders what will happen to Court decisions post Maastricht because, as everybody knows, the judges read the election results. It will be interesting to see if the trend continues. But, in the light of previous policy and in the light of European Court rulings on these issues, one might have hoped that a more vigorous line would have been taken to deal with disparities between national systems of price control and reimbursement.

I think the sort of counter argument you get back on this point is that there is not very much that can be done about it at the moment, these price controls relate to very sensitive sectors and it is not possible for the

Community to allow constraints on parallel trade in pharmaceutical products to stop this export of price control effect taking place. It is a longstanding principle of Community Law, that the existence of price differences caused by government intervention, or any other intervention, is no basis for restrictions of parallel imports, so that no matter how crazy the relative prices are the Community is unwilling to countenance measures which restrict parallel imports. The beer industry has a similar problem with the differences in duty levels at the moment between the UK and France.

From a social engineering point of view, this attitude to parallel imports has a certain logic, the idea I think is to allow parallel imports to put pressure on the member governments to align their policies. This position has been stated by Sir Leon Brittan in a lecture a couple of years ago to the Institute of Economic Affairs. I quote:

> *'The application of market forces in this way, is likely to act as a catalyst for the gradual convergence, not only of prices, but also of price control mechanisms, prices in the high cost countries will reduce, whereas those in the low cost countries, if they really fail to offer pharmaceutical companies a reasonable return on investment will increase in reaction to the real threat of product withdrawal.'*

This brings out the point that a company might cease to supply a market if the price control is too tight.

I think it is very difficult in fact to share Sir Leon's optimism on this point. He also points out that convergence may prove to be a difficult path for Member States, not least because of the implications for some countries' budget policies. On the other hand, given that the Commission is not active on the issue of price controls, the threat of product withdrawal by a company is not actually a very credible threat in most circumstances, because companies will not generally find it optimal to withdraw products from a Member State simply because it is failing to earn a reasonable return on investment. Costs such as research and development costs are common costs and in economic terms are sunk costs; they're bygones, and only if a product fails to recover the incremental costs of supplying a particular market will it be profitable for companies to cease supply. The incremental costs will tend to be well short of the average costs, the average prices that firms need to gain if they're fully to cover all costs and earn a reasonable rate of return on investment. Thus even though you may be getting a less than reasonable return on investment, it is not optimal to withdraw a product. The threat of product withdrawal is therefore a relatively weak one and the mechanism that Sir Leon is claiming will occur is unlikely to occur. Contrary to Sir Leon's view, I think it is more likely that Member States could maintain for some considerable periods of time free-riding strategies based on price control policies that imply a less than proportionate

contribution to the financing of R&D. The consequences of the combination of price controls and parallel trade are not product withdrawal followed by abandonment of price controls and convergence of prices to some average, but rather a tendency for prices to fall to the most constrained level followed by a decline in the returns to innovation, a reduction in innovative competition and a fall in the rate of innovation. And that I think is the more likely outcome, rather than the more optimistic one. In other words, the consequences are exactly those longer term elements of decline that I pointed to as elements of concern at the opening of the Community's Industrial Policy document.

I think, as an economic aside, what is happening in this combination of policies is a good example of what in economics is called the 'second-best problem': it might be the best of all worlds to have relatively free pricing systems with national purchasers negotiating with companies and to have no constraints on parallel imports. But once you take away one of the items of the best policy mix, let's say pricing freedom, it is no longer optimal to impose, necessarily, other items of the policy mix, like parallel imports. It is always one of the difficulties of policy making, and it may have happened here. You try and set down a good package of policies and then somebody comes along and says well we can't take this particular aspect of the policy, and so you take a bit of it out, in response to lobbying or an interest group, but unfortunately what you are left with in taking away one of the components might no longer then be the optimal policy mix. It is quite a common finding that poor policy emerges through that type of process. You start with a good package and lobbying takes bits out and, rather than being something close to best, you've got something which is rather poor.

The way forward: Improving the trade off between static and dynamic efficiency

I shall move on to my third main issue, whether the trade off between static efficiency and dynamic efficiency, or between price competition and innovative competition, can be improved.

Thus far the arguments have been based on the existence of this trade off and if you pull on one side, price competition, you affect the other side, innovative competition. Suppose that there is a given amount of R&D to be funded, we can illustrate the trade off by determining what is the best way of covering the cost of that R&D.

Given the R&D expenditure, intense price competition clearly drives prices towards marginal or incremental costs and that leads to an infeasible outcome because companies with intense price competition in this market would not earn reasonable rates of return on capital, so price competition has to be abated. However if you allowed price competition to intensify I think we would witness growing concentration in the

market, so that in the limit, if you get very intense price competition in this market, the only feasible structure is full monopoly. As you come away from that, as you weaken price competition, you are getting lower and lower degrees of concentration in the market. That's another way of looking at the trade off. Concentration of course is already occurring, but I think that one of the things that the economist would tend to predict is that if you go faster in the direction of price competition what you get is a faster concentration. Prices have to come up above incremental costs, there has got to be some abatement of price competition. Intense price competition is a bad thing all round from the point of view of economic efficiency. The bigger the mark up on incremental costs made, the larger the contribution that's being made to the funding of R&D at any given volume, at any given level of purchase. Let me ask the question, given the R&D spend and given that we have to recover that from somewhere, what would a reasonably good or efficient pattern of cost recovery for R&D look like?

What I am going to argue is probably heresy in some circles, that price discrimination is a good thing. Much of the research and development in pharmaceutical products is devoted to producing higher quality products. As a general proposition I think we can assume that willingness to pay for additional quality of product at the margin is positively and strongly correlated with income. A result which is used very widely in the analysis of product competition in economics, is that willingness to pay for additional quality goes up with income. If we take then one of the classic bases for allocating these fixed and common costs, the willingness to pay, what you come out with, other things being equal, is that richer consumers would make a higher contribution to covering research and development expenditures than poorer consumers. That would be a normal market mechanism which would occur in a market where discrimination was possible and where the competition was occurring in respect of product quality. When one looks around, markets actually abound in all sorts of innovative devices to achieve this type of result. My favourite at the moment, the one I now teach my students, is the 486 computer chip market where the DX, which has an integral maths co-processor, sells at a high price and the SX version, which is almost identical, except that the maths processor is disabled, sells at a much lower price. If anything the costs of the SX are greater because you are disabling a part of it, but let's assume the costs are the same. The DX is sold at a much higher price and so you have two qualities trading in the market at quite different prices when the costs are the same. This is picking up the returns from people willing to pay more for the faster chip, for the higher performance chip. Such people are making a bigger contribution to Intel's R&D effort than the more marginal consumers, the people who place less value on that increment in product performance. So that's one way

of doing it and you can go through market after market and find lots of examples where that is done. In pharmaceuticals, given the public policy intervention, one would hope that one would get a similar sort of outcome in terms of funding without denying to the lower income consumers the best quality of product, because this is not, in a planning sense, the most efficient outcome. The most efficient outcome is to give everybody the top quality device.

That is one type of price discrimination which I think would be quite reasonable to expect in this type of market. The second type is one of volumetric pricing linking prices to actual volumes purchased, something we all know about from ordinary supermarket shopping, if you buy in bigger packages, if you buy more, you get a lower per unit price. This reduction is partly cost related but it is also, partly, a particular form of price discrimination which is helping to promote static efficiency by moving the prices at the margin, prices for additional consumption, closer to incremental costs. If you can raise the same amount of finance for the funding of R&D, but give more efficient signals downstream to purchasers about where true economic costs lie of extra product then that is the same as saying that you have improved the trade-off between static and dynamic efficiency or between price competition or innovative competition. As a first stab, it seems to me that those kinds of discrimination are not terribly upsetting as far as equity considerations are concerned either. The notion that richer countries would pay a higher contribution to R&D funding than poorer countries, and the prices therefore would be high in those countries, or that high volume users often are people with greater problems of health would pay a lower unit price than those buying in smaller quantities, is not unappealing. It is not the whole of the equity story, obviously, but steps in a particular direction. Those principles don't strike me as too bad. What that would amount to in terms of the Community is saying that we would expect to see higher prices for pharmaceutical products in Germany, say, than in Spain, because of income differences, and higher prices perhaps in Britain than in France because of the higher volumes of product sold in France. In other words if you look at the actual pricing of the products through the Community, the pattern, I am not saying the actual levels, but the pattern is one which is entirely defensible in general terms, and I would argue that if you were to try and harmonise those prices, bring them all to a single price, you could be moving away from economic efficiency.

The Community is strongly against price discrimination when the basis of discrimination is purely nationalistic, or geographic in nature. In describing the terms of price discrimination which might achieve economic efficiency it is possible in principle to lay down the resale restrictions without actually mentioning geographic factors. The complicating problem is that we have national health services, the big purchasers tend

to be one to one with geographic regions, and that leads then to price differentials which look to be related to geography and national markets, and of course that's what then gets the European Commission interested because it looks like national segmentation of the market. So I think if one was going further and moving from an outlines of Community policy to more substantive policy, one of the areas that I would be advising them to look at, would be ways of allowing price differentials to emerge which were based on consumer characteristics which would be compatible with parallel trade, but where, if necessary, individual exemptions could be given from the application of the competition laws. And we know that exemptions are possible and that it is recognised that the health sector is a special sector. It is a very difficult problem and I don't think that even the first few steps along that direction have gone very far yet. As I say, the idea of a single price throughout the Community seems to me to be a solution which ultimately implies a sub-optimal or less than best outcome for all parties.

Conclusions

Let me summarise my four main points very briefly.

(i) When assessing the current state of public policy towards the industry, we have to recognise the underlying trade-off between price competition and innovative competition. Whatever the mechanisms are, the more intense price competition is, the less intense innovative competition will be.

(ii) If we can't achieve the best combination of policies, for whatever reason, but usually interest group pressure, then it is better to go back and think from scratch about what is the best response to the altered circumstances than it is to cling to a position which is similar to the optimal combination, (the second-best problem).

(iii) The free-rider problems at the national level mean that it is appropriate for the European Community to take some sort of initiative in these matters.

(iv) Finally, ways of improving the trade-off between price competition and innovative competition or between static efficiency and dynamic efficiency are possible, and one of the possible routes is through the development of more sophisticated pricing mechanisms. However, the tolerance for such pricing mechanisms would obviously have to be negotiated with the European and Community authorities.

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Japanese Industrial Policy and the Pharmaceutical Industry

Professor Ian Neary

Introduction

This paper is based on research that is part of a portfolio of research projects looking at industrial policy which was funded by Economic and Social Research Council in the late 1980s.[1] The portfolio covered various areas of industrial policy, the first phase of projects looked at the impact of industrial policy in Europe and the UK, the second phase of projects looked at examples of industrial policy in the UK and Japan. Nearly all the projects were comparative and there were three projects funded on the pharmaceutical industry, one comparing the UK and France that was conducted by a legal scholar (Hancher, 1990), one comparing the UK and Germany, and ours, which was focused on the UK and Japan (Howells and Neary, 1995). Essentially we have been arguing four points. Firstly, that the structure of the Japanese pharmaceutical industry is the main factor in explaining its relationship to government. Secondly, that the intricacies of the government/industry relationship in Japan, can be explained by reference to Japan's medical culture. A fairly obvious point perhaps, but not one that may be obvious to economists. Thirdly, we want to argue that the main characteristics of the government/industry relationship in Japan, the UK and probably elsewhere, can be deduced from an examination of three policy areas, patents, pricing and the R&D support policy. These three areas we believe are crucial to the development of the international competitiveness of the pharmaceutical industry. Fourthly, that the Ministry of Health and Welfare (MHW) has little or no deliberate industrial policy — where an industrial policy is defined as a policy or series of policies which aim at improving or maintaining the international competitiveness of an industry.

In this paper I want to draw from our research findings to describe briefly the current state of the Japanese pharmaceutical industry and then discuss some aspects of policy making in the three areas mentioned above. Finally, I want to make some comments on recent changes in MHW's policy towards the Japanese pharmaceutical industry, to illustrate the absence of an industrial policy.

The Japanese Pharmaceutical Industry — a portrait:

Globally Japan is the second largest single pharmaceutical market, being slightly less than half the size of the United States market and about four

1 Project No. A418 25 4008.

times the size of the UK market. In terms of production, the growth of the Japanese pharmaceutical industry has been quite steady since the 1950s and in the 1970s the Japanese pharmaceutical industry experienced few problems at the times of either of the two oil shocks. However, as Table 1 shows, whilst the UK industry grew steadily throughout the late 1970s and 1980s, the Japanese drug companies experienced problems in the mid 1980s. In 1984 and 1985 overall production dropped slightly by 0.1 per cent and 0.6 per cent respectively, and more recently in 1992, overall production dropped by 2.2 per cent which suggests to some observers a degree of fragility in the Japanese industry. Government policy was largely responsible for each of these drops in overall production.

TABLE 1 **Output of the UK and Japanese Pharmaceutical Industries, 1975–1992**

	UK		*Japan*	
Year	*£ million*	*$ million*	*¥ million*	*$ million*
1975	1081	2187	1717	5628
1976	1356	2308	2162	10269
1978	1879	3835	2794	13302
1979	1994	4232	3042	13887
1980	2206	5136	3482	15397
1981	2483	5029	3679	16688
1982	2768	4841	3980	15972
1983	3301	5004	4032	16982
1984	3513	4695	4027	16952
1985	3917	5083	4002	16794
1986	4299	6307	4281	25432
1987	4750	7786	4825	33352
1988	5321	9469	5059	39449
1989	6073	11297	5502	39858
1990	6547	11696	5595	33836
1991	7283	13011	5697	44986
1992	8255	14582	5574	50530

Source: Data Book, JPMA, Tokyo, 1993.

In terms of its structure, Table 2 shows that the number of Japanese companies has remained steady over the past 20 years whilst the number of companies in the UK industry has been increasing slightly. The reason for this recent growth in numbers has been the emergence of bio-tech venture companies in the UK. Such companies have not emerged in Japan and this has been a source of concern to government observers. I will come back to this point in a moment.

The main feature of the structure of the Japanese pharmaceutical industry is the existence of a gradual continuum, which goes from the very largest companies, such as Takeda and Sankyo, down to the very tiniest and there is no obvious breakpoint that would distinguish the major actors

within the industry from the smaller actors. There are 88 members of the JPMA (Japan Pharmaceutical Manufacturers Association), and then there is a 'second division' (The Ethical Manufacturers Association) that covers 52 more. There are perhaps 10 or 20 of the largest members of the JPMA which can be regarded as major actors, in the sense that they have a capacity for genuine innovations, but it is difficult to distinguish a top group, and that makes the structure of the Japanese industry quite different to that of the UK, for example, where you can clearly point out the 3 major actors active within the policy field.[2]

TABLE 2 **Number of Pharmaceutical Companies in the UK and Japan**

	UK	*Japan*
1975	286	1359
1980	310	1312
1984	326	1367
1987	352	1315

Source: Data Book, JPMA, 1993.

One significant difference in the nature of the actors within the policy field in Japan compared to that of the UK, is the way in which most of the main actors of the JPMA, are and have been since the 1950s, solely or very heavily committed to drug production. Figures of pharmaceutical and total turnover for ten leading companies for 1992-3 are set out in Table 3. In comparison in the UK, for most of the post-war period, for most of the companies, drug production was only one part of the company's activities. ICI, Boots, Fisons, for example, were also involved

TABLE 3 **Turnover of major Japanese owned pharmaceutical companies, 1992-1993**

Company pharmaceuticals	*Estimated pharmaceutical turnover $ million*	*Total turnover $ million*	*% of total turnover contributed by pharmaceuticals*
Takeda	5172	6208	83.3
Yamanouchi	2407	3082	78.1
Sankyo	—	3438	—
Tanabe	1237	1825	65.4
Fujisawa	2308	2439	94.6
Shionogi	1742	2132	84.6
Daiichi	1474	1698	82.0
Eisai	1705	1952	90.4
Sumitomo	1809	8165	22.2
Taisho	—	1759	—

Source: Data Book, JPMA, 1993.

2 Zeneca, Glaxo Wellcome and SmithKline Beecham.

elsewhere. Pharmaceutical production was not the sole commercial venture of these companies, whereas in Japan historically the main pharmaceutical companies have only made pharmaceuticals.

Whereas the UK industry has generated a significant trade surplus every year since 1945, Japan has always imported more drugs than she has exported and the figures for 1992, included in Table 4, indicate Japan had the largest trade deficit for pharmaceuticals of any country in the world. Overall only 2.5 to 3.0 per cent of total pharmaceutical production is exported, a figure which has remained remarkably constant since the 1950s. Meanwhile government statistics suggest 7.5 per cent of all drugs sold in Japan are imported, a figure which underestimates the importance of foreign drug companies in Japan. Some estimates report that as much as one quarter of drugs consumed in Japan come from foreign companies.

TABLE 4 **Pharmaceutical trade as a percentage of industry output**

	Exports		*Imports*	
	UK %	*Japan* %	*UK* %	*Japan* %
1980	33.8	2.7	10.1	7.6
1987	35.5	2.7	18.0	6.8
1992	38.2	3.2	20.9	7.5

Source: Data Book, JPMA, 1993.

Very recently, there has been something of a change. Table 5 sets out the overseas sales record of major companies over the past four or five years; most of them have increased the percentage of their production that they export. Takeda, for example, has gone up from 5 per cent to 10 per cent and Fujisawa from 5 per cent to 8 per cent in the period 1988-1992. You can draw a line beneath the top 10 companies on Table 5 and show that their export performance over the last four years has increased and has increased fairly substantially. Of course these figures are nothing like the figures of the export record of the UK industry, but nevertheless there is an improvement here, and one might ask is this improvement the result of an industrial policy that the MHW has pursued in the 1980s? This question I will return to.

I would like, at this stage, to comment further on the internationalisation of the pharmaceutical industry. It seemed that towards the end of the 1980s and in the early 1990s a major change was taking place in the Japanese industry. Japanese companies all of a sudden seem to be acquiring foreign companies, both in the United States and in Europe, and building R&D and production facilities abroad. In the UK, there was the decision of Eisai to invest in R&D at University College London, Fujisawa's activities in Edinburgh and Yamanouchi's research efforts in Oxford. A survey conducted for the JPMA, published in 1994, showed

that over the past four years the overseas activity of Japanese based pharmaceutical companies had increased substantially. Of its 66 Japan based members, 38 were conducting research overseas in 1993 compared to 30 and 16 in 1991 and 1989 respectively. Furthermore, 20 companies had production facilities abroad in 1993, some 54 factories in all, of which 35 are in the Asia/Pacific region, 11 in Europe, and 4 in North America.[3] So, there was some evidence of the Japanese pharmaceutical industry creating an international presence, but over the last 2-3 years, as the drug industry has lost ground domestically, and as the economy as a whole has moved into recession, this process has not continued. There has been no recent news of foreign acquisitions, or the establishment of research or production facilities abroad. Despite the trend of the late 1980s, Japanese drug companies are still locked into the Japanese market, rely heavily, or even exclusively on production of pharmaceuticals sold in Japan, and this is also true of the foreign companies in Japan. Foreign companies are in Japan to sell drugs there, not to produce them for sales elsewhere, unlike, for example, the case of United States companies based in the UK. Both the domestic industry and the foreign companies based in Japan are weak in negotiations with government. They must pay very close attention to the effect of government directives. Japanese companies historically have not been able to move into other areas of activity, either immediately or over a period of time. Foreign companies in negotiation with government cannot credibly threaten MHW with withdrawal on the Japanese market and such a threat would not be taken seriously.

MHW then has been more able to impose policy on the Japanese industry than, for example, have ministries in European countries.

The Cultural Context

The Ministry of Health and Welfare (MHW) was formed in 1938 from the health-care related divisions of the Home Ministry, at the time when Japan was becoming heavily involved in the war in China and when there was great concern about the health of the rural citizens whose sons were forming the backbone of the Japanese army. It was MHW's brief, in the 1930s, to protect and promote the health of the Japanese people and that essentially continues to be the role of MHW. Put another way, MHW then and throughout the post-war period was much more oriented to the customers than to the producers. It has a much wider brief than the Department of Health in the UK, and is rather like the Department of Health and Social Security used to be, except that the MHW is a much more integrated ministry than the DHSS ever was. MHW's attitude towards the healthcare industry in general is one of

3 Reported in the Yakuji News, 11 February 1994. The four other factories were located elsewhere in the world. In 1991 there were only four factories in Europe and two in the USA.

control. It aims to control the activities of the pharmaceutical industry and the medical profession. It is concerned with policing rather than promoting. There are many in Japan active in the industry who would argue that this attitude is inherited from the days when the MHW was made up from divisions of the Home Ministry, which in pre-war Japan notably controlled the police force.

Supervision of the pharmaceutical industry is only a very tiny part of MHW's overall activity. The Pharmaceutical Affairs Bureau is small, its budget in 1992 amounted to less than 0.5 per cent of the ministry's total budget and the economic affairs section which attempts to conduct an industry policy of sorts, is only a small part of the Pharmaceutical Affairs Bureau. Nevertheless, it has very jealously protected its right to supervise the industry to the exclusion of all others, and that of course includes the Ministry of International Trade and Industry (MITI).

TABLE 5 **Overseas sales of 20 Japanese pharmaceutical manufacturers**

Company	*1988*		*1992*	
	¥ million	*% of total turnover*	*¥ million*	*% of total turnover*
Takeda	30,235	5.2	59,147	10.5
Tanabe	32,959	16.8	41,192	19.5
Sankyo	7,349	2.4	32,062	8.0
Fujisawa	10,559	5.1	22,224	9.4
Daiichi	8,417	5.0	18.563	9.2
Yamanouchi	17,399	9.4	16,052	6.6
Kyowa Hakko	17,656	15.2	13,765	11.0
Eisai	6,992	3.8	10,010	4.6
Meiji Seika	NA	—	–9,964	4.2
Chugai	5,217	4.2	5,731	4.0
Yoshitomi	NA	—	3,138	3.7
Green Cross	NA	—	2,797	3.5
Shionogi	1,353	0.6	2,448	1.0
Taisho Pharm	1,547	1.1	1,952	1.0
Kaken	768	1.8	1,773	2.6
Dainippon	1,267	1.6	1,285	1.1
Mochida	557	1.1	765	1.2
Ono Pharm	NA	—	743	0.8
Banyu	1,028	1.1	650	0.6
Tsumura	326	0.4	289	0.3

Source: Data Book, JPMA, 1993.

Policy Areas

I want to turn next to look briefly at three areas: patents; R&D promotion policy; and pricing policy and to ask the question, is there any evidence, in these areas, of MHW promoting the pharmaceutical industry and attempting to enhance its international competitiveness.

a) Patent Policy

Until 1976 only process protection was available for pharmaceuticals in Japan, although with the reversal of the onus of proof.[4] This system did not reward investment into genuine innovation; companies were simply encouraged to copy rivals, whether at home or abroad. Where copying was not possible, it was very easy for companies to get approval in Japan for drugs that had already been approved overseas. Profits could be made from the sales of these drugs within Japan, but there was really no export potential. This was no particular problem as the domestic market was growing very rapidly in the 1950s and 1960s, particularly in the 1960s after Japan adopted a health insurance system which ensured that virtually all the population of Japan had access to cheap health care.

MHW was not particularly interested in promoting the industry, its main brief was to provide healthcare to the Japanese citizens, and its hospitals were getting drugs produced in Japan fairly cheaply. In 1976 the patent system was revised to allow full product protection for 15 years, but in the later 1970s and in the early 1980s protests emerged within the industry that the increasing length of clinical trials was cutting down patent protection. They argued that they were receiving poor returns for any R&D investment that they were making. The industry was demanding patent restoration, just like its counterparts in the United States and Europe. The campaign was apparently successful and in 1988 a law was enacted which allowed 'patent term restoration' for up to five years.

The main reason for the earlier changes, in the 1970s, was the perceived need to bring Japanese patent law in line with the rest of the OECD. It was not due to pressure from the industry which was opposed to the changes. By the mid 1970s MITI judged that a) international pressure could be resisted no more, and b) it was, in any case, in the long term interest of Japanese industry for the patent law to be changed.

In the 1980s the JPMA had campaigned vigorously for patent restoration, but after a long campaign had almost given up hope that the MHW would respond to its demands. Very quickly MHW changed its mind and announced its support for the policy. The main reason here was, I believe, to head off criticism in Washington concerning Japan's lack of protection of intellectual property rights, by bringing Japan into line with United States policy. A secondary reason was to persuade the Japanese pharmaceuticals industry that MHW really did take the industry's interests seriously, despite the swingeing price cuts that were being introduced at the time.

4 Normally in a patent infringement action the onus is on the patentee to prove to the court that his patent has been infringed. Reversal of onus of proof meant that, where a compound was new, Japanese courts would assume that it was produced by the patented process unless the person accused of the infringement could prove otherwise.

b) R&D Promotion

As patent policy was changing there were parallel changes being made in R&D promotion policy. In Japan, as elsewhere, from the early 1980s many branches of government started to take an active interest in the promotion of bio-technology policy. MITI and later MHW were concerned that Japanese companies in general and Japanese pharmaceutical companies in particular, were not taking up this new technology. In the early 1980s there was no evidence of the bio-tech venture companies that were apparently popping up all over the place in the United States and to a lesser extent in Europe. To try and compensate for this MITI took a lead with the creation of some bio-technology projects as part of its 'Next Generation' series of research projects, launched in 1981. Soon after that MITI sponsored the creation of BIDEC, the Bio-technology Development Centre, which included amongst its supporters some pharmaceutical companies. By the mid-1980s it seemed as though MITI was taking the lead in the field of bio-technology promotion.

MHW felt it had to respond to this encroachment onto its territory by reassuring the pharmaceutical industry that it was concerned about its future, despite the price cuts that were being imposed, so it launched its own series of R&D promotion initiatives from the mid 1980s. In 1986 the Health Science Foundation was launched, essentially to encourage communication between government research institutions, industrial research institutions and universities. It had some money of its own that it used to sponsor specific projects, mainly on age related disease. There was also a loans project which aimed at providing capital to enable companies to develop bio-tech research of a kind that would otherwise be too risky to fund by themselves. A series of joint research projects were launched in which MHW supported the creation of a venture capital company, formed by two or more Japanese pharmaceutical companies. The aim was to establish two or three of these companies every year and the programme as a whole was to last seven years, so that by the end of it there would be as many as 20 companies active in different areas. The first project, launched in 1987, was one on drug delivery systems, and the lead company was Eisai. Later there were projects on skin graft research, artificial blood vessels and other areas. Overall the aims of this policy were; to encourage co-operation between pharmaceutical companies which hitherto had mainly been competing with each other; to create equivalents to the venture capital bio-tech companies of the United States and Europe; and to encourage links between universities and industry, an area in which Japan was considered to be backward.

What is interesting is that these policies were not the result of demands from the pharmaceutical industry. The industry, particularly in the late 1980s, was very suspicious of MHW's motives and sceptical of the impact that these projects might have on the ability of the pharmaceutical industry to compete abroad.

We were interested in our research to try and look at infra-structural projects and chose as a case study culture collection policy. Public sector culture collections play a wide role in the development of bio-technology related industries but four functions are clear. They are places where standard types of microbial organisms can be lodged, they preserve known types for future use, they can identify strains sent for analysis and they can provide information about, or the facilities for, patent protection. Although the Spinks Report highlighted the need for a co-ordinated system of national culture collections in the UK and funding to assure its long term future, its recommendations were not implemented. The public sector system remains without a coherent structure and is poorly funded. In contrast, the system of culture collections in Japan is well cared for. This is not the result of a single coherent policy but the efforts of the Science and Technology Agency, MITI and the Japan Federation of Culture Collections ensure that overlapping policies maintain three major collections, that in the Institute for Fermentation, Osaka (IFO), the Culture Collection of Micro-organisms (CCM) in Riken and the Patent Micro-organism Depository Unit (PMDU). Each of these has extensive holdings and though they are funded and function differently, they play complementary roles. In other words, this is an area of excellent infrastructural central government; a very good example of what industry/public sector co-operation can achieve.

c) Pricing Policy

Japan operates a fee for service system. A doctor in a clinic or hospital is reimbursed for treatment based on a points system. The more time-consuming a treatment, or the more complex the treatment is, the more points he or she gets. There is full reimbursement at the list price for each drug dispensed and it is still usual for the doctor or hospital to both prescribe and dispense medicine. As one observer writing in the Financial Times observed recently, every time a doctor writes a prescription, he is writing himself a cheque, because although the listed reimbursement price is fixed, the wholesale price is not. In the mid-1980s, the average margin for a doctor was reckoned to be 22 per cent, the wholesale margin 12 per cent, with 66 per cent of the costs going back to the manufacturer. Patented products with few competitors will hold their prices well, in other sub-market sectors, such as antibiotics, salesmen will need to discount aggressively to get sales.

Profits on the sale of drugs are an significant part of the income of all medical institutions, but are particularly important for the small hospitals and clinics. In 1987 an MHW survey estimated that 37 per cent of the income of the smallest clinics, mainly single physician clinics, came from drug sales. Both small clinics and small hospitals have come to rely increasingly on drug profits as the treatment points system has not been

increased in line with the increase in costs. MHW contests that, they do not accept that their review of the points system is inadequate, but MHW has not until very recently admitted that there should be any permitted margin of profit on drug dispensing. Since the current system was introduced in the 1950s, MHW has done a periodic survey of prices and tried to cut the listed prices to reduce the margin that doctors and wholesalers were getting. Table 6 sets out the price cuts that have taken place over the period 1969-1994. If we look at the price cuts in the 1970s we can see they were relatively small, 3-5 per cent, but as we get into the 1980s, the price cuts become much larger, and even into the 1990's, only slightly less than 10 per cent.

TABLE 6 **Reimbursement price revision 1969-1994**

Overall percentage reductions	
January 69	5.6
August 70	3.0
February 72	3.9
February 74	3.4
January 75	1.6
February 78	5.8
June 81	18.6
January 83	4.9
March 84	16.6
March 85	6.0
April 86	5.1
April 88	10.2
April 90	9.8
April 92	8.1
April 94	6.6

Compiled from successive editions of Yakuji Handbook, Yakugyo Jihosha, 1987-94.

TABLE 7 **Reimbursement price revision 1969-1992**

Drugs as a proportion of health care cost	
Year	*Percentage*
1981	38.7
1982	34.1
1983	35.1
1984	30.9
1985	29.1
1987	30.8
1988	28.2
1989	32.1
1990	29.6
1991	30.8
1992	29.1

Compiled from Yakuji Handbook, Yakugyo Jihosha, 1987-94.

This policy has been successful in one sense; it has cut the cost of drugs as a proportion of the health care budget (set out in Table 7) from what was nearly 40 per cent in 1981 down to around 30 per cent by the late 1980s–early 1990s. Now it is believed it is the aim of MHW to cut it down still further to 20 per cent by the end of the 1990s.

The price changes in the 1980s provide the context for the so-called industrial policy. In the 1980s NHI prices were reduced by a cumulative 61.4 per cent. This was a time when MITI was devising its bio-tech development policies that were attracting the attention of the pharmaceutical industry. To maintain control of its own industry it was imperative that MHW adopt its own industrial policy and so a package of policies were put together in the mid-1980s. The policies to launch the

Health Science Foundation, the patent term restoration policy, the launch of the loans system and capital assistance projects, should be seen in the context of this inter-ministerial competition, rather than as evidence of MHW's concern for the international health of the pharmaceutical industry.

In the late 1980s and early 1990s, the Japanese industry argued that its health was being seriously damaged by these massive price cuts and that if the Japanese industry was going to compete internationally, there would have to be fundamental revision of the price control system. In particular, they argued that the way of calculating the downward price revisions, had to be changed. They wanted a system that permitted the existence of a margin for wholesalers and the doctors at around 20 per cent. MHW completely resisted these demands and refused to consider them seriously until 1991, when it announced its decision to adopt the weighted average system, but only to allow an initial margin of 15 per cent and that this margin would only be reduced over the decade to 13 per cent in 1994, 11 per cent in 1996 and 10 per cent in 1998, when the system would be reviewed and revised.

It looks as though the industry had lobbied effectively. But was this really the case? In late 1990 the Japanese government came under intense pressure from the United States; the Structural Impediment Initiatives (SII) talks were creating pressure to break *keiretsu* links by the enforcement of the rulings of the Fair Trade Commission (FTC). One set of rulings that was taken up insisted that the Japanese pharmaceutical producers should abandon their 'restrictive practices', a complex system of rebates and allowances that bound the wholesalers to the producers. FTC argued that this abuse of dominant position should end and that the wholesalers should be free to set their own margins. So it was really as a result of pressure from the United States that the policy changed rather than as a result of industry pressure. In fact the change of the system does not seem to have made a great deal of difference. In 1992 the price reductions were marginally less than previously, 8.1 per cent, compared to 9.8 per cent. Although at the same time some concession was made promising to give better prices to products that were innovative, very useful or of limited marketability. However, few drugs have been given the 'innovative' or 'very useful' premiums, none of the products introduced in 1994 for example, and only three have been given the limited marketability premium, which for obvious reasons is not particularly encouraging to R&D.

Current and Future Issues

The price reductions of April 1994 amounted to 6.6 per cent overall, but as usual the brunt of price reductions was borne by those products most heavily discounted; antibiotics prices were reduced by an average

of 12.7 per cent. More disturbing, was that MHW also decided to reduce the prices of two classes of drugs, apparently just on the basis that they were generating high profits for producers (and high costs for the consumers), rather than because there was any evidence of discounting below NHI prices.

Two cholesterol level lowering products, Sankyo's Mevalotin (the block buster top seller of 1993 with sales of ¥60.6 billion — $606 million approx), and Lipovas from Banyu (1993 sales ¥14 billion — $140 million approx) both had their prices reduced 12.2 per cent.[5] Moreover interferons produced by Roche, Sumitomo, Daiichi and Yamanouchi had their prices reduced by 22.7 and 13.5 per cent. If these reductions are included the overall impact of the price changes of 1994 is closer to 7.6 per cent not much less than 1992. The price cuts imposed on alpha interferon producers are especially unusual as this reduces the price of one of the first fruits of the application of bio-technology. The reassurances from MHW about its desire to promote the industry seem less convincing now.

But there are other clouds on the horizon. Already MHW has abandoned the 'fee for service' reimbursement system in long stay hospitals for the aged and replaced it with a 'flat daily fee' system. Under the latter system there is an incentive to prescribe fewer drugs and to prescribe generics where appropriate. Reports suggest that drug consumption in these hospitals has fallen by as much as 40 per cent. There are plans to extend the scheme to mental hospitals and to study other areas in which it might be implemented. Restrictions were placed on doctors freedom to prescribe vitamins and tonics to outpatients from October 1994 and from the same date only ten prescriptions to any one patient will be 100 per cent reimbursable, the eleventh product onwards will only be reimbursed at 90 per cent of the list price.

The MHW has for some years now been supporting a campaign to encourage the separation of prescription and dispensing. Figures for 1993 indicate that 16.3 per cent of prescriptions were not dispensed by doctors and in the specially targeted areas of Saga, Fukuoka and Akita the 'separation rate' is over 30 per cent. It is part of MHW's grand design to push the overall 'separation rate' up to 50 per cent by the end of the decade. Early reports suggest that where 'separation' was in effect patients were receiving prescriptions for 2-3 drugs rather than 4-5 medicines to take home with them.

Both of these policies are consistent with the aim of reducing the cost of drugs from 30 per cent to 20 per cent of the health care bill, but they are not consistent with the industry promotion policy. Ironically these policies may be encouraging a more international policy in the major

5 Sales of Mevalotin were up 16 per cent on the previous year and Lipovas up 250 per cent on 1992. Figures from Yakuji News, 1 January 1994.

companies as they try to escape the restrictions and price reductions imposed within Japan. However until recently Japanese companies have lagged some way behind their North American and European competitors in the amount they have spent on R&D as a proportion of total sales. Even now most Japanese companies only spend comparatively small absolute sums on R&D compared to their main rivals. The only way they might be able to alter this in the short term would be through mergers or strategic alliances between Japanese companies, or, less realistically, by creating similar links between Japanese and non-Japanese companies. Some observers predict the imminent restructuring of the industry and talk of an alliance between Shionogi, Yamanouchi and Chugai. On the other hand there have been predictions of an imminent restructuring of the Japanese pharmaceutical industry since 1968 when the JPMA was formed but no real change has taken place.

In terms of its policy towards the industry, there was a time in the 1950s and 1960s when MHW health policy benefitted the domestic pharmaceutical industry. However, the primary aim of the policy was not industry promotion but industry protection. From the mid 1980s MHW has sought to characterise its policy towards the industry as aimed at promoting the industry's international competitiveness. Changes to the patent law and the bio-technology promotion policy may have achieved this to some degree. However the cost containment agenda was always of greater priority and its impact has cross cut and worked against the promotion policy. This has been the case in the early 1990s and it is hard to imagine any new promotion policies in the rest of the decade. Pharmaceutical companies, particularly the top ten, continue to report healthy profits despite cost containment. Meanwhile the price cuts are causing problems for doctors in their clinics, changes in the wholesale system are pushing many small hospitals further into the red and the wholesale sector is rapidly restructuring. There is no sympathy domestically for policies that might enable the major companies to generate still higher profits and international scrutiny of Japan's industrial policies will make it hard for MHW or any other ministry to create a promotion programme that might be seen to give Japanese drug producers an 'unfair' advantage at home or abroad. If a Japanese drug company is to succeed in making a major impact internationally it will need not only the products but also to escape from the structure of the Japanese market and the restrictions of MHW control.

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US Industrial Policy and the Pharmaceutical Industry

Professor F M Scherer

Introduction

My assignment is to stake out the metes and bounds of US industrial policy towards the pharmaceutical industry. I begin by confessing astonishment over Professor Neary's observation, on page 22 of this book, that pharmaceuticals account for between 20 and 30 per cent of Japanese health care expenditures. In the United States, the comparable number is nearer 7 per cent. Yet 7 per cent of 14 per cent — the fraction of US gross domestic product devoted to health care — continues to be a sizable number, making the pharmaceutical industry an important focus of public policy.

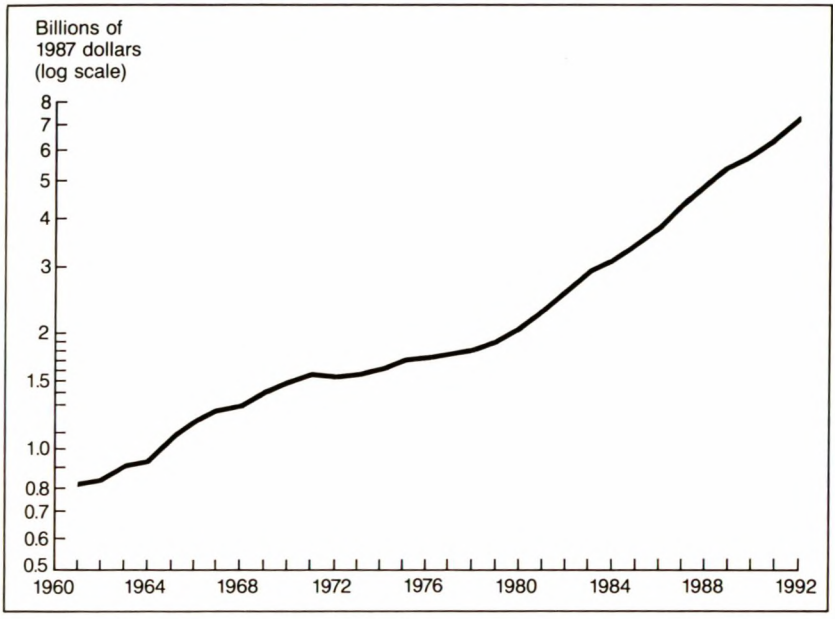
Like Japan, the United States has nothing discernible as a well-thought-out industrial policy toward pharmaceuticals. Rather, what one finds is a hodge podge of sometimes consistent, sometimes inconsistent instruments. The instruments include government research and development provision and subvention, intellectual property laws, the regulation of product quality, and controls or limits on the reimbursement of pharmaceutical purchases by various government agencies.[1] Let me take these up in turn.

Research and Development Support

The American pharmaceutical industry is extremely research intensive. Indeed, of all the civilian sector four-digit manufacturing industries in the United States, it is the most research intensive, devoting in recent years 16 to 17 per cent of its sales revenues to research and development. In 1992 the corporate members of the US Pharmaceutical Manufacturers Association spent $9.1 billion on research and development in the United States, along with $2.04 billion overseas (PMA, 1993). During the 1980s, as Figure 1 suggests, there was an acceleration of R&D spending growth. The diagram is on semi-logarithmic coordinates, so growth at a constant rate would be shown by a straight-line trend. The real (i.e., constant-dollar) rate of growth during the 1980s was an extraordinarily rapid 10.6 per cent per annum. For the totality of all industries tracked by the US National Science Foundation, the comparable figure was 4.3 per cent. Over the longer 1961-1990 interval, the real rate of pharmaceutical R&D growth was 6.9 per cent per year.

1 For a fuller development of my analysis, see F M Scherer, 'Pricing, Profits, and Technological Progress in the Pharmaceutical Industry,' *Journal of Economic Perspectives*, vol.7 (Summer 1993), pp. 97-115; and *Industry Structure, Strategy, and Public Policy*, (Harper-Collins, 1995), Chapter 9.

FIGURE 1 **Trends in US pharmaceutical industry R&D**



Complementing R&D outlays of the pharmaceutical manufacturers are various expenditures from Federal Government sources. The Federal Government's support is mainly for basic pharmaceutical infrastructure research. That is to say, the government provides grants to academic investigators, and it also performs in-house research, especially at the National Institutes of Health, upon which the pharmaceutical manufacturers build.

It is difficult to be certain exactly how much infrastructure research there is. In 1991, the National Institutes of Health were authorized to spend $7.7 billion on research and development (National Science Foundation, 1992). Sifting through the various NIH budget categories and those of other US federal government agencies, I have attempted to determine how much might be relevant directly or indirectly to pharmaceutical manufacturers. My estimate, probably biased on the high side, is that $4.8 billion of NIH basic research support were more or less germane to the interests of the pharmaceutical industry. In addition, $260 million of National Science Foundation grants were for the biological sciences, and therefore potentially relevant to pharmaceuticals, along with something on the order of $1 billion by other agencies.

This basic infrastructure research support is very important to the industry. During the late 1980s Edwin Mansfield, a well-known

American economist, queried a sizable number of industrial R&D decision-makers concerning the relevance of academic research to the development of specific new industrial products (Mansfield, 1991). For the pharmaceutical industry, he learned that 27 per cent of the new products sampled could not have been developed had there not been underlying academic research. In addition, 29 per cent of the other new pharmaceutical products were significantly facilitated by the existence of academic infrastructure research. Academic research was found by Mansfield to be more important to the emergence of new commercialized products in pharmaceuticals than in other surveyed industries such as computers, instruments, electrical equipment, and metals.

Another significant aspect of Federal Government financial support is for training. Substantial training grant programmes are administered by the National Institutes of Health and the National Science Foundation. In 1989 those agencies had training grants outstanding to roughly 7,800 students at the pre-doctoral level and to 6,600 post-doctoral researchers (Office of Technology Assessment, 1993). The total cost of this grant support was approximately $327 million. I am told by pharmaceutical manufacturers that they seek to hire for senior research staff positions individuals who have not only received PhD degrees, usually with Federal grant support, but who have also completed post-doctoral studies, again typically with Federal grant support. As head of the PhD program at Harvard's Kennedy School, I can attest that the situation in biology and the other physical sciences is quite different from that in the social and policy sciences. Very few of our PhD students have federal grant support, and post-doctoral funds are virtually non-existent. In biology, on the other hand, most students at top universities are covered in one way or another by federal grants.

The Federal Government has been much less active in providing direct research subsidies to the pharmaceutical manufacturers. Indeed, the amount of direct subsidy has typically been so low that in most years the exact figure has been suppressed in National Science Foundation survey reports (National Science Board, 1993). For the years when the data were not suppressed, the Federal government contribution was reported to be in the range of $1 to 3 million.

To be sure, in the distant past, one can find examples of major Federal Government initiatives. The most important case is penicillin during World War II. After the results obtained by Oxford's Howard Florey and Ernest Chain were transferred to the United States, the techniques for mass-producing penicillin in corn steep liquor were worked out at a US Department of Agriculture laboratory. Production contracts were let to some 20 companies, who later became the nucleus of the US antibiotics industry (Federal Trade Commission, 1958). The large quantities of penicillin they produced were used mainly for the treatment of combat

injuries during the War. After the War, of course, penicillin became widely available for the civilian population.

Patents and Other Intellectual Property Rights

For the most part, however, the pharmaceutical industry received virtually zero research support from the Federal Government. This is in marked contrast to most other US high-technology industries such as aircraft engines, aircraft, semiconductors, and computers, all of which have benefitted from considerable Federal Government research contract funding. This was a matter of conscious choice. The pharmaceutical manufacturers did not want to receive research subventions from the Federal Government. Their motivation stemmed from Federal Government patent policy. Under the patent policies prevailing in the health science fields until 1980, if the Federal Government provided research and development support to a company, any patents resulting from the research would either go directly to the Federal Government, or the Federal Government would at least receive a non-exclusive and transferable license from the contractor. The pharmaceutical companies were extremely reluctant to accept Federal grants and contracts under these conditions. Indeed, in 1962, when the Department of Health, Education, and Welfare began insisting that it receive patent rights on new chemical entities synthesized by academic researchers and tested for pharmacological efficacy by drug companies, the companies abruptly ceased screening and testing those substances (Harbridge House, 1967).

In their unwillingness to accept contract ties without full patent rights, the pharmaceutical companies were influenced by their experience following World War II. They had patent protection on neither penicillin nor streptomycin, and tough price competition emerged among the many producers of both wonder drugs. In contrast, when they manufactured substances such as aureomycin, tetracycline, and chlorothiazide on which they held patent rights, price competition was much more restrained, and profits were generous. The implication was obvious: contracts with the government that might lead to widespread patent licensing were to be avoided.

As this discussion suggests, patents are considered extremely important by the pharmaceutical manufacturers. In a survey of 650 industrial research and development executives conducted by a group of scholars at Yale University a decade ago, only three industries among the 130 surveyed accorded more importance to patents than did the pharmaceutical industry, and two of those three were industries in which only a single, possibly atypical, response was elicited (Levin et al., 1977).

The reasons are fairly straightforward. Bringing out a new pharmaceutical entity in the 1980s required research, development and testing expenditures averaging $125 million. Almost all of that R&D activity

was devoted to obtaining information: first, information on whether a chemical entity had reasonably interesting therapeutic properties; then, through clinical trials, information on whether the entity worked in human beings and whether it was safe. Once the requisite information was available, absent patent protection or some similar barrier to imitation, another company could appear, spend perhaps $1 million on chemical engineering, duplicate the molecule, and sell it in competition. In other words, the costs of imitation in pharmaceuticals are extraordinarily low relative to the costs of original innovation.

The imbalance between original innovation costs and imitation costs is much greater than in other high-technology industries. Consider semiconductors. An electronics specialist firm can devise a new microprocessor chip. Another firm can try to imitate that chip, but first it has to do chip layout and microcode engineering. Second, it must translate its chip layout plans into photoresist mask designs and test them carefully to ensure that the electronic functions are accurately embodied and short circuits have been avoided. Then it has to establish pilot plant production and, when full-scale production commences, it must move down a steep learning curve, at the beginning of which the cost per good chip is perhaps $300, progressing downward until the cost per chip is less than $3. All of these necessary expenditures mean that imitators' front-end costs approximate those of the original innovator, and in addition, the imitator operates at a substantial time disadvantage.

Again, in pharmaceuticals, the R&D expenditures go mainly to discovering information, on the basis of which subsequent imitators can free-ride or cheap-ride. Because patent protection was considered so important to the pharmaceutical manufacturers, they simply refused to take research money from the government because it meant a forfeiture of their intellectual property rights.

Gradually that has changed. New patent policies were adopted following the Stevenson-Wydler Act of 1980. Now companies receiving Federal R&D funding can obtain exclusive patent rights to products that emerge from the research. As a consequence, pharmaceutical houses now accept modest amounts of Federal research support, sometimes in the form of direct grants, sometimes through so-called CRADAs, that is, Co-operative Research and Development Agreements. In 1990, the National Institutes of Health obligated approximately $238 million for clinical testing, usually of drugs originated by pharmaceutical manufacturers; $7.6 million in direct grants to private firms for the development of so-called 'orphan drugs'; and a substantial amount of resources for cooperative R&D with pharmaceutical companies as partners (Office of Technology Assessment, 1993).

The Orphan Drug Act, passed in 1983, provides another form of intellectual property rights. The first company to receive marketing

approval for a new orphan drug, defined as a drug treating symptoms affecting fewer than 200,000 persons in the United States, is entitled to market that drug exclusively during the first seven years after approval. In effect, orphan drug status acts as a surrogate patent, valuable especially for biological substances whose patentability is uncertain. Between 1984 and 1992, 79 new drugs designated as orphans emerged from the testing process with marketing approvals.

The great importance attached by pharmaceutical makers to patent protection has spilled over into the international arena. During the 1980s the US pharmaceutical manufacturers organized a group to lobby for stronger patent protection in nations that offered little or no patent protection for new drug entities. These were typically less-developed countries, although until 1987, Canada was also included because it freely granted compulsory licenses to drug patents and required royalty payments of only 4 per cent. At first the drug makers' lobbying (along with that of computer software, motion picture, and music producers) led to actions taken under Section 301 of the US International Trade statute. If the targets of Section 301 threats did not provide what the United States considered to be adequate intellectual property protection, the US could erect trade barriers against their exports. Joining forces with enterprises in Europe and Japan, the drug patent lobby succeeded in having harmonization of patent policies made a high-priority item in the Uruguay Round of multilateral trade negotiations. Under the compromise reached at Geneva in December 1993, all GATT signatory nations must within ten years offer substantial patent protection for drug products. This is likely eventually to enhance the profits US and other multinational drug manufacturers obtain in less-developed nations.

Tax Advantages

Pharmaceutical manufacturers also benefit from an array of tax advantages, some specific to the industry but most applying across all industries. All companies, whether pharmaceutical makers or not, are allowed to write off their research and development expenditures as an on-going cost. There are also various tax credits, allowing a dollar-for-dollar offset against remaining tax liabilities. Firms in all industries have been allowed since 1981 to claim tax credits for increases in their R&D spending above moving average base-year amounts. In 1987, pharmaceutical companies claimed R&D tax credits estimated at about $97 million (Office of Technology Assessment, 1993). For contributing equipment to universities, their tax credits in that year amounted to about $2 million. Under the orphan drug programme they realized credits of $5.4 million. By far the largest value comes from an oddity in the US tax laws, the so-called possessions tax credit. By conducting manufacturing activities in certain US possessions, most prominently Puerto Rico,

companies can claim very substantial exemptions from US Federal income tax liability. The pharmaceutical manufacturers have been especially aggressive in this regard. They have incorporated manufacturing subsidiaries in Puerto Rico, assigned patent rights to them, and claimed tax credits in 1987 amounting to $1.34 billion. To the best of my knowledge, no other industry has benefitted nearly as much from the possessions tax credit.

Regulation of Safety and Efficacy

Another most important aspect of US policy toward the pharmaceuticals industry is the regulation of product quality. Since 1938, institutions were in place to exercise rather loose regulation of drug safety. The regulatory process then took an important turn in 1962, when the Kefauver-Harris Act was passed. The genesis of the 1962 law is in itself interesting. During the late 1950s, Senator Estes Kefauver was investigating the drug industry as part of his so-called 'Administered Prices' hearings. The rationale for the investigation was the allegation that prices and profits in the industry were excessive as a consequence of monopoly power. At the time, Senator Kefauver was a leading candidate for the US presidency (losing out at the 1960 Democratic Party convention to John F Kennedy). He found that his investigation of drugs won much more press and public attention than earlier hearings on steel and automobiles. Despite this, he was unable to marshall support for legislation curbing drug patent rights or intervening directly in the drug pricing process. However, the discovery that many mothers gave birth to deformed babies after taking the tranquilizer thalidomide (mostly in Europe, because the drug was still undergoing safety tests in the United States) created an opportunity for a quite different legislative initiative. The result was the Kefauver-Harris Act, which strengthened the regulatory powers of the Food and Drug Administration (FDA), among other things requiring scientific evidence of *efficacy* as well as *safety* before new drugs can receive approval for marketing in the United States.

Detailed rules issued subsequently by the FDA contributed to a substantial increase in the cost of developing new drugs. Before the post-1962 rules took effect, the average cost of developing a new chemical entity, counting also the cost of failures, was roughly $10 million in 1990 dollars. By the 1980s that figure had escalated to more than $125 million. Some of the increase would have occurred even without the 1962 legislation as companies realized the need to protect themselves against tort liability suits and accumulate the test information needed to differentiate their products from the numerous drugs already on the market. Comparing the cost per new chemical entity in the UK, which during the 1960s required testing only for safety, with the cost of safety plus efficacy testing in the

United States, Grabowski and colleagues estimated that the FDA regulations roughly doubled the costs of pharmaceutical clinical testing (Grabowski et al., 1978). L G Thomas has argued more recently that the international competitiveness of the US industry actually increased as a consequence of the regulations, because the high cost of meeting FDA requirements forced companies to focus their efforts on developing important new therapeutic contributions, and that in turn served them well in winning sales outside the United States (Thomas, 1993).

The 1962 law and its implementing regulations also slowed down the process of drug development. New chemical entities developed during the 1980s took more than eight years on average from the time they entered clinical testing to the time when they received FDA approval to market a new drug. Within this eight year period, roughly 30 months were taken by the Food and Drug Administration to reach a decision on whether pending applications for new drug marketing rights should in fact be approved. This 30 month decision-making lag has been widely criticized. For nearly 20 years the US. Congress have been prodding the FDA to shorten its approval lag, thus far with only modest success. In 1992 Congress passed a law permitting the FDA to levy fees on pharmaceutical companies and use the money derived thereby to hire an additional 600 application analysts. Whether that will solve the problem, or whether adding still more employees to an already bureaucratic agency with 7,200 employees will aggravate the workings of Parkinson's Law, remains to be seen.

Certainly, reducing avoidable decision-making lags is important. In addition to letting consumers benefit earlier from the availability of new drugs, it would enhance the rewards to drug developers, helping them offset the high costs of R&D. Gains to companies would come from three sources: cost avoidance during the eliminated decision time, an earlier transition to positive cash flows, and (less certainly) from enjoying a longer period of patent protection. Using data assembled by the US Office of Technology Assessment, and assuming that the duration of effective patent protection would in fact rise, I estimate that under 1980s conditions, cutting the decision-making lag by one year would increase the discounted present value of net revenues on the average new pharmaceutical entity by $40 million.

The patent aspect of this estimate, accounting for roughly half of the gain, is complicated by other important legislation, the Waxman-Hatch Act of 1984. Because of the long time required to test new drugs and obtain approval for their marketing, the pharmaceutical companies complained that after their patents expired, they had too few years of exclusive protection remaining. To combat this, the new law permitted for drugs and other regulated products a patent extension of up to five years to compensate for regulatory delay, provided that the total period

of exclusive post-approval patent rights not exceed 14 years.

As a quid pro quo, the Waxman-Hatch Act also eased substantially the entry of generic drugs into the marketplace once patent protection had ended. Under the new provisions and rules, it is possible to bring a generic drug onto the US market by showing that its active ingredient is chemically identical to that of an already approved drug, that the applicant will pursue sound manufacturing processes, and that in clinical tests on 24 human subjects, the generic formulation achieved blood levels plus-or-minus 20 per cent of the standard set for the originally approved entity. This relaxation of generic testing requirements induced a proliferation of generic drug applications. Between 1984 and 1991, the FDA processed more than 2,000 generic drug applications. As large numbers of generic substitutes entered the market, price competition intensified.

Pressure for Price Controls

Even though the share of retail prescriptions filled by generic products rose to 30 per cent in 1989 and has continued to increase since then, there have been persistent complaints that prescription drug prices in the United States are too high and that the drug manufacturers have gained monopoly profits. Among those making this claim was another presidential candidate — one more successful than Estes Kefauver — William J Clinton.[2] Bases for the allegation included the very high annual costs of some new maintenance drugs such as AZT and Factor VIII, an increase of 8.8 per cent per annum in the Producer Price Index for drugs during the 1980s, comparisons showing that drug prices in the United States were much higher on average than in nations where patent protection was weak and/or price controls were imposed, and the repeated appearance of the pharmaceuticals industry at or near the top of *Fortune* magazine's annual return-on-stockholders'-equity rankings.

The drug companies defended themselves by emphasizing the high costs and risks of pharmaceutical research and development and by arguing, with robust theoretical support, that the accounting conventions used in computing profit returns on the book value of stockholders' equity imparted a systematic upward bias for research-intensive industries. The controversy led Congress to commission a study by its Office of Technology Assessment evaluating the various arguments and counter-arguments. In 1993 the Office of Technology Assessment issued a report affording ammunition to both sides in the debate (Office of Technology Assessment, 1993). Among its conclusions were the following:

(1) That reported accounting profits were in fact exaggerated;

(2) That even after the accounting biases were corrected, drug com-

2 See 'President Assails 'Shocking' Prices of Drug Industry,' *New York Times*, February 13, 1993, p1 (continuing in office a theme established during his campaign).

pany returns exceeded those in comparable industries by two or three percentage points;

(3) That profit returns exceeding the estimated cost of capital on new drugs introduced during the early 1980s amounted to roughly 4.3 per cent of those products' estimated lifetime sales; and

(4) That there was considerable volatility of returns over time, so one could not be certain the observed profit relationships would persist in the future.

The first significant Federal interventions into pharmaceutical price-setting (ignoring some antitrust actions) occurred in connection with the Medicaid program, which provides inter alia out-patient prescription drug reimbursement for low-income citizens. Since 1977, the federal and cooperating state governments implemented Maximum Allowable Cost policies, reimbursing for drugs with generic substitutes no more than the cost of the lowest-priced approved substitute.

The next step has a complex political history. In 1988, Congress passed a new law which, among other features, extended government reimbursement of prescription drug costs to Medicare patients — i.e., those 65 years of age and older. There was considerable public discontent over new taxes levied to support the extension, and in 1989 the law was repealed. Pharmaceutical companies played a role in fomenting, or perhaps more accurately orchestrating, the protest, apparently in the fear that extension of governmental reimbursement to the large Medicare population would precipitate a demand for price controls. Some members of Congress were furious about the industry's role, and in retaliation, they added to the Medicaid law in 1990 provisions requiring drug makers to rebate to the government the difference between their wholesale prices (i.e., those charged to pharmacies) and the lowest price at which drugs were sold to non-governmental entities — typically, those tendered to large hospitals and health maintenance organizations. The rebates were to be not less than 12.5 per cent of the wholesale price (later increased to 15 per cent). In addition, the drug companies were required to rebate any surplus by which their prices rose over time at rates exceeding the change in the Consumer Price Index. Companies refusing to make these rebates could have their drugs declared ineligible altogether for government reimbursement. An elaborate accounting scheme was established to enforce the new provisions.

Several other price control proposals, including one that would require rebates of the amount by which prices charged under Medicaid exceeded the lowest price at which a drug was sold overseas (e.g., to national health care agencies), were proposed in Congress during the early 1990s, but failed to gain approval.[3] I pass on therefore to what

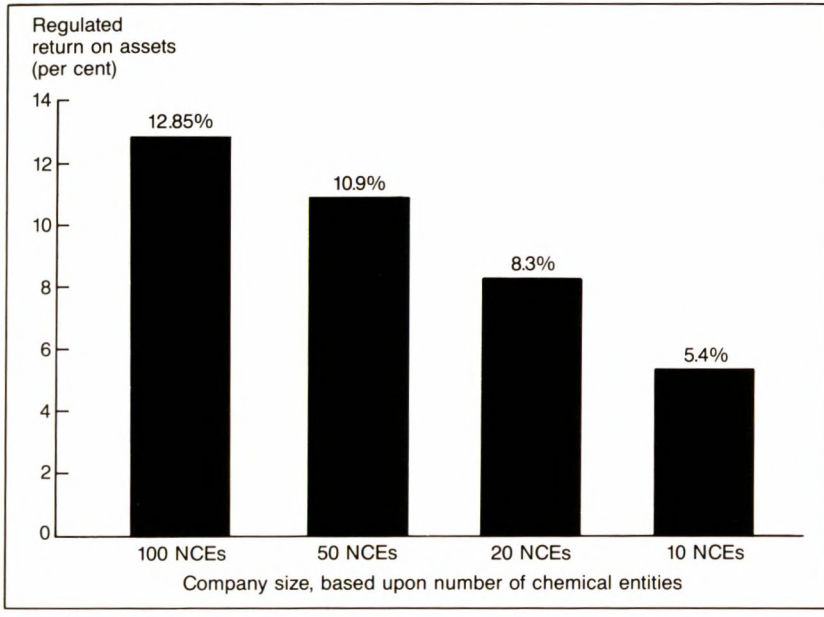
3 For a survey, see 'Prescription Drug Prices', *CQ Researcher*, July 17, 1992.

appeared a more potent threat: President Clinton's comprehensive health care program proposal (Congressional Budget Office, 1994). The original Clinton proposal, which at the time this paper was revised had been rejected by Congress, would create an Advisory Council on Breakthrough Drugs. The Council would be charged with reviewing the prices of new drugs and taking action against drugs whose prices appeared to be 'excessive'. Giving the Council binding price control authority was seriously considered but rejected within Mr Clinton's health care reform task force. Instead, the Council would seek price rebates through 'jawboning', i.e., publicizing the matter and urging voluntary rebates, or, in the last resort, by having the drug removed from the list of those eligible for reimbursement. This form of regulation, which targets the relatively few 'blockbuster' drugs identified in a separate paper by Professor Grabowski (pages 77 to 91), has been called 'Willie Sutton' regulation after the 1930s American anti-hero who, when eventually apprehended and asked why he robbed banks, replied, 'Because that's where the money is'. From one of Professor Grabowski's diagrams (Figure 7 page 86), it is apparent that if such Willie Sutton regulation won large price concessions from the few most profitable new drugs, returns on the totality of drug R&D investments could easily be driven below total investment outlays, including the cost of the many drugs that fail to receive marketing approval or, among those marketed, that failed to earn back their original R&D investment. As a result, investment in pharmaceutical R&D would surely fall.

The numerous alternatives to President Clinton's health care reform plan pending before Congress at the time this paper was revised all avoid an explicit drug price control apparatus, although some reserve the possibility of creating one if health care costs escalate in the future. Continuing increases in generic drug competition plus the spreading use of competition by large health care providers to extract price concessions from branded drug suppliers may lessen the pressure for direct price controls. The asymmetry between prices paid for drugs in the United States and those received under price controls abroad may work in the opposite direction. As always, the future remains uncertain.

If further controls do come, they are more likely to resemble those implemented in the UK than the 'Willie Sutton' model. Given that possibility, I have carried out a simulation analysis of how drug makers' profits would be affected. Specifically, I assume that the distribution of new drug sales is highly skewed, as all past studies have indicated, with mean lifetime sales of $334 million and median sales of $77 million. The average R&D investment is assumed to be $100 million; other assets are six-tenths of sales. The average margin of sales revenue less production and marketing costs is taken to be 50 per cent. If no regulation existed, the mean return on assets would be 22.3 per cent, but with a wide range

FIGURE 2 **Company size implications of UK return on assets regulation, assuming log normal sales distribution and maximum 15 per cent return**



of variation similar to what is shown by Professor Grabowski's analysis. Regulation is then imposed so as to reduce to 15 per cent the return on assets for any company that earns more than 15 per cent; the profits of other companies are left undisturbed. 'Companies' are created by drawing random samples of individual new products ranging in size from ten to 100 new chemical entities.

The rather surprising results are illustrated in Figure 2. Not surprisingly, no company size cohort earns a return exceeding 15 per cent. But there is systematic discrimination under the regulatory system against smaller companies. Those with only ten new chemical entities earn on average a return of 5.4 per cent. Those with 100 NCEs average 12.85 per cent. The reason is straightforward. If small companies are lucky and develop one or more 'blockbusters', their returns will be curbed by the regulators; if they are unlucky and sell only new chemical entities comprising the right-hand-side tail of Professor Grabowski's decile distribution, their returns will be constrained by the market. Large companies, on the other hand, will have sizable portfolios of winners and losers. The losers will increase the asset base to which the regulatory 15 per cent is applied, making it unnecessary to reduce the returns on winners

downward as much as they would be adjusted when a small company has few losers in its asset base.

I do not know enough about the UK-based pharmaceutical industry and the workings of the Pharmaceutical Price Regulation Scheme to tell whether this simulation analysis reflects UK reality at all well. Perhaps the flexibility built into the UK system permits smaller firms to fare better than my analysis implies. But in the United States, regulation is seldom flexible, so one would expect an outcome rather like what I find, unless an explicit small-firm bias is built in — a bias toward which the Congress has in the past shown sympathy.

Conclusion

Whatever model of regulation one imposes — and the UK model seems particularly intelligent, compared to such alternatives as the existing Medicaid rebate system or Willie Sutton regulation — regulation is a clumsy instrument for fashioning the delicate tradeoff between securing competitive prices on the one hand and maintaining incentives for investment in new product discovery on the other hand. One does not wish to kill the goose that lays so many golden eggs. Because new drugs yield substantial consumers' surplus untapped by their developers, even when profits are high, consumers would lose along with producers with price or profits regulation. Should a tradeoff be required between modestly excessive prices and profits versus retarded technical progress, it would be better to err on the side of excessive profits. My own preference is for a policy approach that erodes profits by actively stimulating generic competition after patents have expired, rather than attempting to beat those profits down through regulation in the early product life cycle stages. In that way, incentives are maintained for investment in new products, but after a lag, consumers obtain the full benefits of price competition. And indeed, the only way drug makers can continue earning substantial profits is to *continue* seeking important new drugs and laying additional golden eggs.

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The Value of the Pharmaceutical Industry to the UK Economy

David Hale and Adrian Towse

Introduction

The UK-based pharmaceutical industry is a highly successful sector of the UK economy producing over £8.5 bn (at manufacturers' prices) worth of output in 1992, providing employment for over 76,000 people, and creating a trade surplus of £1.3 billion in 1992. Given these impressive figures it is of interest to assess the overall net benefit which the UK economy derives from the existence of a successful pharmaceutical industry based in the UK. This paper attempts to estimate this. We have benefited from discussions with economists within the Department of Health (DH), and the Department of Trade and Industry (DTI), and with George Yarrow of Hertford College, Oxford. Any estimates or errors in this paper are, however, attributable solely to the authors.

The Counter-Factual

In order to calculate estimates of benefit it is necessary to have some baseline case, or 'counter-factual', from which to measure. This paper compares the current performance of the pharmaceutical industry with a theoretical alternative in which there is no UK-based pharmaceutical industry.

We have assessed three potential situations which would match the counter-factual:

(i) There are no research or production facilities located in the UK. Sales and marketing facilities are for the UK market only, which is served by imported products;

(ii) There are no corporate headquarters of pharmaceutical companies located in the UK;

(iii) Institutional investors choose not to hold UK pharmaceutical companies' shares in their portfolios, which are dominated by shares in domestic concerns.

The main focus of analysis is (i). We discuss the relevance of (ii) and (iii) on page 47.

Estimation issues

In measuring the net contribution of the UK based pharmaceutical industry we are assessing the opportunity cost value of the resources currently utilised by the industry, essentially asking how else the resources could be used. We must determine how much better or worse off the UK would be by having resources employed in the pharmaceutical

industry rather than in other sectors of the economy. This approach raises two issues, which we consider in turn.

Short-run vs long-run

If the entire pharmaceutical industry were 'lost' suddenly there would be significant unemployment and large amounts of redundant capital in the pharmaceutical industry and in sectors supplying services to the industry. It is likely that in the short term the UK economy would suffer substantial adjustment costs before all these resources could be re-employed elsewhere in the economy, as many assets have relatively specific uses and many employees have highly specific skills. These adjustment costs may be greatly reduced if the change occurred gradually over a very long time horizon.

Any estimate of short-run adjustment costs incurred is highly dependent on the way in which the counter-factual is assumed to come about. This is not the focus of this paper. This paper focuses on the long term effects which would remain even after the economy has regained 'equilibrium'. All the resources currently being used in the pharmaceutical industry are assumed to be utilised in other sectors, in the long run. The question is the extent to which these alternative uses are of less value to the economy.

Transfer payments

The aim of this paper is to estimate the degree to which the UK-based pharmaceutical industry benefits the UK economy in aggregate. We are not, for this exercise, considering benefits which redistribute income from one part of the UK population to another part of the UK population, although such redistributions can have an impact on economic incentives. Any element of benefit or cost which is a direct 'transfer' within the UK is excluded from the net value estimates.

Outline of potential benefits accruing to the UK economy

We have identified several ways in which the UK economy, in theory, may benefit from the 'presence' of the pharmaceutical industry. These are as follows:

- *Supply Side Benefits;* positive externalities which may accrue to universities, to the NHS, and to other industries resulting in lower unit costs and the ability to provide improved services or products. Knowledge gains produced by R&D will not be utilised exclusively within the originating company. Parties other than the originator benefit from the advancement of knowledge. Although some information exchange is not location dependent, for example, presentations at conferences and publications, other benefits do result from informational exchanges due to proximity, or from the same individ-

uals working on projects for different organisations.

- *Benefits to Patients;* these may in principle arise from the speedier introduction of therapeutically beneficial medicines to the UK market, because development work is undertaken in the UK, and to the introduction of treatments which may never have been discovered but for work in UK laboratories.
- *Direct Benefits;* rents which accrue to UK residents through three sources: higher wages to employees; higher profits to owners; and higher tax receipts to the UK Exchequer.
- *Terms of Trade Effects;* the competitive advantage held by the UK based industry enables it to sell large volumes of product in competitive domestic and foreign markets. If this output were to be lost and replaced by imports it is likely that there would be a terms of trade effect, in that national income would be reduced by the need for a lower exchange rate to enable other goods and services to be exported.

Outline of potential costs to the UK economy

It appears to be the case that the existence of an innovative pharmaceutical industry in any country is linked, to a significant degree, to the treatment which companies receive in their domestic marketplace. In the UK, the government purchases the overwhelming proportion of ethical pharmaceutical products consumed in the UK, through the NHS. This relationship between government and the industry is important. In the UK market companies have freedom in the pricing of new products to the NHS, whilst the government, through the Pharmaceutical Price Regulation Scheme (PPRS), controls the overall profit earned from sales to the NHS. This 'relational contract' built up over a significant period of time is intended to provide companies with 'reasonable' prices for their products. If there were to be no UK-based pharmaceutical industry, the government could, in theory, abandon the PPRS policy of providing a reasonable return and attempt to push prices paid for the newly imported products below current UK price levels through opportunistic purchasing. If lower prices could be paid by the UK, then the calculation of the net value of the UK pharmaceutical industry would have to allow for the opportunity cost to the UK of not currently achieving these lower prices. The potential costs associated with this are detailed below:

- *Direct Costs;* savings that could be achieved by obtaining lower prices on products currently imported. In the case of products currently supplied by UK production, lower prices could save an element of the revenue which is currently remitted abroad as profit or dividend. The rest of any saving from the NHS paying lower prices for UK supplied products would only give rise to a transfer payment within the UK;

- *Distortionary Costs;* costs to the wider economy resulting from having higher prices than necessary paid out of public funds. This might result in one or more of public expenditure on other programmes being lower, taxes being higher than otherwise, or higher government borrowing increasing upward pressure on interest rates;

These costs exclude general 'deadweight' losses. Deadweight losses occur when prices are above socially optimum levels, because consumers tend to buy less of a good when the price is high than they would have done had the price been lower, closer to the socially optimal price. As a result there is a loss of satisfaction to the consumer (lower consumer surplus). This 'deadweight' loss becomes smaller and smaller the more inelastic, or less responsive to price movements, demand is. Aggregate UK consumption of pharmaceuticals does appear to be relatively inelastic with respect to aggregate price changes, (depending more on clinical need than the general pharmaceutical price level). If we assume no change in the pattern of prescribing is likely in response to a general lowering of price levels (rather than a switch from one product to another because of a change in relative prices) then deadweight losses are zero.[1]

Estimation of long-run benefits

R&D spin-offs (supply-side externalities)

The pharmaceutical industry in the UK spent £1,451 million in 1992 (ABPI, 1993) on research and development. This gross expenditure in itself does not benefit the UK economy because these resources, would, in the long run, be used in other sectors. However R&D is a use of resources which may substantially benefit companies, institutions, and individuals other than those who pay the bill. These additional benefits of R&D would be foregone were the resources employed in non-research environments. Pharmaceutical R&D is primarily an investment in the acquisition of knowledge. The nature of advancements in knowledge make it unlikely that only the originating company will take advantage of them. Knowledge is largely non-rivalrous in consumption, and it is difficult to exclude people from utilising it, not withstanding patent law, giving it some characteristics of a public good. Non-excludability is greater in respect of pharmaceutical R&D if investigation is carried out externally, in academic institutions, in hospitals, and in other firms. Thus the funding pharmaceutical company receives the information which it has paid for but the researchers also retain the knowledge.

1 We should note that in theory there is a trade off between direct cost savings and deadweight losses. If we assumed demand was elastic then deadweight losses would be higher but direct cost savings lower.

Relationships between external researchers and industry are enhanced with proximity and this promotes increased informational exchanges in both directions, which increase the 'spin-off benefits' of R&D.

In order to assess the potential of these spill-over effects it is useful to assess how much is spent in the various areas of R&D. Table 1 shows an approximate breakdown of revenue R&D expenditure into the constituent areas.

Revenue R&D expenditure divides in an approximate ratio of 2:1 into development and discovery.

Discovery by its nature is initiated by 'basic research', defined by the CSO as 'work undertaken primarily for the advancement of scientific knowledge without a specific application in view'. Chemical development similarly deals with knowledge which is not pharmaceutical industry specific. These initial stages witness a significant degree of collaboration between the companies and academic research institutions. In the region of £100 million is estimated to be spent on university collaboration. Much of this research expands the scientific knowledge base and benefits other industries when they require particular, related, problems solved.

TABLE 1 **Breakdown of pharmaceutical industry's R&D expenditure by function**

	% of revenue R&D[1] *approx.*	*£ millions (1992) approx.*
Discovery	30%	350
Development		
– Pharm/chem development	20%	230
– Animal studies	12%	115
– Clinical evaluation	22%	255
– Regulatory affairs	3%	35
– Miscellaneous	13%	175
Capital:	20% of total	290
Total		1,450

Source: 1. OHE, adapted from Lumley C et al, 1989.

A significant amount of clinical evaluation is carried out within hospitals, under contract. When clinical testing is carried out in teaching hospitals there is again an increase in the knowledge base and, as in the case of universities, there is direct benefit in terms of the improved teaching and practice of medicine.

Examples of benefits to related industries would include the growth of bio-informatics where pharmaceutical research into areas such as DNA analysis have assisted a new UK-based industry to develop an

international advantage. The agriculture, food, and brewing industries can also utilise some of the advances in scientific understanding which come out of pharmaceutical R&D expenditure. Informational spin-offs can lower costs or boost product quality improving the competitiveness of other sectors.

The pharmaceutical industry spends a significantly higher proportion of its income on R&D than any other major sector of the UK economy (as shown in Appendix 1). Even if the resources 'released' under the counter-factual were to be utilised in another hi-tech sector it is likely that a significant reduction in R&D levels would result. This would entail foregoing the spin-off effects associated with the 'lost' R&D.

A literature search has not given us a basis for attempting to quantify these spin-off effects and so no further analysis is attempted.

Patients' consumer surplus/health gain

Benefit to patients is a second area of benefit where we have not found a basis for calculating a reliable estimate. Patients gain a great deal of benefit from pharmaceutical products. However, the narrow question posed by this paper is to what degree patients would be worse off if there were no UK-based industry, and the NHS was importing all of its pharmaceuticals. The situation we are seeking to assess here is whether or not some beneficial products will reach the UK market more slowly if the innovating company is no longer UK based. Additionally some compounds may simply never have been invented. We have not attempted to develop a method for estimating these important benefits.

Labour rents

Recent studies show that significant inter-industry wage differentials exist. These differentials are not only large but persistent over time and space, internationally and domestically. The wage differentials persist even after controlling for a wide variety of worker and job characteristics, and they run through the full range of posts in the industries affected.

The evidence laid out in Appendix 1 indicates that the pharmaceutical industry is one of the industries supplying labour rents. Everyone working in the pharmaceutical industry in all countries earns these rents. With a total UK-based industry labour cost of £1,530 million (Appendix 4) and the final wages after adjustment for skill differences being 11 per cent above the industrial average, the expected rents are £140 million. However some of the rents are earned from the payments made by the NHS for its medicines. This element of labour rent is a transfer payment within the UK and so, as detailed earlier, will not be claimed as a benefit to the UK economy. If we make the simplifying assumption that 50 per cent of the labour rents are due to production

for domestic consumption (approximately one half of UK output goes into the domestic market) then only 50 per cent, or £70 million, of the labour rents calculated are in fact a benefit to the UK economy as a whole. Such gains would be additional to the export rents discussed below, as labour cost including labour rent is incorporated in long run average cost.

Rents from exports

Rents are by definition the revenues taken over and above the long run average cost (LRAC) of production. Included in the calculation of LRAC are all the short run expenses which must be incurred and also an allowance for the risk adjusted cost of capital. LRAC is therefore the return which is just sufficient in order to keep a set of resources in their current use in the long term.

We have made the simplifying assumption that the UK price level approximates to the LRAC of producing pharmaceuticals in the UK. There is reasonable a priori justification for assuming that the overall UK price level approximates this LRAC better than other available price level measurements. In the UK market, unlike most other European markets, companies are allowed to freely determine the price of new products. Whilst at the same time the PPRS controls the level of profit which companies can earn on sales to the NHS, each firm is, in principle, being allowed the opportunity to cover the cost of capital which is included in long run average cost, but not to earn excessive returns. At the same time the purchasing policy of the NHS promotes competition by not favouring domestic products. The UK market is therefore competitive and limits profit to a 'reasonable' level.

Appendix 2 illustrates the calculation of export rents. Any country which pays higher prices than the LRAC (LRAC is based on UK price index of 100) will have a price index in excess of 100. The value of rent earned by UK pharmaceutical exports to these markets depends on the total value of exports and the degree to which their price levels exceed UK prices. The estimate produced for total export rent equals £615 million. This includes some rents which are remitted abroad to foreign owners and so can not be termed beneficial to the UK economy in our framework. The benefit to the UK economy will equate to £615 million less post tax earnings remitted abroad. Corporation tax will be paid to the UK Treasury before any dividends are calculated so the tax revenue from these rents will all be regarded as a gain. We realise that the tax calculation depends on accounting procedures, however we will assume that rents are treated as profit. Assuming a long run tax rate of 33 per cent, the benefit to the UK ranges from £410 million to £615 million, assuming 50 per cent and 100 per cent UK ownership respectively. The alternative 'value added' approach, discussed below on pages

48-9, gives an estimated range for export rents of £490 million - £730 million. The benefit to UK economy from export rents is therefore estimated as in the combined range £410 million - £730 million.

Rents on sales which originate overseas

Rents from export sales by UK-based companies, both UK-owned and foreign-owned, have been assessed above. Companies which are labelled as UK-owned, i.e. with corporate HQs located in the UK and significant UK share ownership, generally have significant production and research facilities located overseas, for example Glaxo Wellcome's overseas manufacturing output is over 2.5 times its UK manufacturing output.

It is a reasonable assumption that production located overseas is also able to earn rent because of the research and development and managerial base which exists UK. The loss of UK managerial expertise and high quality UK research and development makes it entirely possible that rents from overseas-based sales would be lost, i.e. companies would be less successful.

A conservative estimate of the sales which UK-owned pharmaceutical companies generate abroad, which originate overseas would be £6 billion. Assuming that these sales contain a rent element, contributed to group post-tax profits, of 5 per cent, which is also conservative given our estimates that UK exports generated 13 per cent of revenues as rent, the rent attributable to overseas sales originating abroad is in the region of £300 million.

It is likely that some rents would continue to be earned by pharmaceutical companies after they had shifted all R&D and manufacturing activity and their corporate HQ out of the UK. If the companies continued to be owned by UK shareholders then the UK would receive these rents. It is likely in practice that UK shareholdings would also diminish, as most institutional and personal share portfolios are dominated by companies with UK HQs. In principle, however, even if shares were sold, the price obtained would reflect the expected value of future rents. In practice, of course, this may not occur.

Our estimate of £300 million does not depend on a change of share ownership. It is assumed to arise from lower rent earning following the loss of the benefits of UK location. If shares were disposed of by UK citizens, and prices did not reflect future rent earning capacity, additional losses would occur.

Terms of trade effect

The UK's competitive advantage in pharmaceuticals has allowed it to produce 'premium quality' products which sell well in the competitive purchasing environment of international markets. Appendix 3 discusses the impact which the movement from the current situation to the

counter-factual would have on the exchange rate and the terms of trade. The removal of the UK-based pharmaceutical industry would bring about, in the short run, a deterioration in the trade balance equal to the gross output of the domestic industry, around £7.5 billion (total output less inter-company trading within the UK). All exports would disappear and all domestic production purchased by the NHS would be replaced by imports. In order for this deficiency to be made up, other industries would have to increase their output of exportables. The resources to produce this increased output are available, in principle, from the resources freed by the pharmaceutical industry. However the UK has a competitive advantage in the market for pharmaceuticals. Other industries would have to lower the prices of their goods and services to a degree in order to sell the extra output which they are able to produce. The lower the unit price falls the more units that must be sold in order to make up the £7.5 billion, and the greater is the loss of potential rents and surpluses in these other sectors. As more resources are used to make goods which must be exported to maintain equilibrium, fewer goods are available for domestic consumption. The estimated impact set out in Appendix 3 is in the range £1.05 billion – £1.4 billion per annum.[2]

Alternative rent calculation – a value-added approach

An alternative to assuming that certain market conditions produce prices which approximate to LRAC is to estimate the LRAC directly from cost data. The Census of Production provides estimates of industry sales, bought-in materials and services, wages and salaries, and depreciation of fixed assets. These figures provide the basis for calculating the net profit of the industry. In order to calculate 'rents' we must subtract the risk adjusted opportunity cost of capital from this. The Census also provides an estimate of capital employed. We have applied a recent estimate of the nominal opportunity cost of capital in the pharmaceutical industry by the Office of Technology Assessment of 14 per cent per annum. This compares closely with estimates used in other studies. Appendix 4 lays out the value-added based rent calculation. The overall rent estimate is £1,487 million. This estimate includes rent on sales to the NHS which we exclude from the rent calculation as a transfer payment.[3] There is, however, no simple and accurate mechanism whereby we can divide this value added into export rent and transfer payment. Roughly one half of

2 This terms of trade effect, whilst being a real cost which the economy would have to bear, is not necessarily unique to the pharmaceutical industry.

3 It could be argued that the value added rent on NHS sales should not be regarded as a transfer but as a proxy measure for the additional benefits derived by NHS patients from the quality of the medicines supplied by the UK-based industry. We have, however, treated this aspect of benefit as unquantifiable.

the output of the UK industry is purchased in the UK, so if we crudely assessed the transfer payment as half of the value added, the total export rents, as calculated using the value added approach, would be around £730 million. Not all of this value added will accrue to the UK economy some will be paid out, after tax, to non-UK owners. If we apply the same rate of long run corporation tax, 33 per cent, and the same range of non-UK ownership, between zero and 50 per cent foreign ownership, which were used earlier, then the value added remaining in the UK economy is in the range £490 million – £730 million. As discussed, we can combine this with the £410 million – £615 million range estimated above using price comparisons, to arrive at a combined estimate for export rents of £410 million – £730 million.

Estimate of potential cost savings

Cost savings and transfer payments

If we initially assume that some cost saving by the NHS is feasible it is important to understand which elements produce cost savings for the UK economy as a whole. If the industry were entirely UK-owned, supplying the NHS from UK plants, then any payments made to the pharmaceutical companies by the NHS would remain within the UK. There would be no direct savings for the UK under these circumstances. Any cost saving to the NHS would be a redistribution of income within the UK and so a transfer payment. Potential savings for the UK economy accrue only to the extent that lower prices would reduce the amount of monies paid by the NHS which 'leak' abroad via profit remitted to overseas owners, or alternatively that lower prices are obtained for products currently imported. Only if all products were currently imported, or the entire UK-based industry was foreign-owned, would savings to the NHS be equal to savings to the UK economy. In practice therefore, any estimates of savings have to be adjusted to remove the transfer element.

The potential for cost savings

Opportunistic purchasing of pharmaceuticals might, as in other industries, be based on three approaches:

- obtaining volume discounts
- 'spot' purchases where suppliers sell at below average cost
- finding suppliers with lower costs or who are able and prepared to accept lower profits.

Adjusting for volume

The ability of a country to employ leverage on the price paid through opportunistic bargaining may be directly linked to the volume of products it purchases. France, along with some other European countries,

purchases a much higher volume of medicines than the UK and so may be able to 'negotiate' lower prices more easily (France spends £9 bn per year on pharmaceuticals, over twice the UK expenditure). The price indices calculated by IMS (Appendix 2) show ex-manufacturer prices for the top 50 products for the UK having a similar price to France. Other indices however, do show French prices as being lower (for example the 1989 BEUC index and 1991 IWI index). Analysis of 'volume adjusted' international prices place the UK price at the low end of the scale, questioning the ability to achieve much lower prices, given low UK per capita consumption of pharmaceuticals.

Spot purchasing aimed at free-riding

Cost savings may well be available in the short run, although the ability of wholesalers and entrepreneurs to move product across national boundaries, combined with a likely reluctance of companies to signal to other governments a willingness to accept lower prices, will limit the willingness of the industry to supply at low prices in the long run.

A lower long run cost?

It may well be that our assumption that UK price levels represent a good approximation to long run average costs is incorrect. Overall French price levels, for example, may well be below UK levels, and France has some domestically owned companies with international capability. As discussed above, although the IMS index we have used shows a French price level for new products close to the UK level, older indices have suggested French price levels may be half those of the UK. If French prices were lower and approximated to long run average cost, then the UK may be able to purchase at lower prices than current UK levels under the counter-factual.

A calculation of cost savings

If it were true that, say, the Spanish price level in the IMS index and not the UK price level could be achieved by the NHS when opportunistically purchasing medicines then the potential cost saving achievable would be approximately 17 per cent of NHS expenditure on pharmaceuticals. In 1992 the NHS expenditure on pharmaceuticals was £3,490 million. The potential cost saving to the NHS which would be obtained if Spanish prices were paid is thus approximately £600 million. If account is taken of the transfer element (assuming that one third of NHS purchases are imported and that UK ownership of the UK-based industry lies in the range 50-100 per cent) of this NHS saving, then the saving to the UK is reduced to between £200 million and £400 million.

If Spanish prices reflected LRAC then the calculation of export rents would have to be adjusted. The estimated level of gross rents would rise

to £950 million which, using the same assumptions regarding taxation and ownership patterns as before, revises the estimate of gain to the UK economy in the range £630 million – £950 million. The net benefit calculation would thus not change significantly overall. Our assumptions are, however, that UK prices represent LRAC, and that, given low UK volumes, and cross border arbitrage within Europe, it is unlikely that in the long run, the UK could make savings.

Conclusion

On the basis of our assumptions and estimates, the UK-based pharmaceutical industry provides a substantial net contribution to the UK economy. Our calculations provide us with a range of figures, shown below, which can be summated to provide an estimate of the value of the UK-based pharmaceutical industry to the UK economy.

If all the quantifiable benefits are assumed to be relevant we obtain a valuation within an estimated range of £1,800 million to £2,500 million per annum. This valuation excludes those elements which we felt a reliable estimate could not be provided for, i.e. the supply side externalities of R&D and the benefits which patients receive.

	£ million per annum
Benefits:	
Supply side externalities	unquantifiable
Benefit to patients	unquantifiable
Labour rent	70
Export rents	410-730
Rents from non-UK production	300
Terms of trade	1,050-1,400
Cost saving	nil
Total	1,830-2,500

Our overall conclusion is that the value of the industry to the UK economy is around £2 billion per annum. The results are however highly sensitive to the assumptions used. On some assumptions the annual value would be below £1 billion. Our view is that under all reasonable assumptions the industry is making a net contribution to the UK economy of several hundreds of £millions per annum.

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Appendix 1

Labour Rents

Katz and Summers (1989) identify three key relationships which help in determining which industries will be paying a large wage premium:

(1) a significant positive relationship exists between value added per worker and wage premium;
(2) a similar relationship exists between the capital-labour ratio and the wage premium;
(3) a high level of research and development tends to coincide with a high wage premium.

The pharmaceutical industry scores highly on all three counts. In terms of R&D expenditure the following comparisons can be made

Industry	**R&D spend as % of Sales**
Pharmaceuticals	17.5%
Electronics	10.5%
Aerospace	9.5%
Chemicals	6%
Motor Vehicles	2%
Electrical Engineering	1.5%
Mechanical engineering	1%

Source: OHE adapted from Pharma Facts, ABPI, 1993.

Pharmaceuticals are a high technology industry, exactly the type of industry which Tyson (1992) indicates will make the payments of labour rents. Hence pharmaceutical companies the world over are paying their employees a wage which is above that which they could achieve in other, less intensively hi-tech, industries.

The implication is that displaced workers from the pharmaceutical industry would find it extremely difficult to match the remuneration which they currently receive. In reference to Airbus Industrie, Katz and Summers conclude that 'policy analysis should not treat the rent component of the wage bill as a social cost of production but as a component of the social surplus generated by the industry'. Such a conclusion applies equally to the pharmaceutical industry.

In the hi-tech, export intensive, industries of the USA, wages were around 10 per cent above the average, *after being adjusted for skill differences.* International comparisons show such patterns to be similar across developed countries. On this basis an approximate figure for total labour rent in the UK would be £140 million based on wages and salaries of £1,530 million in 1992. This gross rent will be adjusted in the main body of the paper for transfers.

Appendix 2

Calculation of export rents

Country	*Price index (UK=100)*[1]	*Total pharmaceutical exports from the UK*[2]	*Total long run cost of exports (£000s)*[3]	*Rent element of exports (£000s)*
Belgium	114	113,400	99,474	13,926
Denmark	163	46,300	28,405	17,895
France	99	332,800	336,162	–3,362
Germany	168	266,100	158,393	107,707
Italy	109	229,200	210,275	18,925
Netherlands	155	257,600	166,194	91,406
Spain	83	71,251	85,845	–14,594
USA	171	429,182	250,984	178,198
Totals		1,745,833	1,335,730	410,103

Sources: 1 IMS 1992 index based on top 50 products in UK market.
2 Customs and Excise, Business Monitor LSD.
3 Total Long Run Cost = {Total Export from UK * (100/country's price index)} Price index of 100 equals UK price and is assumed to equal LRAC.

Total pharmaceutical exports to the top 50 markets (£000s) 3,500,000
Total pharmaceutical exports to the 8 markets (£000s) 1,745,833
Percentage of the top 50 export market held by these 8 countries 50%

Export rent calculated for these 8 countries (£000s) 410,103

Total export rent if we assume that the sales to rent ratio in the other half of the market is 50 per cent of that for the markets assessed (£000s) 615,153

Rents based on Spanish prices as LRAC

If the LRAC were to coincide with Spanish prices the export rent would be significantly higher. Using the index of 83 as LRAC equivalent, rents are estimated as £950 million.

Appendix 3

Measuring the terms of trade effect

If the pharmaceutical industry did not exist in the UK exports would be reduced by approximately £3 bn. Current supplies to UK customers, other than inter-industry trade, would be replaced by imports, adding about a further £4.5 bn to the national import bill. There would, therefore be a net deterioration in the trade balance of around £7.5 bn. It is unlikely that this degree of disequilibrium could be corrected without some deterioration in the terms of trade.

Two distinct steps are taken in order to estimate the terms of trade effect.

(i) Estimating the change in the exchange rate required to correct the balance of trade position; and

(ii) Estimating the terms of trade effects of the required depreciation.

To calculate these we require the elasticity of the trade balance with respect to the exchange rate E_{tb}, and the elasticity of the terms of trade with respect to the exchange rate E_{tt}. The established formulae for making these calculations together with two sets of assumed values for the elasticities are shown below.

$$E_{tb} = \frac{Vx}{Vm}\,\frac{dx+1}{dx/Sx-1} - \frac{Sm+1}{Sm/dm-1}$$

$$E_{tt} = \frac{SxSm - dxdm}{(dx - Sx)\,(Sm - dm)}$$

	Case 1	**Case 2**
d_x (elasticity of demand for exports)	−3	−5
d_m (elasticity of demand for imports)	−1	−1
s_x (elasticity of supply for exports)	3	5
s_m (elasticity of supply for imports)	6	10
v_x (value of total UK exports)	£142.5 bn	£142.5 bn
v_m (value of total UK imports)	£150 bn	£150 bn

E_{tb} is dependent on the value of total imports and exports, which in this case are given as £150 bn imports and £142.5 bn exports, and on the elasticities of demand and supply of both exports and imports. E_{tt} depends upon the elasticities of supply and demand for both imports and exports. The precise figure for each elasticity is open to much discussion. However this analysis is based on long run elasticities which are likely to be significantly higher than the short run elasticities which would tend to produce higher transitional losses.

We have assessed a range of sets of elasticities to ascertain the impact these differences have on the resultant terms of trade effect.

Case one illustrates an example with lower long run elasticities. E_{tb} = 1.95 and E_{tt} = –0.36, these combine to produce a loss to the economy of around £1.4 bn per annum.

Case two illustrates the effect of using higher long run elasticities. E_{tb} = 2.9 and E_{tt} = –0.41, these combine to produce a lower loss to the economy of around £1.05 bn per annum.

On the basis of these two cases we assume that the terms of trade effect probably lies in the range £1.05 bn – £1.4 bn per annum in the long run.

Appendix 4

Value added approach to export rents

	£ Million (1992)
Total industry sales revenue	8,540
Bought-in materials and services	4,130
Gross value added (at factor cost)	4,410
Wages and salaries	1,530
Gross profit	2,880
Depreciation of fixed assets	270
Net profit	2,610
Fixed capital	5,380
Net current assets(1)	2,640
Capital employed	8,020
Opportunity cost of capital at 14 per cent(2)	1,123
Economic rent	1,487
Economic rent as a per cent of sales revenue	17.4%

(1) ICC figure for 90/91 scaled up for 1992 industry sales.
(2) Office of Technology Assessment (1993).

Data source: Report on the Census of Production, PA 257, 1992.

Scientific Challenges Facing the Industry and Trends in the Costs of Discovery and Development: The Implications for the UK Science Base and UK Science Policy

Professor Trevor M Jones

Introduction

In my paper I want to look briefly at the development of UK science policy in relation to pharmaceutical industry research and development. Before considering recent science policy, I want to set out the scale of scientific development in the 20th century, discuss some of the many significant challenges of disease that remain, outline the process of research, discovery and development for a new medicine, and comment on the strength of pharmaceutical R&D in the UK.

Four Revolutions in the Treatment of Disease

Up to the 1930's, most medicines in common use were based upon natural products and inorganic substances that had their origins in centuries of both medical mystique and therapeutic trial and error.

The 20th century has, however, been witness to a series of revolutions in the treatment of suffering and disease.

We might usefully describe these revolutions as, viz:

1 the Chemotherapeutic revolution
2 the Pharmacological revolution
3 the Molecular biological revolution and, for the future,
4 the Genetic revolution

The *Chemotherapeutic revolution* was characterised by advances in chemistry (notably in the application of chemistry developed for dyeing processes) which led to major advances, particularly in the treatment of bacterial infections through drugs such as the sulphonamides, then through penicillin and its semi-synthetic derivatives, through aminolglycosides such as Gentamycin and Streptomycin, macrolides such as Erythromycin, the tetracyclines to (more recently) the cephalosporins and the quinolones.

In the developed and the developing world the introduction of these pharmaceutical products has dramatically benefited patients in both domiciliary and hospital care, saving millions of lives and reducing the

spread of disease.

The *Pharmaceutical revolution* has brought many benefits, but is perhaps best illustrated through the advances made in the treatment of diseases of the brain and circulation.

Basic medical research into mental illness and disease and biomedical research, notably pharmacological research, into the functioning of the central nervous system and the cardiovascular system, has provided freedom for those patients who, formerly, needed to be institutionalised in mental hospitals, has provided relief and comfort to those with anxiety and depression — and their families, and has, for example, provided a means of reducing mortality from myocardial infarction as a result of both improved procedures and thrombolytic therapies.

These represent only a small proportion of the benefits provided in the Pharmacological revolution by pharmaceutical R&D, which also include products as wide ranging as anti-diabetic agents, products against migraine, dermatological agents, diuretics, anti-asthma treatments, contraceptive agents, anaesthetics and many, many more.

Currently, we are starting to benefit from the outcome of the *Molecular biology revolution* where the structure and functions of the proteins that comprise our tissues are revealing new approaches to the discovery of medicines. Examples of this include the availability of drugs of biotechnological origin such as erythropoetin to bolster the immune system and the use of monoclonal antibodies in both diagnosis and, potentially, therapies against lymphomas, and transplant rejections.

Molecular biology is providing the essential tools for an even better understanding of physiological and pharmacological function.

As an example, we know that drugs such as lamotrigine, recently introduced for the treatment of epilepsy, also (in the laboratory at least) demonstrate potential to relieve pain.

The drug is known to act in the brain by blocking the release of an excitatory amino acid; glutamine, which when released in excess, triggers the convulsions of epilepsy.

Very recent research, at the molecular level, has shown however that this class of drugs achieves this blockade via several mechanisms including the regulation of the diffusion of sodium ions through molecular pores located at specific sites on membranes in brain tissue and elsewhere in the body.

Using advances in molecular biology, it has been possible to determine the chemical structure of these 'sodium channels'. This is an essential prelude to understanding why these processes change in epilepsy and pain and, importantly, how they may be modified or controlled.

It is now possible to clone different sodium channels and determine their disposition in a membrane and the primary chemical units of structure that compromise the channel (Catterall, 1992). From such

research it may be possible to design entirely novel drugs with much more specificity of action.

Such research, although targeted at finding new therapies, is based upon an academic approach to understanding the function of membranes and membrane physiology rather than drug hunting by first intent.

As we shall see, it is important that the environment of science in the UK (and in other developed nations) maintains and encourages this type of enquiry led research rather than investing in the 'short-termism' of applied research which often leads to predictable, similar, solutions rather than entirely new and novel ways of affecting disease processes.

The next revolution is likely to be that associated with *Genetics*. The international collaborative exercise to map the human genome is likely to revolutionise our understanding of the functioning of both animal and plant physiology and pathology, which, in terms of human disease, should lead to a better understanding of why we inherit or contract disease and hence the availability of new methods for both diagnosis and treatment of a wide range of conditions. In addition, the availability of, so called, transgenic animals provides much closer models of human disease than has been possible to date.

The structure and assembly of a genome defines the unique characteristics and hence workings of a cell or organism. Thus, genome sequencing provides the basis for determining the cause of many physiological and pathological changes that result in deformity, disability or disease. Determining familial traits will be an essential component of this research. Once the genes responsible for a specific disease or condition are identified, the next step is to determine familial traits that are linked to differences in gene composition. From this it should be possible to identify specific genetic components that could be modified to prevent disease or reverse an aberrant condition.

Stem cell biology follows genome sequencing as a next level of complexity in biological phenomena, and will increasingly become a central feature of evaluating interactions of different biological processes, particularly degenerative processes of the brain and circulation with age.

Replacing defective genes, or inserting genes to produce more effective biological processes presents considerable challenges both to the pharmaceutical scientist in terms of the laboratory process of gene transfer and, potentially, the delivery of genes to selected sites in the human body, and to Society in terms of the ethical considerations involved.

Gene delivery systems are being developed based upon compromised micro-organisms such as herpes viruses or some retroviruses. In these systems, the new gene is encapsulated within a virus which has been modified to retain those properties which allow it to penetrate to specific sites in the body, but has been compromised to prevent it carrying

out its normal replicative procedures. Indeed, the study of both the genetic and molecular biology of viruses is leading to the discovery of new antiviral drugs.

Advances in X-ray crystallography and techniques such as nuclear magnetic resonance spectrometry now allow us to examine the structure of proteins in considerable detail and draw these as computer images. Thus, we are now able to examine the enzymes of viruses such as HIV that are vital to its replication, to determine how they are affected by new antiretroviral drugs and how they mutate to resist their attack. From such studies, it may be possible to design drugs specifically to interact at particular points in biological processes so to provide either prevention or treatment.

Although, for many years, the *treatment* of illness will continue to be the predominant feature of medicine, advances in genomic research could lead to early diagnosis and therapeutic intervention which could allow 'wellness' to be a design criteria in a manner analogous to the use of vaccines as prophylactic agents in the prevention of illness.

Thus it is likely that we shall see the advent of a new class of diagnostic agents which can detect accurately defects or differences in genetic composition (unlike most current diagnostic reagents which are used to analyse for the presence of 'tell-tale' markers of infection and disease or quantify the biochemical composition of body fluids).

These new diagnostic procedures could provide information as to the likely prognosis of disease e.g. whether a subject may develop asthma, a particular cancer, a heart disease etc. and, importantly, *when* such a condition may arise and be fatal. Together with advances in gene modification and gene delivery, such diagnostic tests could lead to therapeutic or surgical intervention to prevent the condition arising later, so revolutionising the way in which current major diseases affect human health. Indeed, such genetic screening is already possible for conditions such as Duchenne's muscular dystrophy, so providing parents involved with information upon which to make choices relating to their offspring.

Whilst we should not underestimate the major ethical considerations that will be involved in such genetic research, especially consideration such as who should be screened and for what conditions; who should know the results (patient, relative, employer, insurer, state) and when, what kind of intervention should be allowed etc. Notwithstanding these major complexities, the potential benefit that could accrue is enormous.

These biological principles can be developed not only in terms of an understanding and, potentially control of disease, but also exploited in the manufacture of materials of biological origin. The control of gene expression is a key feature of understanding virus replication, but also is vital to the development of efficient biotechnology processes for the manufacture of materials such as vaccines and cytokines.

This 'Brave New World' is no longer one of Science Fiction but of exploitable reality to the benefit of human and animal health.

Scientific Challenges

Although biomedical research and pharmaceutical R&D has made a most significant contribution to health, there remain significant challenges to provide improved benefit. In the developed world at least, increased life-span brings with it an increased responsibility (and burden) of care which together with advances in diagnosis and detection, inevitably lead to a greater demand for more effective treatments.

An analysis of the deaths in England and Wales over the past 20 years shows a significant reduction in some conditions, e.g. infectious diseases and respiratory conditions, many others are on the increase, for example, neoplasms and mental disorders (OPCS, 1992). The latest figures for the top ten causes of mortality in England and Wales (1991) show a continuing alarming number of deaths from ischaemic heart disease as well as cerebro-vascular disease and cancer of the trachea, bronchus and lung. Perhaps surprisingly, the fourth largest cause of disease is still pneumonia, although thankfully the number of deaths is significantly less than 20 years ago.

Heart disease and cancers still represent major challenges despite the enormous focus of international research that has been a feature of the past 20 years.

Cancers cause almost 150,000 premature deaths a year in England and Wales and heart disease and allied conditions kill more people in the UK than any other group of ailments (ABPI, 1993).

Although we can treat, relatively effectively, conditions such as anxiety, depression, we have a long way to go before we understand the basis of these states, let alone the ability to treat effectively chronic mental illness such as schizophrenia and manic depression.

Muscular dystrophy and multiple sclerosis have gained much public attention and advances are being made in these areas. Meanwhile, chronic degenerative conditions such as Alzheimer's disease are still largely not understood and, hence, effective intervention and therapy not yet possible.

Despite the advances in the treatment of infection, viral diseases such as those due to HIV and hepatitis, let alone papilloma virus (which may predispose for cervical carcinoma) remain as significant challenges for more effective medicine.

The recent introduction of antiretroviral agents such as azidothymidine for use in HIV positive, asymptomatic patients as well as those with AIDS, the use of cytokines such as interferon in the treatment of hepatitis B and hepatitis C all add to our ability to fight these viral infections, but resistance remains a problem and more resource, more R&D spend

and more effort will be required if we are to provide answers for viral infection in the manner that has been achieved in bacterial infection.

This is equally true in more minor, yet very compromising infections such as influenza and the common cold.

Parasitic infections such as malaria, and toxoplasmosis know few geographical boundaries and are increasing in the developed as well as the developing nations.

The ability of nature to resist the efforts of biomedical researchers is evidences from the increasing among of multidrug resistant infectious protozoa and other parasitic diseases that are found internationally (a situation that is not helped by either inappropriate, incorrect or conservative prescribing or compliance).

In consequence the need to continue Research & Development into these and other diseases has not abated, indeed it should be increased.

The R&D Process

The discovery and development of entirely new compounds for the alleviation of suffering and disease is a truly global endeavour, but the most commercially successful companies are based in the USA, Europe and, more recently, Japan.

Society has come to expect such products to be readily available, reasonably priced and acceptably safe. Whilst patients and providers must have confidence in the efficacy, safety and quality of the medicines they take, in general, the layman has little understanding of the complexity, time frame and cost of bringing a new drug to the market and especially the high investment risk involved in bringing a successful product to therapy or prophylaxis.

The process of research and development by which new effective and adequately safe products are brought to the market is expensive, prolonged and risky.

Over the past ten years, global R&D expenditure (excluding capital equipment etc.) has risen from US$5.4bn to over US$25bn, with an average annual increase of 14 per cent and, expansion has been particularly noticeable in Europe in the past five years (Lumley, 1994).

By any industrial comparison, these are large sums invested in R&D and although tangible health and economic value can be gained from new medicines it is questionable whether the health ministries of the developed world economies can or will provide an adequate return on this global investment, i.e. there are bound to be both winners and significant losers in the race for limited healthcare budgets.

For major international research based pharmaceutical companies, this investment in R&D represents about 15 per cent of turnover, the figures in Japan being somewhat lower at 10–12 per cent (Halliday et al., 1992a).

Although the turnover of major pharmaceutical companies has been increasing at a level that would sustain such annual investments in R&D, the slowdown in earnings capacity as a result of major changes in health-care policies, is likely to impact significantly on the ability of some companies to sustain the high cost base of R&D necessary for its future success.

R&D covers both the complexity of drug discovery and the exactitude of drug development. In general, for companies in the USA and Europe about one third of the total R&D spend is in drug discovery (Drasdo et al, 1993), the other two thirds being the major expenditure incurred in evaluating the safety of the new chemical entity, its efficacy in clinical studies and its technical development, both in chemical or biotechnological manufacture and in the formulation of the dosage forms that the patient receives.

Traditionally, the ratio of discovery to development has been higher in Japan than Europe or the USA, largely due to the focus of Japanese pharmaceutical R&D on its own population such that development costs have been lower than those incurred in full international development.

This is, however, changing as Japan enters the more global markets of Europe and the USA, and develops more innovative products than the 'copy' or 'me-too' products, which have been traditional in Japan in the past 20 years, i.e. products that are chemically very similar to products discovered in Europe or the USA.

For every product that eventually passes the rigours of development and enters the armamentarium of the prescriber, many thousands are synthesised and rejected. Typically, in excess of 4,000 compounds are synthesised for every one product that is marketed. In the USA, this figure has been much higher (as much as 6,000:1) (Halliday et al., 1992b).

This apparent low 'strike rate' is for a variety of complex reasons including:

- screening a broad range of chemicals and biological materials of various origins and types against known biological targets,
- the synthesis of structurally related compounds to establish trends in activity as part of the discovery process,
- the optimisation of a lead series of compounds to ensure that the properties of the one finally selected for development are appropriate to the end use of the product.

Nowadays, it takes about 12 years from the date of first synthesis to the date of first marketing of a new drug (20 years ago this time would have been nearer 6-8 years).

This period may be divided, approximately, into several phases, viz

1 Discovery activities in the laboratory.
2 Pre-clinical activities (largely safety evaluation) to provide a basis for

first administration to humans.

3 Clinical studies

Phase I — usually in healthy volunteers to establish tolerance and likely dosage (average 1 year)

Phase II — first studies in patients to assess tolerance and potential efficacy (average 2 years)

Phase III — major (usually international) studies in patients to determine the adequacy of the product in terms of efficacy and safety (average 3 years).

During the clinical phase, parallel studies are in progress to establish the likely safety profile of the compound in long term studies. Technical development work proceeds to design and scale up chemical/biotechnological processes for manufacture and to formulate and scale up appropriate dosage forms such as tablets, injections, or aerosols. The complexity and extent of studies that are now an inherent part of international (global) drug development are likely to continue to increase the cost of successful R&D.

In addition, few companies are likely to have sufficient in-house resource to accommodate their international needs. Indeed, it can be argued that it is prudent to plan resources to cope with 'normal' as distinct from, 'peak' activity. This leads, inevitably, to the likelihood of an increasing component of R&D being carried out by contract research organisations in collaboration with multinational research based pharmaceutical organisations.

This is particularly the case for the newer, start up, (often biotech based) companies who are typified by research laboratories without development facilities.

Thus, growth in alliances, contract houses and other collaborative endeavours is likely to be a growing feature of pharmaceutical R&D, over at least the next decade.

Even when compounds reach the point of development where they are first administered to man, development is often terminated during the subsequent phases of study. This is due to various causes, but the principal reasons for terminating the development of compounds that enter clinical trials are inappropriate pharmacokinetics and limited efficacy. These two features taken together represent about two thirds of all discontinuations (Prentice et al, 1988).

The final stage of development involves a review by the many international regulatory authorities appointed by ministries of health, most of whom have different views relating to efficacy, safety and quality of medicines.

Regulatory approval times vary considerably around the world and can be very prolonged (>5 years). In the USA the average has been about $2^1/_2$ years from the time of submission. The recent changes in the

Medicines Control Agency have considerably shortened the UK approval times for new chemical entities; the 'track record' now standing at about 6-9 months, a major improvement on the performance of 10 years ago. In France the time is about 1 year. However, in Germany, the last 5 years or so has seen an increase from approval time from about 1 year to 3 years or more. (Harvey et al., 1993).

A typical submission for marketing authorisation runs to about 150 volumes in the USA and about 5,000 volumes to cover the member states of Europe plus Australia, New Zealand and South Africa (comprising over a million pages of information!). The collation and production of such reports, even when the studies are completed, is a major exercise, largely in hard copy format, although computer assisted regulatory submissions are likely to be a feature of the next century.

Regulatory authorities vary considerably in the numbers of questions they raise on these submissions, the numbers being typically 50-100 in the UK and USA but upwards of 200 in Germany! (Harvey et al., 1993) These delays, together with the requirements for additional data that have been a feature of the past decade or so, have clearly influenced the effective patent life available once the product is marketed. In the 1970s, pharmaceutical companies investing large sums in R&D might anticipate between 10 and 15 years patent term remaining once a new chemical entity was marketed. This time was eroded and in most developed countries the effective patent life in the early 1990s was in the order of only 8 years. (Karia et al., 1992).

The introduction of recent legislation in Europe should help this matter somewhat but, clearly, the industry is disadvantaged in terms of effective patent life by comparison with most other industrial endeavours.

Taking all these features into account, the average cost of bringing a new product to market is estimated to be US$369m (OTA, 1993), and although the compounds will have therapeutic utility, their commercial success cannot be guaranteed. Indeed, it is estimated that only 4 per cent of marketed new chemical entities achieve world sales in excess of $200m and only 3 per cent world sales of $100-200m (Lehman, 1993).

Pharmaceutical R&D in Britain

Why has Britain been such a fruitful source of new pharmaceutical products? Undoubtedly, it is because of the strong foundation of basic science upon which biomedical research is based, together with a long and confident tradition of clinical science and practice both in our world renounded university hospitals and, in-depth, in our national health service infrastructure. This, combined with a stable economy and continued investment in the science base of the nation has provided confidence not only to indigenous pharmaceutical companies but to many

international companies whose inward investment is apparent both in our universities and in the establishment of research and development facilities throughout Great Britain.

It is important, therefore, that Britain retains a strong science and medical base in order to maintain and further develop her excellence in pharmaceutical drug discovery and development. This, in turn, relies heavily upon a strong recognition by government of a policy for science which provides adequate facility for those sciences which underpin and contribute to biomedical research and development.

The 1993 White Paper 'Realising our Potential. A Strategy for Science, Engineering and Technology', has been an important step in creating a national (and international) debate on the nature, scope and focus of research funding, its management and co-ordination.

It recognised the essential need for high-quality education and training; particularly the need for increased scientific education, career guidance and vocational qualification so to provide the scientists for the new science of the 21st century.

Many scientists trace their career origins to inspired teaching both at school and university level, and although the past 30 years has seen swings against science education, as the White Paper pointed out, recent trends in the supply of specialist scientists show a healthy growth and an increasing proportion of young people are now continuing into higher education. But, science does not form a sufficient part of our nation's liturgy, is not giving sufficient prominence by news media and the scientific activities of our universities and industries are often cited in negative publicity on the environment and safety rather than in the excitement that can be gained through science and in the contribution that it provides (especially biomedical science) to our nation's health and wealth.

Recent initiatives such as 'Save British Science' and the National Science Week; together with increasing co-ordination between scientific societies in their outreach to schools and universities are encouraging signs that, hopefully, will turn into a continuing adequacy of candidates for scientific careers.

Such efforts, however, can be frustrated unless there is national commitment adequately to fund the science base.

This is important not only in terms of research grants but, particularly, in terms of the fabric of our laboratories in universities and national research institutions, many of which now show marked signs of deterioration.

The restructuring of the Research Councils by the Office of Science and Technology that has recently taken place provides new impetus for even further investment in biomedical research and development, but it will be important to ensure that in the competition for limited funds,

the world class biomedical science that is available in Great Britain is not diluted so that it loses its international competitiveness. Indeed, pharmaceutical R&D in the UK is a national flagship pointing to what can be achieved by selective funding and collaboration between government and industry. It is hoped that focusing on success and building on strengths will be a feature of research award allocation and support by the Higher Education Funding Council.

The 1993 White Paper included the launch of a Technology Foresight Programme.

Whilst this should not detract from adequately funding the long-term enquiry led research that could provide entirely new biomedical discoveries and developments, a structured approach to the partnership between academia, industrial research and scientists of different disciplines should provide a significant forum to strengthen existing and create new networks and provide an agenda for biomedical research focus and partnership, at least for those activities which are sponsored by government funds.

Foresight initiatives such as those carried out in Japan on energy can be successful when applied to short-term realisable goals. They may be less appropriate to the long term, entirely novel discovery research that is essential to new diagnostic, prophylactic and therapeutic medicine but could offer real value in terms of the mid-term science and technology that is at the heart of pharmaceutical research and development.

It is perhaps significant that R&D expenditure as a percentage of gross output in the UK has steadily increased in the pharmaceutical sector from approximately 4 per cent in 1966 to over 16 per cent in 1992. Compare this with the figure for all manufacturing industry in the UK which has been a steady 2 per cent of gross UK output over the past 25 years. (ABPI 1993). Indeed, a recent Department of Trade and Industry sponsored report on R&D spending in the UK (DTI, 1994) shows that in the year 1993-4, the pharmaceutical sector carried out 32 per cent of all industrial R&D in the UK and that 4 of the top 7 companies measured by R&D spend were pharmaceutical.

The history of successful pharmaceutical R&D in the UK and the recent government initiatives to support and strengthen the science base will be important components of the challenges that both the Molecular Biological and the Genetic revolution will bring as we move into the 21st century.

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Public or Private? Governments versus insurers/HMOs as 'good purchasers' of pharmaceuticals — lessons from the US for Europe

Lois Quam

Introduction

It is difficult to ask the question of who is the better purchaser for two reasons. First it is always hard to define what 'better' really means. I'm going to focus on consistency, health gain and innovation. Secondly, it's increasingly difficult, at least in the American context, to distinguish between public sector purchasers and private sector purchasers. We therefore need to bear in mind three other aspects of purchasing which are arguably more important. The first is what is the composition of purchasing, are there many or few purchasers in the market? The second is the objective of the purchaser. Is it health gain? The third is the nature of the purchasing decision itself. Is it a purchasing decision that's focused on a medicines budget, or is the purchasing decision focused on total medical care cost? My paper begins by elaborating on the blurring of the public/private distinction in the US, then considers the composition, objective and focus of purchasing, before concluding with some remarks on the implications for Europe.

Public Versus Private — Blurring the Edges

Public entities in the US are increasingly hiring private entities to do their purchasing for them. The proposed introduction of a pharmaceutical benefit for the Medicare programme has led to discussion about putting in statute that Medicare use a Pharmacy Benefit Manager. In essence, HCFA, the Federal agency, would hire a private sector vendor to purchase for it.

Would that PBM activity become public sector purchasing or private sector purchasing? States are ahead of the Federal Government in this area. They already purchase coverage and medical services for millions of Americans who have pharmaceutical benefits, both for their own employees and for low-income Americans who receive coverage through the Medicaid programme. Increasingly, States are using private sector purchasing bodies to advise on purchasing decisions, and in some States, Tennessee is probably the most notable, they are off-loading financial risks. Tennessee has recently put out for bids to Health Plans to

provide coverage for the whole Medicaid programme. It will agree a premium with the Health Plans and then Medicaid will be covered by them.

Public entities are giving up this degree of control for three pressing reasons:

- to remove themselves from the first line of political pressure. For example, a private PBM will negotiate more aggressively on dispensing fees with local pharmacists. If the political heat comes, the State can say 'it's not us, it's them';
- it's a means of escaping some of the budgetary pressures, by outsourcing the financial risks;
- it offers the public purchaser access to scarce medical care management expertise.

The other difficulty in defining a public/private distinction is that private entities in the US either follow what the public sector does or are constrained by it in two important ways:

- the decisions the Medicare programme has made about when experimental therapy becomes a covered benefit, paid for by insurance, have been replicated by private sector purchasers. It is a good legal defence to cite Medicare's decision if a Health Plan member says you should have made another decision. In addition the costs of doing the research and making these decisions independently can be avoided if Health Plans follow Medicare. If Medicare does expand to cover pharmaceuticals, we can expect to see private purchasers following Medicare signals;
- private sector purchasers are forced to act within political constraints. Where we have had stiff competition between private sector purchasers, the response has been for practitioners to seek legislative relief to put constraints on competition. In Minnesota, for example, the legislature recently passed a law that although HMOs could pick which physicians they wanted in their network, they had to take all chiropractors, pharmacists and psychologists. Those allied health professionals, fearing that the Health Plans would cut them out, i.e. provide very reduced access to them for their members, having few chiropractors in the network, or requiring people to go to a general practitioner for a referral, circumvented the Health Plans, recognising that they had a stronger bargaining position with the legislature.

The Composition of Purchasing

Turning to the composition of purchasing — many or few purchasers. Purchasers in the US face a national market for pharmaceuticals and local markets for GPs, surgeons and chiropractors. Purchasing at both levels has been consolidating.

Historically purchasers in the US were weak. Physicians prescribed

medicines, they were dispensed with patients frequently paying either a substantial co-payment or the whole cost. That has changed with the development of HMOs or Health Plans, which now are quite widespread in the United States, though with varying degrees of control. Health Plans initially consolidated purchasing locally to confront hospitals and physicians and negotiate better rates, and to put controls on the volume of services provided. Initially pharmaceuticals were left almost entirely out of that calculation. Over time it was recognised that the same kinds of changes could be made in the purchase of pharmaceuticals. Pharmacy Benefit Managers (PBMs) emerged from the Health Plans to negotiate on a national basis with pharmaceutical manufacturers on product price and with pharmacy chains and independents on dispensing fees. More recently they have been trying to address use rates and set up formularies.

Five years ago these PBMs were very small. Today they are large with several companies each with over 15 million members and therefore with significant negotiating power. Of course, there has been a recent vertical integration in this market with pharmaceutical manufacturers purchasing the largest PBMs. We have yet to see the impact of that change.

Consolidation is also occurring elsewhere in the US healthcare market with Health Plans linking up with care providers, and States and private employers consolidating purchasing power.

Consolidation in Public and Private Purchasing

In addition to the emergence of PBMs, consolidation is taking place in three other ways.

(1) Health Plans are changing from being solely purchasers by merging back with the practitioners of care. In Minnesota, for example, where the majority of the population has been enroled in HMO's for the last fifteen years, all of the major Health Plans have merged with systems of hospitals and clinics. In Minneapolis St Paul, with a population of 2 million, there are three large integrated service networks, Health Plans that both bear the financial risks and provide health care with hospitals and clinics. The reasons for mergers are two-fold:
   - the pressure, both from States which set budget targets for the Health Plans to meet with their premiums, and from employers that have coalesced to negotiate as a group with Health Plans, pushed them to the point where they need more control over the clinical delivery setting. They had negotiated price decreases only to see much of that counteracted by volume increases. They were not having the desired effect on total cost;
   - it enhances their bargaining position relative to the new purchasers of care, be that the state legislature or employers associations. As

the market consolidates, it gets more difficult for the new purchasers to move people around.

(2) States have consolidated their purchasing of health care. They are responsible for around 20 per cent of the total market. They have hither to typically not used their purchasing power. They have had separate Medicaid programmes, State employees programmes, and odds and ends of other programmes. States are now consolidating their purchasing into a single department and going out to negotiate with the market. In most States, by doing that, they become by far the single largest purchaser of health care in that State.

(3) Employers have concluded employer alliances in American cities in a very rapid fashion. Large companies employees constituted quite a small amount of the admissions at any given hospital. Companies realised they had a poor negotiating position with local facilities, and bonded together with other very large companies in a given geographic region. In Minnesota, for example, the two employer alliances now comprise the majority of the employer market in the metropolitan area.

This trend to increasing bargaining power leads us onto consider what are the objectives of purchasers, and what pressures do they face.

The Objectives of Purchasers

The States are now major purchasers of health care, and, in the absence of Federal health care reform legislation, will become the main agent for change. States cannot run budget deficits. They have enormous obligations and they are under tremendous financial pressure. In Montana, for example, the overrun, not the whole programme, is equal to the entire university system budget for the next year.

States have not typically engaged in industrial policy or in the funding of research, both of which they consider the domain of the Federal Government. In general the Federal government has been concerned about industrial policy, jobs, exports and innovation. A single payer Federal system may give the industry a far sighted purchaser. However that is not on the political agenda. At the State level, by contrast, the role of practitioners as lobbyers is quite a powerful one relative to the industry itself. The industry plays a role in providing jobs but it's a role that's very uneven State to State. Pharmacists, for example, have proved to be very effective lobbyists in all States. As States face pressures on medicines budgets there will be times where dispensing fees and the price of a drug appear as trade-offs. States are confronted not only with budgetary short term pressures but the politicisation of decision making, creating a very difficult set of circumstances.

Competing Health Plans face other kinds of pressures. In principle, they have a great interest in looking at total cost over time, which should

mean focusing on long term health gain. However, currently in much of the US there is a desperate grab for market share. Health Plans enter a new local market knowing they have a window of about eighteen months where they are either going to make it or go out of business. There are two main challenges for the industry in this environment. The first is that, to date, differences in pharmaceutical provision have not been factors in consumers' choice of Health Plan. Secondly, in this environment a focus on health gain is difficult. It is easier for a Health Plan to lower its costs by being careful about who they include in the Health Plan, than it is to manage difficult disease conditions. Whilst there are many trends towards more constructive disease management, there is a tension — for example, if you get too good at the treatment of asthma, in a non-universal coverage environment, you could attract a lot of asthmatics to your Health Plan, pricing you out of the market. This is further complicated by the very high turnover in the market, Health Plan enrolment in the States varies from about 20 per cent to 60 per cent of the total membership of a Health Plan from year to year. People switch jobs and therefore Health Plans, employers switch their offering. This makes the focus on health gain in a non-universal environment more difficult to sustain, because many of the outcomes are not available to benefit the firm in a given year.

Focus of the Purchasing Decision

We would like purchasers to focus on the total cost of medical care, not just the medicines budget, factoring in the relative costs of preventable illness and the costs of avoiding acute episodes of chronic care, so that purchasers look at the trade-offs and recognise, for example, that effective management of asthma which may cost more in medicines, can be quite advantageous to total costs, as acute episodes requiring hospitalisation are avoided.

Historically for Health Plans, although the incentive has been to look at total cost, there have been factors that have meant this hasn't happened. We are now seeing, a real move to a disease based focus on total cost.

Conditions for a Disease Based Approach to Cost

Three conditions need to be met, however, to look at total cost, as opposed to medicines cost.

(1) The benefit package has to allow the Health Plan to move the type of therapy around. Typically in Health Plans, co-payment had been placed more on pharmaceuticals than on other kinds of services and this has skewed things. When designing benefit packages actuaries know that up to half the savings from a co-payment on medicines come from prescriptions that go unfilled as patients elect not to pay.

The benefits set needs to provide equal co-payment treatment of pharmaceuticals relative to alternate therapies.

(2) A management structure and availability of information to enable managers to make trade-offs. That is something that Health Plans were created to do and they are increasingly getting the information to go with the management structure to make those kinds of assessments relatively easily.

(3) Continuity of membership. With turnover it is always a concern that you invest in managing the care of the asthmatic only to have that patient be at your rival next year as their parents change jobs or because the price of the rivals coverage was just a little bit lower than yours. Lack of continuity undermines the focus of health gain.

Lessons for Europe?

Are there lessons for Europe? The US scene is complicated, but I think it leads us to consider two alternative purchasing models for European countries.

The first option is to try and make public single payers far sighted. Can we ensure that they will respect the objective of long term health gain and also the multiple objectives of nations in terms of long term competitive strength, which brings jobs and exports? The potential advantage is that a national single payer corresponds to the national pharmaceuticals market and the national economy. The challenge to get the far sighted single payer to shift its focus to total medical care costs and away from the medicines budget per se. Management structure and information availability are a key factor here.

The second option is to develop effective competing purchasers that also focus on health gain. In one important respect Europe is way ahead of the US, because it has universal coverage systems reducing the temptation for competing purchasers to move people out rather than managing them from within. Europe has a greater continuity of membership, even in 'competing' systems, because the relationship to employment is not so rigid as in the US, and the comprehensiveness of benefits is also better. It would, however, require a framework within which entities competed, and an industrial policy that is supportive of innovation underpinning that framework. It will be challenging to make choice of pharmaceuticals a key weapon for a competing purchaser seeking to gain market share on service rather than price grounds. The best means of doing so will be to develop disease management approaches around chronic conditions so that a Health Plan can distinguish itself, for example by the effective management of asthma using innovative pharmaceuticals, or by the effective management of hypertension using pharmaceuticals. In the US, doing that is a risk because in a non-universal coverage environment you are like to attract people who want that care

and are sick. In a universal environment in Europe that could be done effectively to gain market share.

In summary, the US faces a crucial period of adaptation, where it is going to have to look at the relative strengths of public and private sector purchasers, and figure out how to keep them focused on the right things. Whilst the US scene provides insights, health reform within a universal coverage environment in Europe may soon be able to provide some useful examples of good purchasing to the US.

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

Professor Henry Grabowski

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.

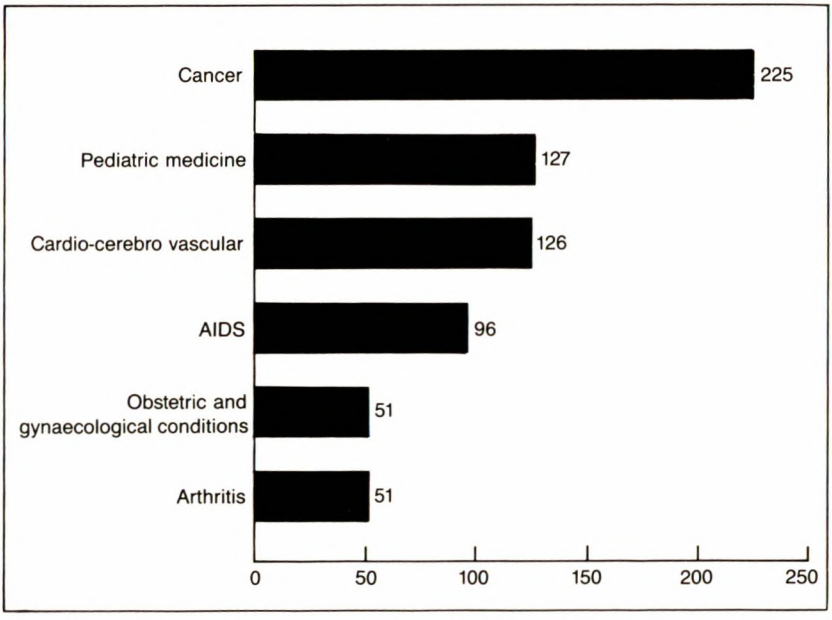
In terms of public policy, pharmaceuticals are also the focus of vigorous cost containment efforts in virtually all major countries. Price regulators tend to be driven by short-term budgetary considerations. The extreme skewness in new drug sales and returns make the blockbuster or top decile of drugs 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 $2^1/_2$ 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**

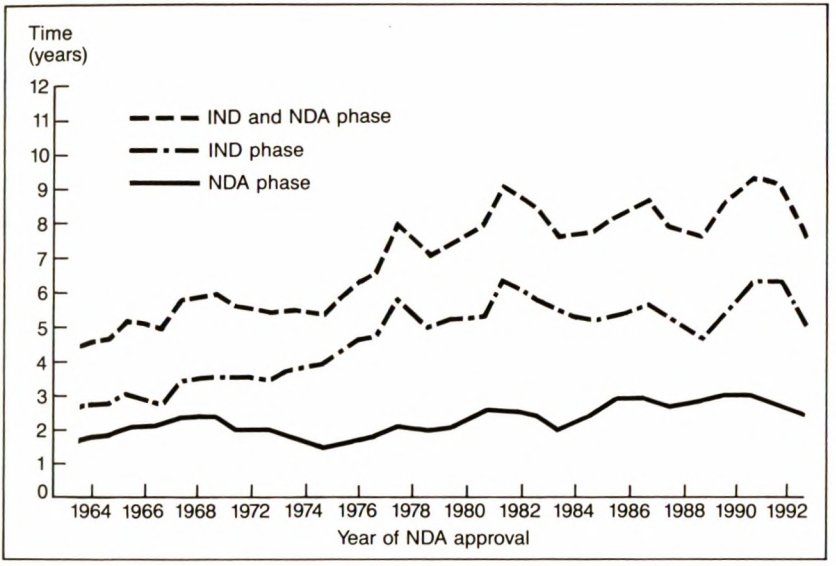
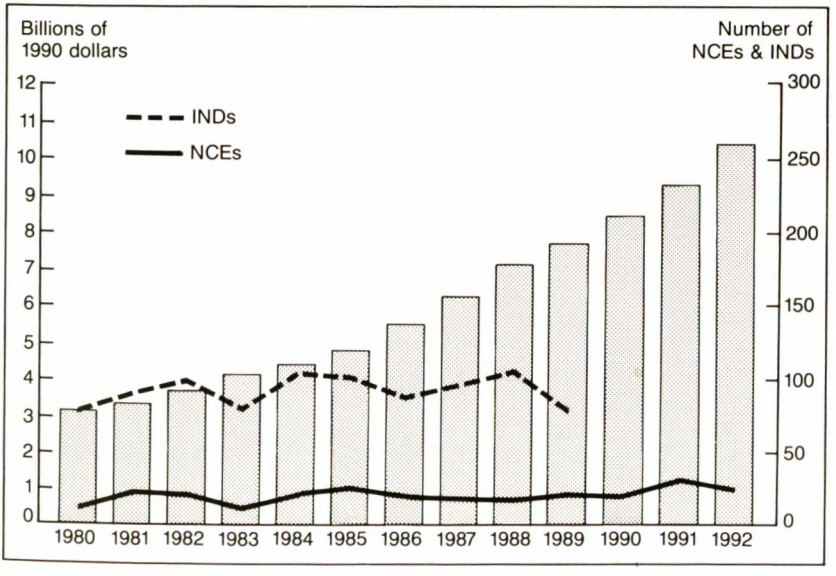


FIGURE 3 **R&D expenditures, NCEs and INDs**



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]

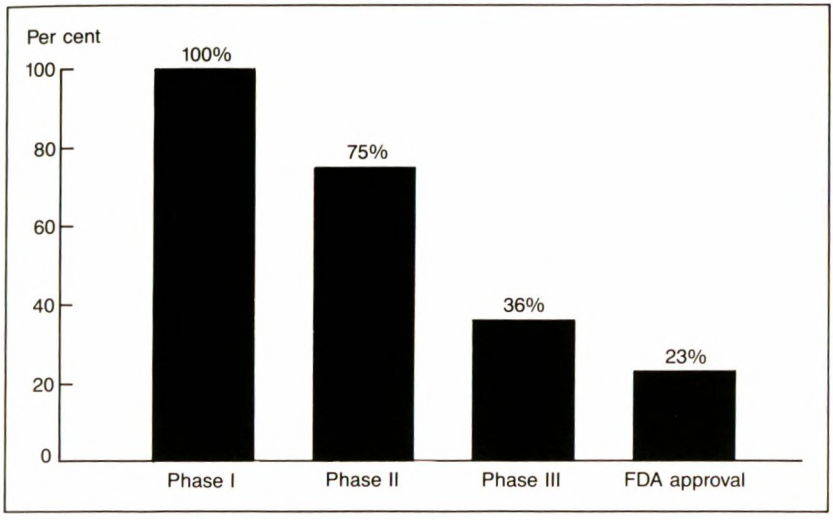
Our best estimate is that it takes an average of $231 million (in 1987 dollars) and 12 years to discover and develop a new drug. Of this total, $114 million is the out-of-pocket R&D costs and $117 million is the time cost associated with the 12-year average investment period. In addition, we find substantial 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 $2^1/_2$ 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 tables 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 tables 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.

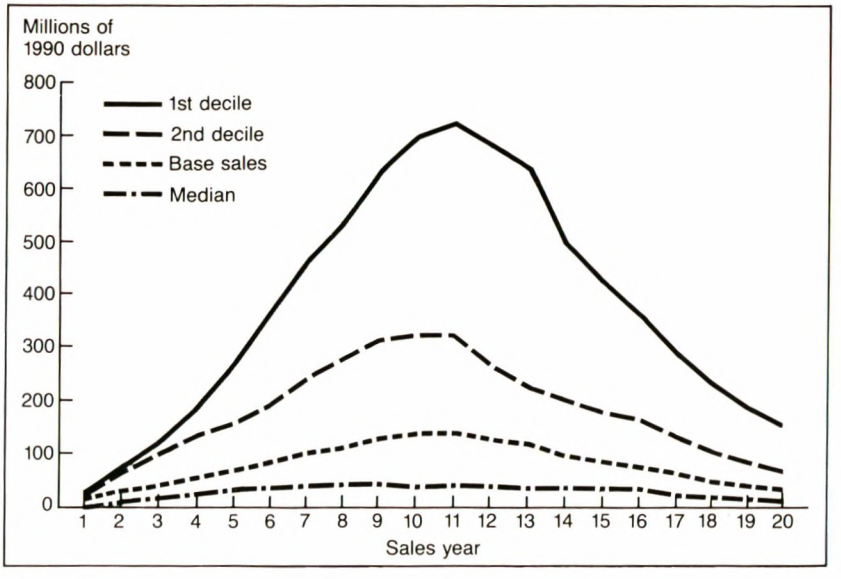
Returns to Pharmaceutical R&D

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**



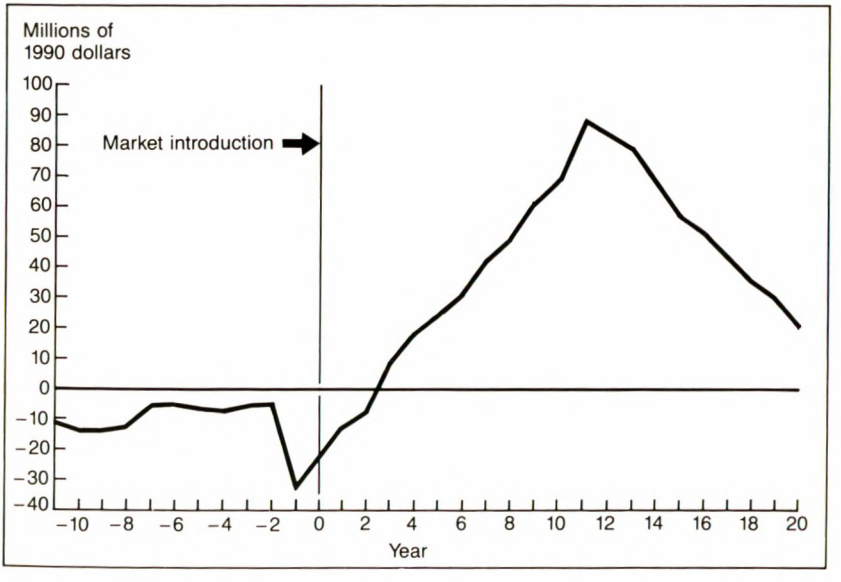
median one. This is a very important point in terms of understanding the pharmaceutical industry economics. A few top-selling drugs are really key in terms of economic success in providing the funds for future research.

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**

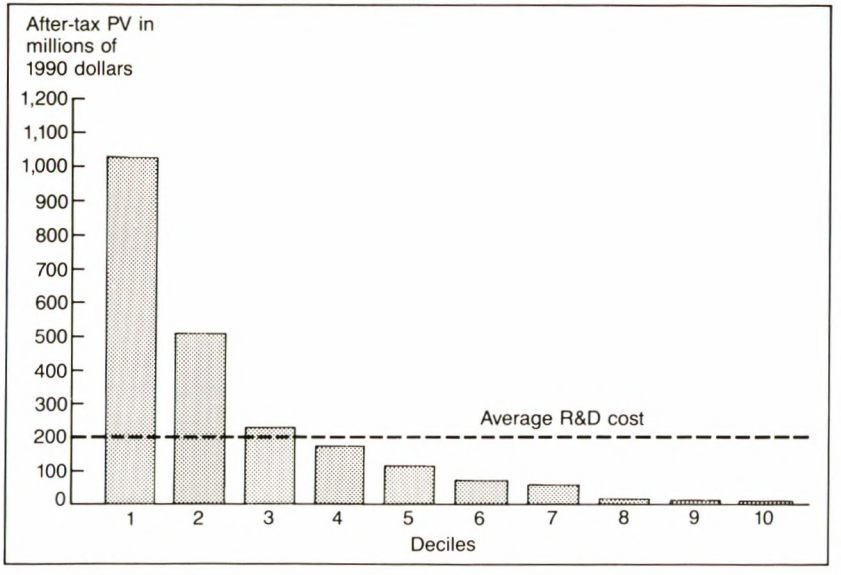


NCE is $201.9 million after tax (in 1990 dollars). The discounted value of net cash returns resulting from this R&D investment is $224.1 million. Hence, the net present value (NPV) for the mean 1980-1984 NCE is $22.1 million.

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 enrolees 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-

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).

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.

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'Factors Influencing the Location of Multinational Investment in the Pharmaceutical Industry'

Jeremy Holmes and Professor John Dunning

Introduction

Throughout the 1980's flows of foreign direct investment overall grew at a rate that was faster than both world GDP and world trade. In the 1990's, after some periods of scepticism in the last 20 years, national governments are again regarding foreign direct investment — by which they usually mean inward investment, but also to a lesser degree outward investment — as 'good news'. Why is this?

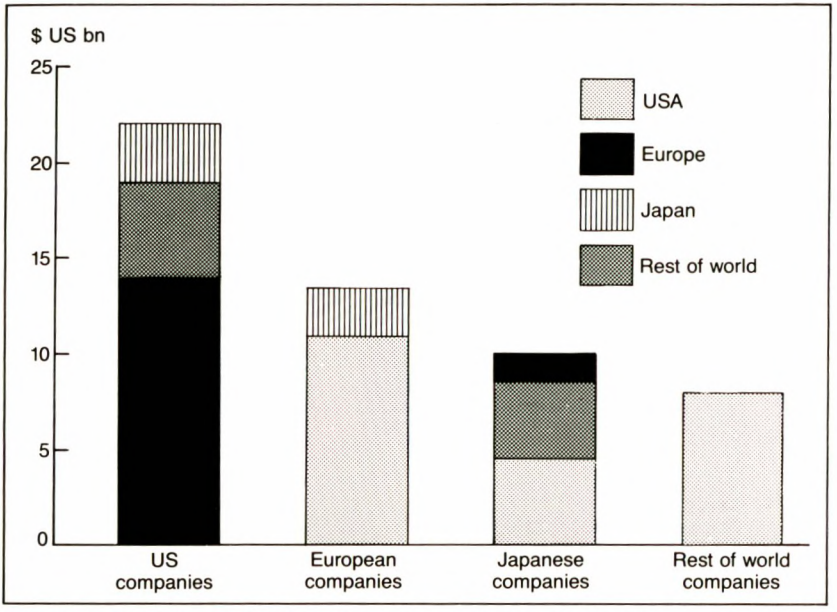
The renaissance of the market economy, particularly in Central and Eastern Europe, India, China, and countries such as Mexico and Chile, has fuelled a positive attitude on the part of government. But there are other reasons too — the increasing globalisation of economic activity in many sectors, the convergence of economic structures in the advanced industrial nations and the consequent pressures on their firms to be competitive in international markets have all acted to propel foreign investment forward. Most significantly for today, the criteria have changed for judging the success of inward investment by so-called 'host' governments.

The emphasis has shifted from a somewhat confrontational stance, based on the direct contribution of such investment to domestic output or employment, to a more co-operative stance founded on an evaluation of its wider impact on the upgrading of the competitiveness of indigenous assets — particularly created assets such as technology and 'know-how', rather than natural assets such as land and unskilled labour — and the promotion of comparative advantage in a global economy through that continual upgrading process.

36 years ago one of the authors of this paper, John Dunning, published the first comprehensive analysis of the costs and benefits of inward direct investment (Dunning, 1958). The subject of the study was the UK but the issues it raised have now been taken up world-wide. In particular, attention has been paid to the pharmaceutical industry, and the factors influencing its foreign investment, because of its high value added and its role in the internationalisation of what might be called 'technological activity'.

Stocks of foreign direct investment in the pharmaceutical industry grew more rapidly than trade in the 1980's, although with a slight pause at the turn of the decade. The industry is distinguished by the fact that foreign-controlled production and foreign-controlled sales are substantially more important than imports. For most countries on which data

FIGURE 1 **Stocks of inter-region direct investment in pharmaceuticals (end 1988)**



Source: Sector Case Study of Globalisation in the Pharmaceutical Industry, OECD, 1994.

are available foreign controlled production is at least twice as large as total imports, and sometimes as much as five times as large. So we are talking about an investment intensive industry.

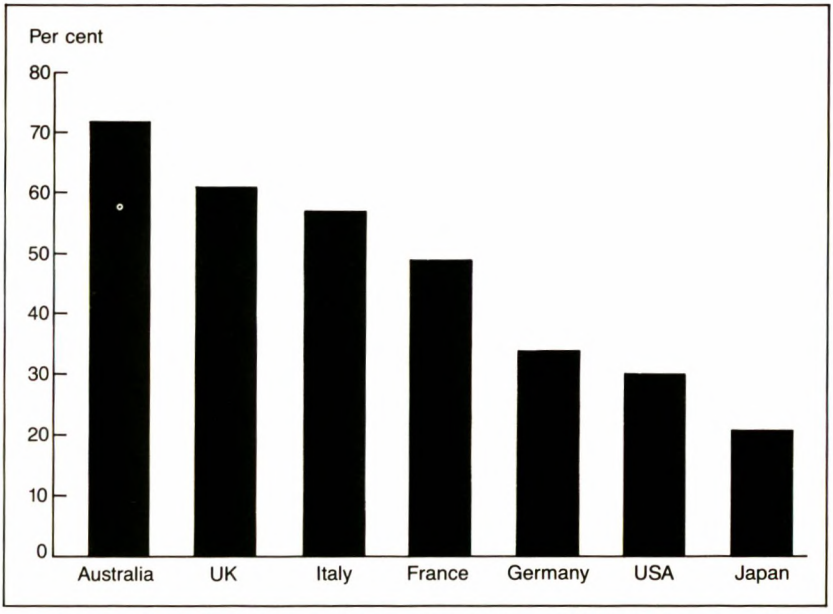
Inter-Region Direct Investment

Figure 1 shows the position approximately 5 years ago in terms of the stocks of inter-region direct investment. We see that *US* pharmaceutical companies were substantially the largest foreign investors. This is still the case; in 1990 the overseas assets of US pharmaceutical companies amounted to some $28 billion.

The host region for that investment is predominantly Europe. For *European* companies, the host region is predominantly the USA, accounting for 11 bn or 80 per cent of the $13.5 bn of European outward investment at the end of 1988.

Japanese pharmaceutical companies invest significantly less overseas than their American or European counterparts, although activity from this area has recently been increasing. Nevertheless, in chemicals and pharmaceuticals as a whole, Japan still showed a clear surplus of outward investment, along with the UK and Germany, at the end of 1990, whereas the USA was a net recipient.

FIGURE 2 **Foreign controlled production as a percentage of total pharmaceutical production (1989)**



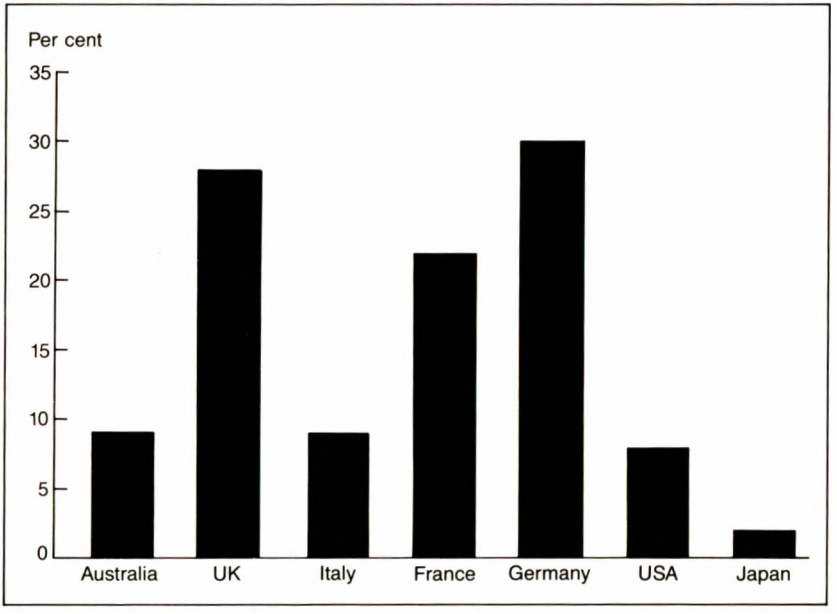
Source: Sector Case Study of Globalisation in the Pharmaceutical Industry, OECD, 1994. (Australia data 1986/7)

Japanese companies invest more in the Rest of the World as a proportion of their outward investment — approximately 40 per cent — than do US companies (23 per cent) or European companies (for whom firm data are not available). Overall investment in the Rest of the World appears to have *declined* in proportional terms over the 1980's. The Rest of the World itself invests overwhelmingly in the USA.

Foreign Controlled Production

How important is this investment to the overall pharmaceutical industries of the recipient or 'host' countries themselves? Taking seven of the major host countries and calculating the percentage of total pharmaceutical production accounted for by foreign investment, we see from Figure 2 that Australia was well in the lead even in 1986/87, which was before the 'Factor f' scheme was introduced. Data for the other countries are for 1989, so roughly equivalent to the time of the snapshot given in the previous chart. The UK, with 61 per cent, heads a group of four major European countries, which are all ahead of the USA and Japan. As we mentioned before, all these countries have a high ratio of foreign controlled production to imports — in the case of Italy it is 4.8

FIGURE 3 **Exports as a percentage of total pharmaceutical production (1988)**



Source: Sector Case Study of Globalisation in the Pharmaceutical Industry, OECD, 1994.

times, for the US 4.6 times and the UK 4.2 times.

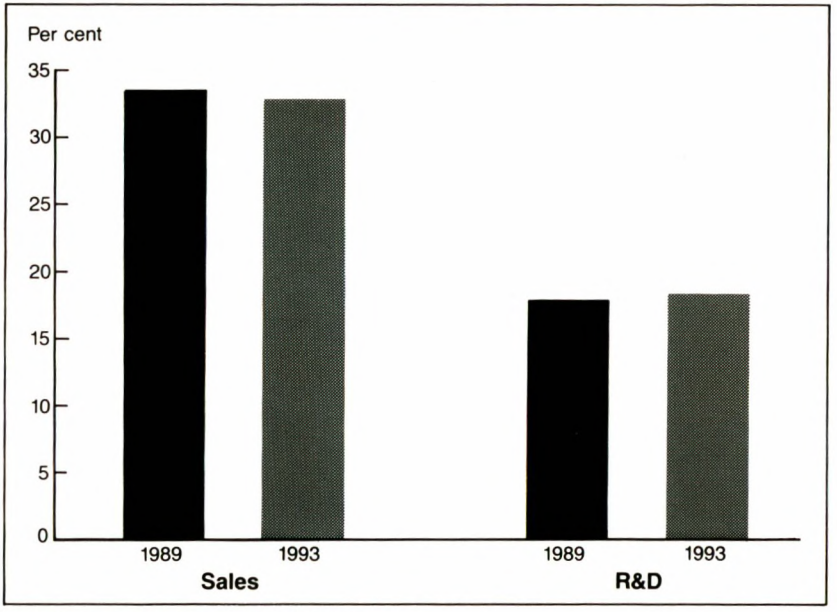
Exports

Are these countries the recipients of foreign investment because they represent important export bases to third markets? In the case of Australia clearly not, as exports represented only 9 per cent of total pharmaceutical production in 1988 (Figure 3). The level of exports, principally to New Zealand, is rising but not as fast as either imports or inward investment. In 1990, IMS data indicated that 94 per cent of pharmaceutical sales in Australia were accounted for by multinational companies.

The UK on the other hand is a very different story. In 1988 28 per cent of total production was for export. This increased in 1992 to 35 per cent.

Italy and the USA are at about the same level as Australia, but France and Germany are in the same category as the UK with 22 per cent and 30 per cent respectively. Japan has the lowest export share with only 2 per cent — but as we saw before it also has the lowest foreign controlled production share.

FIGURE 4 **Foreign Sales and R&D as a percentage of US pharmaceutical companies' total sales and R&D**



Source: Pharmaceutical Manufacturers Association.

Foreign Sales and R&D

How has the position changed in the last four years? As the major outward investors it is instructive to look at US companies and to compare their foreign sales and R&D as percentages of their total sales and R&D in 1989 and 1993. These are shown in Figure 4. Foreign sales actually dropped in proportional terms — and this drop would have been even more marked if we had taken a 5 or 10 year comparison.

However, foreign R&D actually increased slightly in proportional terms, up to 18.3 per cent in 1993. In a moment we want to focus on R&D more specifically, because of its value added and its attractiveness for host country governments.

Principal Foreign Investment Strategies

But first let us set this discussion in the context of what drives the foreign investment strategies of firms in any industry. This is familiar territory, but it is worth recalling that, classically, there are four principal reasons for firms to engage in foreign investment:

- to seek out natural resources such as land, oil and minerals or unskilled labour (none of which really apply to the pharmaceutical

industry);
- to seek new markets, and by establishing a foreign production facility to substitute for imports to those markets;
- to seek organisational or operational efficiencies through a process of international or global rationalisation;
- and to seek out strategic assets, such as technology, know-how or the acquisition of brand names, in order to improve the firm's overall competitive position.

In today's pharmaceutical industry, *market seeking* investment is partly influenced by the political and regulatory environment in developed markets, but it is also strongly biased towards the developing and newly industrialised world.

Efficiency seeking investment is occurring mostly in the economically integrated regions of the world, particularly the European Union and the NAFTA. Importantly, *strategic asset seeking* investment is also occurring mostly in these regions, and between the countries of the Triad of Europe, N. America and Japan.

In general, the supply — or firm-specific — factors influencing foreign investment have shifted in the last 20-30 years away from those related to the availability and cost of natural resources towards those related to the availability and cost of created assets. Put another way, the key issues in foreign production, especially in high technology industries, have switched from those associated with the manufacturing process per se to the *strategic assets* required for effective *pre* and *post* manufacturing — i.e. R&D and marketing or distribution.

Location-Specific Factors

In 1988 EAG conducted some detailed research into the other side of this coin — the location-specific factors involved in foreign investment decisions (EAG, 1988). The findings reflected the views of a wide range of US pharmaceutical companies with operations in the UK. They distinguish between factors influencing production investment decisions and those influencing R&D investment. The results are summarised in Figure 5.

The two most significant factors related to foreign *production* were the presence of stable government policies towards the pharmaceutical industry and Government subsidies or incentives for investment. Other important factors included the size of the local market (implying some level of market-seeking investment), the prevailing level of prices, the availability of suitable personnel and the national tax regime.

Regarding *R&D* investment, the two most significant factors were the country's track record in R&D and the availability of suitable personnel. Again, government incentives were also considered important.

FIGURE 5 **Location-specific factors in US pharmaceutical companies' foreign investment decisions (1988)**

Production	R&D
• Stable government policies towards the industry	• National track record
• Government incentives	• Availability of suitable personnel
• Size of local market	• Government incentives
• Prevailing level of prices	
• Availability of suitable personnel	
• Tax regime	

Source: Economists Advisory Group

Key Stages of R&D

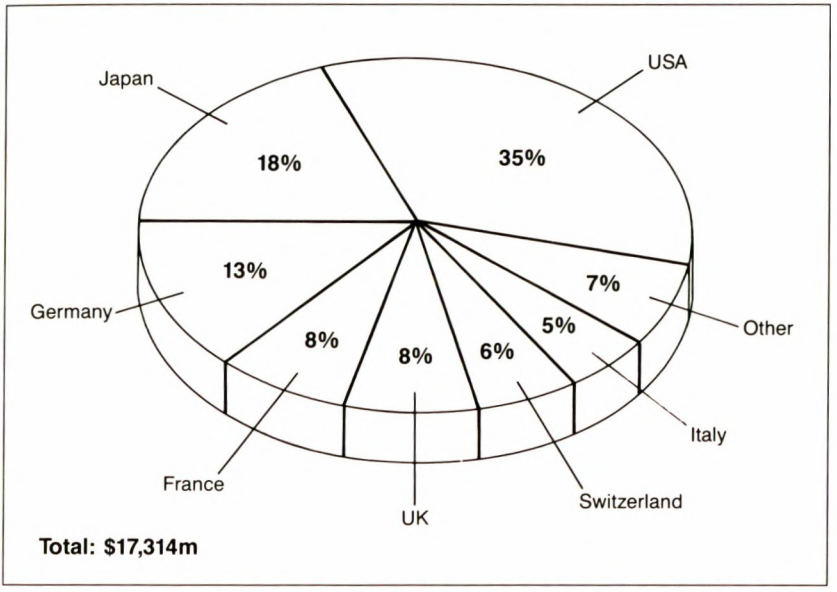
Let us now concentrate on R&D and consider some of the issues that are particular to the location of R&D activities. Essentially one can distinguish between three key stages of pharmaceutical R&D:

- the discovery of New Chemical Entities, which is not highly location-mobile as it is often performed by large concentrated research teams in central laboratories;
- the Development of new products on the platform of NCE's, which exhibits a higher degree of decentralisation. (As a footnote here it is relevant to mention the role that anti-industry groups such as animal rights organisations play in the location decisions of firms with regard to their product development.);
- thirdly, Clinical Trials, which comprise the largest single component of most R&D budgets and which exhibit considerable and, we would suggest, increasing location-mobility.

There are of course trials for new global products, the location of which will be influenced by the quality and reliability of medical facilities, and the timeliness with which trials can be approved and carried out, as well as factors such as cost and the local language. But there are also trials that are country-specific and intended to assist in the local registration and marketing approval process.

The first type of trial — that for global product launches — can be influenced, as it has been in Canada since 1987, by government incentives for R&D activity. The second type of trial, however, while maybe not a mandatory requirement for local drug approval, is also strongly influenced by the political and policy climate in which the pharmaceutical company has to operate.

FIGURE 6 **Share of world pharmaceutical R&D by country (1989)**



Source: Parry, T & Creyke, P, 1991, *The Australian Pharmaceutical Industry*: Achievements, Prospects and the Policy Environment, Sydney: APMA.

Taken as a whole, there has been a progressive internationalisation of pharmaceutical R&D. Ten years ago it is estimated that 17 of the top 20 pharmaceutical companies in the world has R&D facilities in 3 or more countries; what has happened is that what was called the 'local for local' approach of innovation at the national level has been replaced by a 'local for global' approach, in which these innovations are rapidly translated and applied to other markets. And the old fashioned 'centre-for-global' approach, based on one central R&D facility, is slowly being replaced by what has been called the 'global for global' approach in which the resources and capabilities of many different R&D units are pooled to arrive at a jointly developed general solution to a world-wide problem. Increasingly therefore, one of the key competitive advantages of successful multinationals is their ability to co-ordinate and exploit this global network.

Share of World R&D

Figure 6 shows the share of world pharmaceutical R&D by country. We see that the USA dominates with 35 per cent, or over $6 billion worth, in 1989. That level of R&D expenditure has more or less doubled in the last four years.

Japan has the second largest slice of the pie, followed by Germany,

FIGURE 7 **Analysis of location-specific factors influencing pharmaceutical R&D investment (1989)**

	Weightings	
	US firms	European firms
Market Factors	1.5	1.5
General regulatory factors	1.2	1.0
Drug regulatory factors	1.1	1.3
Resource factors	1.4	2.0

Source: Taggart, J, 'Determinants of the foreign R&D locational decision in the pharmaceutical industry', University of Strathclyde, unpublished papers.

France and the UK. (It should of course be said that historically much Japanese R&D has been of a different nature to that in the US and Europe.) This is a competitive market and it is increasingly clear that there is considerable rivalry between these leading countries to attract R&D activity. Not only do multinationals compete for market share, but so, in a different way, do national governments.

Of course the key issue in this competition is the cost-benefit trade-off between the incentives provided by governments in order to attract multinational investment, and the gains that can be realised for the host country, as well as the multinational, through that investment.

What incentives, and what national attributes, really pay dividends?

Analysis of Location-Specific Factors

One of the most statistically robust analyses in recent years of the location-specific factors influencing pharmaceutical R&D investment was undertaken by Jim Taggart (Taggart, 1989). It involved a detailed survey of 14 US and 8 European pharmaceutical multinationals. Their attitudes were analysed in relation to 30 possible location determinants which were divided into 4 groups. The results are summarised in Figure 7.

The *Market Factors* group contained 8 determinants. Without going through the findings on each of these in detail, the US and European firms on average gave this group of factors the same level of weighting, which was high in relation to the other groups. However, US firms placed greater importance on the level of local market consumption of pharmaceuticals, while European firms emphasised the importance of a high level of R&D activity by their competitors.

General Regulatory Factors were rated of lowest importance by the European firms and next to lowest importance by the US firms. However, within this group of 6 variables, the existence of efficient

patent law was not surprisingly given a very high rating, especially by the US firms. There was some evidence from the research that the European firms were more relaxed about working with different patent law systems in the international arena.

The European firms considered *regulatory factors specific to the drugs industry* to be more influential in their investment than did the US firms. Their attention seemed to be focused on whether new regulations were formulated in such a way that enabled firms to find a logical and progressive way to deal with them, rather than simply on their stringency or laxity. Clear-cut regulations were preferred to those which might be lax but ill-defined. Of the 8 specific factors analysed in this group the willingness of a host government to consider the implementation problems and cost consequences of new drug safety regimes was considered much more important by the European than the US firms.

The *Resource Factors* group contained 8 determinants, of which the two most important were found to be the present stock of scientists, technologists and engineers and the quality of the tertiary education system - which will clearly impact on the future stock of that human capital. The present stock was rated as more important by the US firms, while the future stock, as indicated by the education system, was rated as more important by the European firms. This emphasis by the European firms, together with the importance they placed on the country's track record in new drug development, gave the resource factors group the highest weighting of all for the European firms.

Of course the role of each of these groups of factors, and the individual determinants of which they are composed, is affected fundamentally by the perceptions of the various protagonists of what they potentially have to gain or lose from foreign investment.

Possible Gains and Losses from Internationalisation

There are essentially three protagonists in the internationalisation process: the multinational company, the host country and the home country. The possible gains and losses for each of these protagonists in relation to the internationalisation of pharmaceutical R&D are summarised in Figure 8.

The *multinational* potentially gains an enhanced capability in product innovation or development by tapping into a new resource base. It can also use the R&D entry point to improve access to local markets. Against this, it has to weigh up the possible reduced economies of scale in its R&D operation overall, and the impaired communication which, even in the age of computer links and video conferencing, can result from a wide geographical spread of experts. In practice there are sometimes dis-economies of scale in R&D and the down-side of internationalisation may apply when a local subsidiary is obliged for political or

FIGURE 8 **Possible gains and losses from the internationalisation of pharmaceutical R&D**

Protagonist	*Gains*	*Losses*
Multinational company	Enhanced capability in product innovation and/or development	Reduced economies of scale
	Improved access to local markets	Impaired communication
Host country	Employment	Damage to indigenous companies
	Access to high technology and/or scientific skills	Dilution of control over local innovative capacity and profits
	Strengthened links with other sectors	
Home country	Strengthened position of donor companies	Loss of employment
		Reduction in local innovative capacity

Source: Dunning, J, 1988, *Multinationals, Technology & Competitiveness*, London: Allen & Unwin.

quasi-political reasons to expand its local R&D beyond the level it considers to be economically or strategically appropriate.

For the *host country* the possible gains in employment, particularly if greenfield investment is involved, are obvious. The potential access to high technology or scientific skills is more subtle, but in our view substantially more important. It is this access which contributes in an increasingly important way to the upgrading of a host country's created assets and hence to its competitive advantage. The internationalisation process may also strengthen the links between pharmaceuticals and other sectors, for example through biotechnology or backward linkages with suppliers or research institutes, which again impacts on overall industrial competitiveness.

But inward investment is not 'cost free' for host countries. There is the potential damage to indigenous companies — although if they can confront and survive the challenges posed by the new entrants who seek a share of (for example) limited skilled manpower, they will have improved their own international competitiveness. And there is the dilution of control over local innovative capacity and the profits that result from successful R&D — although this dilution can be minimised through careful regulation.

For the *home country*, internationalisation can substantially strengthen the position of the donor or investing companies but has to be set against the loss, or the export, of employment and the possible reduction in total innovative capacity.

FIGURE 9 **The influence of Government policy**

Market factors
National pharmaceutical expenditure

General regulatory factors
Inward investment policies
Industry & technology policies
Competition policies
Environmental policies
Employment policies/culture
Intellectual property protection
(Trade policies)

Drug regulatory factors
Pricing control
Control of promotional expenditure
Product development/approval regulations
Government empathy with the industry

Resource factors
Quality of tertiary education
Physical infrastructure

Influence of Government Policy

The key question for this conference is what influence government policy can or should exert on this trade-off of gains and losses. We would not presume to offer a prescriptive answer, but we would point out the principal areas in which government policy exerts a direct influence on the location decision process with regard to pharmaceutical R&D. These are summarised in Figure 9.

If we take our four groups of factors, the *size and structure of the local market*, which you will recall was rated as important by US and European firms alike, is clearly affected by the policy on national pharmaceutical expenditure. Policies in this area can take many and varied forms, which are outside the scope of this presentation, but they come down to control on either the *supply* of drugs (for example through formularies, reference pricing systems or the promotion of generics) or the *demand* for drugs (for example through higher patient co-payments).

General regulatory factors are affected by a wide range of government policies. Specific *inward investment* initiatives might relate to other elements of the policy matrix such as the tax regime or general regional policy. The concept of national treatment — that is whether foreign investors enjoy the same economic and non-economic advantages as indigenous companies — is directly relevant to the pharmaceutical industry. In fact the notion of positive discrimination in favour of internationally oriented investment — such as that which operates in Australia and in Ireland — is sometimes critical to inward investment in pharmaceutical R&D.

The main areas of relevance in terms of *industry and technology policies* are government support for the science base and the encouragement of venture capital investment. The pharmaceutical industry receives very little direct R&D support from governments — less than 2 per cent in most OECD countries. This is in sharp contrast to other R&D-intensive industries such as aerospace, computers and electronics, which are

often linked to government policies on defence. Nevertheless, there is extensive government support — in the US and at the European Union level as well as in individual European countries — for biotechnology research. Some of this feeds into general industry programmes such as those related to SME's and inter-firm collaboration.

This kind of collaboration of course raises questions of *competition policy*, which is a still evolving area of debate in both the USA and Europe. The acceptance of R&D joint ventures, and the debate over joint exploitation of the results of such alliances, may become more critical in the shaping of future cross-border investment in the pharmaceutical industry.

There are also, as we all know, a number of strategies in place by governments to increase competition within the industry through changes in the restrictions affecting the distribution of drugs and the encouragement of parallel imports.

We won't dwell on each of the other areas related to environmental policies, employment policies and the workforce culture of a country, or intellectual property protection which, as we saw earlier, is of critical importance. Suffice to say that although these policies affect *all* industry generally, many of them have particular angles which affect the pharmaceutical industry especially.

In Figure 9 we have bracketed *trade policies* because, as we mentioned above, the pharmaceutical industry is less trade intensive than investment intensive. Prior to 1986 certain export restrictions in the USA gave companies an incentive to establish manufacturing facilities abroad for drugs not yet approved at home. But currently the focus is on the reduction of non-tariff barriers, particularly in the area of drug-testing guidelines, and these could properly be included in the drug regulatory factors group.

This third group includes all the policies with which readers will be familiar, particularly those related to *pricing control, promotional expenditure* and *regulations over product development and approval*. A number of these include some sort of investment 'carrot', which reflects the general attractiveness to host governments of pharmaceutical R&D activity.

One area, however, that is often overlooked is what might be called *government empathy with the industry*. Does government policy as a whole treat the industry with understanding? Is there an effective consultative mechanism in place? And is there a logical and well-balanced approach to negotiation that results in clear guidelines acceptable to all parties?

Lastly, but perhaps most important of all for R&D investment, resource factors are affected by the quality of a country's *tertiary education system*. The physical infrastructure is also important (telecommunications being one obvious example) but it is difficult to over-state the importance of government policies in developing and upgrading the

human capital base and the influence of this on the location of R&D — and success in this area breeds success in inward investment; a virtuous circle.

The Future

Let us conclude by making two key points about the future of multinational investment decisions in the pharmaceutical industry.

The first is related to the attitude of both home and host countries to issues of *industrial competitiveness*. We have seen these issues climb the political agenda very rapidly in recent years and it seems clear that a more holistic approach will be taken by many governments in their pursuit of sustained competitive advantage. This means that education policy may be more closed integrated with technology policy which may be more closed integrated with industry and SME policy, with tax and employment policy and so on. We have already seen the stirrings of this holistic approach in the Delors White Paper (CEC, 1993) and Michael Heseltine's Competitiveness paper in the UK (HMSO, 1994); it will exert a profound influence on the process of internationalisation.

The second point is that the traditional form of cross-border investment, namely merger, acquisition or greenfield, is increasingly being overtaken by the *strategic business alliance*. We are seeing a wide spectrum of these alliances, ranging from cross-shareholdings and formal joint ventures, through co-marketing and licensing agreements to much more ad hoc. project-specific collaboration.

After the (still continuing) wave of M&A activity of the last 10 to 15 years we may be about to enter a new era, in which cross-border investment is as much about alliances and partnerships as it is about unilateral investment decisions. The winners will be the multinationals that can co-ordinate and manage a range of such alliances on a global network basis more effectively than their competitors.

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