

# **The Pharmaceutical Industry and Society**

a study of the changing  
environment and economics  
of the international industry

Symposium held at the  
Imperial College of Science and Technology  
by the Office of Health Economics in 1972

Edited by George Teeling-Smith

Please note: blank pages have been deleted from this file.



Office of Health Economics 162 Regent Street London W1R 6DD

© 1972  
Office of Health Economics

Printed by White Crescent Press Limited, Luton

# Contents

---

Preface <i>John E Vaizey</i>	vii
---------------------------------	-----

---

The modern multinational structure of the pharmaceutical industry <i>Robert H Jones</i>	1
---	---

---

The cost of safety in medicines <i>Arnold H Beckett</i>	19
--	----

---

The cost of compliance with international regulations <i>Gordon C Hellyer</i>	31
--	----

---

The pharmaceutical industry and the balance of payments <i>Peter Mould</i>	45
---	----

---

Profitability, risk and investment in research and development – the UK pharmaceutical industry <i>Kenneth G D Smith</i>	59
--	----

---

Social and economic pressures on the pharmaceutical industry <i>George Teeling-Smith</i>	89
--	----

---

Index	105
-------	-----

# Preface

John E Vaizey

Our ancestors died or recovered with or without the aid of a doctor: though his experience might be great his technical skills were minimal. The doctor now is one of a large team that keeps us in good health and, indeed, often prolongs our life beyond what is reasonable. This change is due, ultimately, to research work in the natural sciences and largely to pharmaceuticals. The over-riding purpose of scientific research is nosiness; the over-riding purpose of medicine is recovery from or avoidance of illness; yet both over-riding purposes are subordinated to the practical test of what society, and the families that make up society, is prepared to pay. There is little doubt that the astounding changes in medicine have been largely due to pharmaceuticals. Here, then, is an industry that began with virtual quackery, that is now at the heart of modern scientific research, in pharmacology, biochemistry and related subjects, and which is a major supplier of a large sector of public and private health provision. It is a new industry – newer than aviation and little older than electronics – and we know comparatively little about it.

This series of essays is designed to show how the industry has shaped itself in response to the vastly rising demand for its products and the continuous surge of experimentation which provides its basis. In so doing, the series reveals certain key facts about the industry which, though of deep interest to people connected with pharmaceuticals, ranging from pharmacists to doctors, from public officials to individual patients, are also of general interest to economists, businessmen and trades unionists and others concerned with modern industry. Pharmaceuticals is the model of one kind of a modern industry. It is built, first, upon continuous technical change. It has, next, to communicate this change to a series of specialised buyers such as hospital procurement officers and doctors and ultimately to the general public, who, after all, pour its products down their throats and other available orifices. It has a major public responsibility. This responsibility is direct, for its products may maim as well as cure, and it needs to be carefully watched. Its responsibility is indirect, too. The birth-control pill, for instance, has basically altered demographic patterns; the virtual elimination in some areas of malaria and other tropical diseases has caused a population explosion; that is to say the environmental and ecological effects are important. It is international, like science itself and as a result the study of a 'national' industry makes little sense, a point well brought out by Robert Jones in the first lecture. It is not extremely capital-intensive, but the production process is very 'round-about', and it employs a small

## *Preface*

but extremely highly-trained and expensive labour force. Lastly, almost everybody outside it is deeply suspicious of it.

Here, then, is a subject indeed; the list of topics that could be embraced by it is almost endless, and would vary from writer to writer. In these essays, Mr Jones sets the frame exactly. He had studied innovation, with special reference to pharmaceuticals, and concentrated on how the international structure of the industry affected the transmission of knowledge. For a new discovery to be marketed, the technology has to be developed which is expensive, and it is protected by patents. To get costs down, and get your money back, you need a big market, and as the patent will eventually expire, you want to sell as much as possible as quickly as possible. So you try to sell everywhere – America to the Yemen, Australia to Alaska. And, as the job grows more complex, the firms specialise in different therapeutic areas, so by dividing the field they internationalise the market. But they internationalise it in fairly idiosyncratic ways.

It seems clear that a firm tries as soon as may be to market its own products directly, rather than to sell through agents, even when it exports rather than manufactures abroad. This is partly to get a bigger sales effort, and partly to control the product's use. The alternative to this is a joint marketing agreement with another pharmaceutical company. Mr Jones explains why merged companies, as opposed to joint marketing arrangements, are scarce in this field.

The usual form of overseas marketing of an important group of products is by the overseas subsidiary. But even here, as Mr Jones explains, 'pure' cases are not as common as might be thought; an overseas company is often more a marketing than a true manufacturing subsidiary.

The lecture by Professor Beckett drew attention to the growing costliness of procedures to make drugs safe. It is, of course, a very simple fact that a middle way has to be chosen between what might be termed complete recklessness on the one hand, that is to say that any material might be pumped out for general consumption, regardless of how many people died as a result of it, a procedure which was unusual but not unknown in the early days of industrialisation in the 19th century, and at the other extreme, that nothing will ever be issued which can conceivably harm anybody, which is of course an impossible condition to fulfil but one which has become increasingly seen not merely as a limiting case but as a desirable one. The cost of preventing literally any kind of disaster, whether pharmaceutical or environmental, is astronomic, and a balance has to be struck. It is fairly obvious, however, that the increasing care which has been taken over the use of drugs for therapeutic purposes has raised the cost of their production.

Similarly, it is fairly clear that the therapeutic revolution which had its origins in the German chemical intellectual break-throughs of the late

19th and early 20th century entered the pharmaceutical field in the 1930s, and there were some voices in the audience who claimed that the therapeutic revolution based on pharmacology was to all intents and purposes over. It is interesting, moreover, that the therapeutic revolution has been associated with innovations from the privately owned pharmaceutical companies (very little has come out of the Eastern Bloc countries), and also that in most of the Western countries, even including the United States, the main ultimate source of payment for the drugs used in therapy has been government or quasi-government agencies, but operating through some form of market mechanism.

A number of very important problems immediately are raised. The first is that unlike other industries, the development of new products is not only extremely expensive – Professor Beckett talked in terms of a range of £5m–£9m for the cost of producing a successful new drug – but is also extremely chancy. In Professor Beckett's language, it was a 'pure gamble', and this is quite different from the marketing of a new form of motor car or developing a new kind of aircraft.

Secondly, the pharmaceutical products are not directly sold to the public or at least not usually sold directly to the public, but are mediated through skilled pharmacists and prescribed for the most part by the medical profession, either individually or in hospitals. Thus the market is a very strange one – limited but expert.

Thirdly, it is subject increasingly to public control, both of prices, in order to secure economy in the use of public money, and of qualities and standards.

Now a number of questions immediately arose. In the process of regulating prices and standards, were people in danger of so cutting profits that they killed the goose that laid the golden eggs? Secondly, was the therapeutic revolution indissolubly linked to the market structure and to the form of ownership of the pharmaceutical companies which had broadly prevailed in Western countries in the period from the 1930s to the present? Thirdly, was it possible (and this is a pure hunch and speculation which is almost certainly untrue) that the therapeutic revolution was the result of a sudden outburst of creativity which had arisen for reasons not fully understood, and which was now over? If that was so, it would indeed be a depressing phenomenon.

Mr Hellyer, in his study of the cost of compliance with international regulations, emphasised many of the points that Professor Beckett had dealt with. Indeed the accumulation of significant detail will make these two essays, taken together, extremely important contributions to the study, not only of the pharmaceutical industry, but to the study of the diffusion of innovation and of the structure of firms and industries which are built on continuous technological innovation on the basis of scientific work.

## *Preface*

It is fairly clear that each country feels that it needs to have rules and regulations controlling the sale of drugs, not only because of the possibility of drug abuse, but chiefly because of the grave dangers of side effects, of which the thalidomide disaster was, of course, the chief recent instance. Yet, since each jurisdiction fulfils and lays down its own standards and requires its own trials, the international market is being very rapidly broken up into very small units relative to the production capability of the large firms. The result is that ingenious ways have to be devised in order that perfectly reputable products may appear to be produced in different countries and may then legally fulfil all the requirements of the local regulations. While the laws frequently have a very sound basis of common sense and are based upon a genuine desire to protect the public, the way that they are implemented has the effect unintentionally of raising costs and not in many cases to any degree safeguarding the public. It is quite clear that there is room here for significant international action, particularly when regard is had to the need for the development of new therapeutic techniques for the poor countries, where diseases are prevalent which are not widely prevalent in the countries where the therapeutic advances, broadly speaking, have taken place.

All of this, then, is leading to a fragmentation of the market at the same time as the raising of the cost is leading to a concentration of the means of production.

We therefore see an international industry with a fragmented market whose costs are rising and which is facing a very uncertain future because of the increase in regulations affecting its products and the way that they are manufactured, and a threat that the rate of innovation will fall away.

Mr Mould of the Economic Development Office therefore raised a very apposite question in his lecture on the balance of payments. A few years ago the balance of payments was omnipresent in every discussion of the economic, social and political condition of the United Kingdom. Since the effects of the devaluation of 1967 the United Kingdom has turned into a huge creditor country, it seemed therefore less important to develop exports and less important to discourage imports than it was before. But, in the long-term, the balance of payments was clearly deeply significant.

Mr Mould points out that the consumption of pharmaceuticals is very closely correlated with national income per head. It follows therefore that the highly developed countries are the chief consumers of medicine, which confirms the judgment that if the EEC, United States and Canada can reach agreement on many issues, the major part of the world market is embraced, particularly if the agreement includes Japan. Furthermore, the pharmaceutical industry tends to follow more or less the trends of international trade, but its peculiarity is that it is centred on a number of

exporting countries, West Germany, the United States, Switzerland, the United Kingdom and France. All these are, of course, within either the EEC or the United States, with the exception of Switzerland which, as we shall see, is the odd man out. Within this relatively simple picture, which shows that newly industrialising countries are tending to increase their output and that smaller European countries are also coming into the picture, a situation of real complexity is revealed by the fact that a number of companies within any jurisdiction are 'foreign' owned. Thus, two thirds of the medicines bought by the National Health Service come from foreign-owned companies. Nevertheless United Kingdom exports from both British and overseas owned companies have continued to grow, reaching almost £170m in 1971. The question whether this will remain a growing part of the export field depends on a number of factors; first, upon the state of world trade and the British economy in general, and secondly, whether or not the rate of innovation in the United Kingdom rises above, remains the same, or falls below that elsewhere.

In this respect Mr Mould was relatively optimistic, since the United Kingdom remains an important centre for research, though he argues that the research is becoming more difficult because the diseases now being treated by the new drugs are more difficult to cure. Here the feeling was that the relative effort in research of the United Kingdom might be dropping behind, since no company was spending as much on research in the UK as in the USA, Switzerland and Western Germany. Mr Mould took the view that if there were international harmonisation of regulations on pharmaceutical exports and use, this could not occur before the 'eighties and there was therefore a relatively difficult decade ahead. In these circumstances, the apparent relative decline of the British research effort in terms of all of the size of the research effort by different companies might be fairly serious, and it is also accompanied by a fall in the profitability of the UK industry associated with the lower prices prevailing in the United Kingdom as a result of recent government negotiations and decisions concerning the industry. Both of these factors could reduce the level of investment in new products. This also would suggest that the structure of the industry might change through mergers and amalgamations, so that the UK could produce a company really large enough to take on foreign companies. This, of course, raises certain very central questions, which the other lectures touched upon, namely the relationship between genuine innovation in terms of new ideas and the follow-through in terms of product development and marketing, and the structure and organisation of the firms and of the industry. Is there a possibility that the larger the organisation, the less creative it is likely to be? Might it not be the case that the industry is largely the creation of a few maverick individuals with brilliant ideas?



## *Preface*

Mr Smith's lecture provided verification and confirmation of these views. As he pointed out, his own studies had suggested that the costs of research were rising for the reasons that have been given, and it seemed probable that as costs rose the pressure on prices would lead to a fall in profits. His own view was that this fall in profits had not yet occurred on any significant scale because the firms engaged in pharmaceuticals were by and large firms covering a wide range of activities; consequently their general level of profitability during the 1960s had been kept up. Furthermore, he argued that the level of profit in this industry in general was significantly higher than the level of profit throughout the economy. In other words, the level of normal profit, as Marshall would have called it, tends to be higher in this somewhat risky industry with limited entry than in many other industries.

Mr Smith then faced up to the central question that if the neo-classical criteria for determining the level of investment were applied to expenditure on research and innovation, the level of research and innovation would inevitably fall, for the very simple reason that if the rate of return was declining, firms seeking more profitable outlets for their capital would tend to move away from research. Yet, according to his own studies, this had not yet happened. What was the reason for this?

He suggested first of all that it was extremely probable that the discounted cash flow technique, which lies behind so many modern accounting principles, and which is the basis of modern government economic techniques, such as cost-benefit analysis, was certainly not applied to research, if only for the very simple reason that if it were applied to research with its heavy initial payments spread over many years and its returns coming late on in the process, between eight and fourteen years after the first investment has been made, little or no research would in fact be undertaken, because the present net value of the returns would be so low. He suggested, therefore, that in pharmaceutical companies there tended to be a conventionally-determined budget for research which was allocated according to fairly rigid criteria which had been determined at an earlier stage in the firm's career, and that so long as the firm's profits kept up, these criteria were not likely to be changed. Mr Smith argued that by convention a certain amount of the research was devoted to new products, a certain amount to development of alternative products to those already on the market, and so on. Obviously the proportions of the expenditure allocated to research would vary from firm to firm, but he thought there was strong evidence to suggest that the proportions, once established, tended to prevail. He argued also that this expenditure tended to be closely linked to sales volume and, above all, to the level of profits, that is to say, so long as sales and profits of the firm as a whole kept up, research was regarded as a 'Good Thing'. And he also suggested that when profits were

squeezed people tended to spend *more* on research rather than *less* because they thought that they might get a big break-through into a new product, something quite extraordinary – which would lift the whole firm on to a new profitable level, and which, above all, would ensure the firm's growth and survival. In other words, Mr Smith was an adherent of the Marris doctrine of the theory of managerial capitalism, that it is the survival and growth of the firm which is the object of the managers of modern enterprises.

This is, indeed, an interesting and important thesis because, if true, it would tend to suggest that the squeezing of prices would not necessarily lead to a decline in the level of research. He also argued that the level of research having been kept up, there was little evidence that there had actually been a decline in the number of significant new pharmaceutical innovations; but clearly this is an area which merits further study, since there was a substantial conflict of evidence among the various speakers on this matter, some of them suggesting that the rate of genuine innovation was substantially and catastrophically declining, largely because of the excessive and quite untoward effects of government controls designed for the safety of the patient, but which had had the unintended effect of prolonging the period between a successful innovation and the time at which it could be widely marketed, thus so raising costs that the innovation process was actually short-circuited.

Mr Smith was not an adherent of this view, though, if pressed, one suspects that he would have been prepared to say that the number of major innovations, judged on some scale of heroic, magnificent proportions, was not very substantial in the 1960s. Whether or not this is connected with the economic circumstances of the market is, of course, the sixty-four thousand dollar question, because if the level of innovation is connected not with the market but with the level of scientific creativity, then it is to the level of scientific creativity that attention should be paid rather than to the state of the market. Indeed, Mr Smith suggested that the harder up firms became the more likely they were to be concerned with basic science. It was in this connection that he saw both the least and most hopeful features of the 1970s and 1980s. On one interpretation, if profits fell because of government controls of price, and the cost-raising effects of safety precautions, then research would be stimulated. That is hopeful for us – the drug takers – but depressing for the pharmaceutical industry. Yet his argument seemed to contradict this because he agreed with the NEDO experts that the size of the pharmaceutical market was likely to grow very rapidly in the 1970s and early 1980s, and that this would tend to raise profitability. This would keep the level of investment up. If the level of investment were indeed kept up, this would tend to accelerate applied research. By accelerating applied research the level of product innovation was likely to be raised.

In other words, Mr Smith, far from being a neo-classical economist, was

## Preface

a follower of Professor Nicholas Kaldor, because more investment out of higher profits is his prescription for raising the rate of economic growth in the United Kingdom.

Hidden behind all this one suspects there is a key question. Supposing that there was a break-through in cancer treatment, or supposing that a successful course of drug therapy for coronary patients was developed. The market in both cases would be very extensive, both because of the large number of patients concerned and also because people would be prepared, either as families or through the State, to devote substantial resources to these drugs. What are the circumstances in which such drugs could be developed? And are present market conditions, which are necessarily controlled by the government, both because the government is the chief purchaser, and also because the government protects and represents the public interest in this field, appropriate? Should the government intervene in order to accelerate the process of research? And furthermore, would the development of such drugs in some sense be in the public interest if it occurred earlier rather than later? At what point do you reach the break-even point between growing expenditure on research and the development of new products?

All these points are brought together in the lecture that concluded the series, by Mr Teeling-Smith. His argument was that the pressures for drug safety, while perfectly legitimate, had been acceded to in such a degree that drugs were, if anything, now safer than almost any other kind of human activity. As he points out, we can always trade off safety against efficiency. Clearly, nobody would expect people to be allowed to drive between London and Oxford as fast as they like and on any side of the road, because it would be running unreasonable risks. On the other hand, the only way of preventing any kind of motor accident of any sort is to forbid the use of motor vehicles altogether and, while ultimately that might come, at the present time the world is not ready to take such a step. Similarly with drugs, occasionally someone dies because they have taken an overdose of aspirin. The only totally effective way of preventing people from taking overdoses of aspirin is to prevent aspirin from being available at all. Yet to do that would be to condemn many, many millions of people to mild headaches without the alleviation that aspirin gives them.

Mr Teeling-Smith's argument is that the line at the moment has been drawn too much on the side of safety, and as he rightly points out, if the same tests of efficiency were applied to other medical procedures as are now applied to pharmaceutical procedures they would themselves come under heavy suspicion. Perhaps somebody who is not professionally engaged in the economics of health might also suggest that in other walks of life, notably in education, *nothing* would happen at all if the conditions for efficacy were as stringent as they are with drugs.

Mr Teeling-Smith then points out that one of the major factors which has determined the public attitude to the drug industry is that because people want to feel well and drugs offer them the way of either feeling better or becoming better, they may be over-persuaded to take them. This is undoubtedly an important point which has to do also with a large number of other modern consumer industries. He points out that in fact the pharmaceutical industry has a better record than most, since its products are only available with medical assistance in general, and this medical assistance is itself pretty heavily protected.

The result of all this activity with the pharmaceutical industry is the controlling of prices and profits in the way described earlier in this introduction. Mr Teeling-Smith raises the central point as to whether or not, in taking the short term view of the need to depress profits at least to the overall average for the economy as a whole, and to keep prices reasonably in line, the nation is not in grave danger of killing off pharmaceutical research. This does seem to be the central question, and it may well be perhaps that Mr Teeling-Smith slightly overstates his case at this particular juncture, since the earlier essays had tended to suggest that nobody yet knew exactly what was the connection between research and pharmaceutical innovation, and what was the connection between prices, profits and research. Yet, even if that be granted, there is no doubt at all that Mr Teeling-Smith's central point is well taken; that so long as there is a mixed economy and the pharmaceutical industry falls within the private sector, it must have an adequate flow of profit in order to finance research. It is worth pointing out that if the pharmaceutical industry were nationalised, the problem of pricing and of the allocation of funds for research would remain, and there is no obvious set of criteria that could be applied to this. It is also worth pointing out, perhaps, that in the fuel and power industries, which are mainly nationalised, the problems of pricing and investment are unsettled as yet, although a quarter of a century has passed since nationalisation occurred. It is hardly surprising, therefore, that the Department of Health and Social Security with relatively narrow experience in economics should have found it difficult to find a solution to questions which have bothered governments in the United Kingdom and elsewhere in broader fields for many years.

Mr Teeling-Smith finally concludes with a major social question, which is whether or not we are right to press for further research in medication, so that more and more ills can be cured, or whether in fact in so doing we are not disturbing some sensitive kind of ecological balance. This is the kind of argument for which I personally have little instinctive sympathy, since it seems to me that on the whole, given the choice, almost all people would choose to be cured rather than to remain ill, provided that the cure of that illness did not involve even more drastic consequences.

## *Preface*

### **Conclusion**

A number of questions, therefore, are seriously raised by this series of lectures. The first is, how fast and how far successful research in pharmaceuticals ought to be pursued. There is clearly a growing backlash of people who feel that 'nature ought to be left to itself'. I must say openly and directly that I am not one of this number. I believe that only the very rich or middle class people can afford the luxury of thinking about macrobiotic diets, and those who have seen the poverty of our great cities, not to speak of the poverty of Asia, will realise exactly how much in terms of ordinary human happiness has been added to the world by the series of technological advances, of which pharmacology is one, in the last half-century. Furthermore, what is within grasp is the cure to a number of diseases of extreme hideousness, including cancer, and it must be thought that this therapeutic revolution would win the support of the great majority of our fellow-citizens anywhere on this planet.

Secondly, it seems as though the desire for safety in drugs has at the moment gone too far, and that the time may be coming when there might well be a slight swing back of the pendulum, not very far back, but slightly, because the benefits to be gained from the use of new drugs so greatly outdistance the small number of tragedies to which they give rise. And in addition, when it is considered that a great many medical procedures at present undertaken undoubtedly do more harm than good, some surgery being an example, it is realised what an imbalance there is in our present procedures for monitoring drugs compared with the majority of other things.

This then raises certain central questions. The first is, what price should be paid for drugs? To which obviously the answer is, the cost of their production, plus a reasonable level of profit. This then raises the further question of what is the reasonable level of profit. Hitherto, the main argument for higher profits in pharmaceuticals, other than the normal return on capital, which is expected to be earned both in public and private enterprises, is that the profits are ploughed back into research and development. It is by no means self-evident that the research and development has to be undertaken out of profits. It could be conducted, for example, entirely at public expense in National Health Service laboratories. On the other hand, it has to be said that so far successful research has been associated with privately-owned corporations, perhaps because there are no publicly-owned pharmaceutical corporations outside the Eastern Bloc countries. And it also has to be said that the therapeutic revolution has not only saved and ameliorated many millions of lives, it has also, in sheer economic terms, saved the health service many, many millions of pounds. It therefore follows that there is some justification for believing that super-normal profits, if used in research, do in fact lead effectively to important

long run benefits. But it is also clear that it is very difficult to put this on any rational basis according to the accounting and economic techniques at present available. We are therefore unable to give any firm and detailed conclusion about the desirable structure of the industry in relation to overall needs, except perhaps to suggest that the suspicions under which the industry has laboured for many years have so far not been very justified, and that it is probable that the level of research, if kept up, is likely to lead to further break-throughs in therapeutic advance which would be well worth the money spent on them.

There is urgent need for a much more careful investigation of the structure of the pharmaceutical industry in order to see what its investments and pricing policies ought to be, but at the moment it must be said that a verdict of 'not guilty' must be returned on many of the charges that have been levied against the industry, and that in some respects a major vote of thanks must be paid to it for having supported the therapeutic revolution.

One final doubt, however, does remain, and this is an area where further research would be particularly interesting, and that is, what is the connection between money spent on research and development and subsequent innovation? My own judgement, after listening to these lectures and reading around the subject, is that during the later part of the 19th century the German chemical industry and German chemical research blossomed together, that some time during the early part of the 20th century the results of this chemical research were dispersed into a number of other countries, partly by ordinary migration, but mainly by the forced dispersal of emigrés after the coming to power of Hitler, and that for some reason or other this chemical expertise went into the field of pharmacology, leading to the outstanding discoveries of the 1930s, 1940s and 1950s. It certainly seems, from discussions with scientists, that this great burst of creativity has died down, though it has not yet petered out. Sciences do blossom and then die, and there is no logical or historical reason why this should not happen in pharmacology. But this is to enter very deep waters indeed, and waters which are extremely difficult to investigate.



# The modern multinational structure of the pharmaceutical industry

Robert H Jones

## Introduction

The Centre for the Study of Industrial Innovation was commissioned by NEDO in 1970 to carry out a review of the forms taken by the pharmaceutical industry's international marketing and how the patterns of its multinational operations are conditioned.(1) This paper discusses some of the findings of this survey. First of all it looks very briefly at companies' objectives in 'going abroad' at all. Secondly, the various methods which companies use in developing overseas sales are summarised. These are influenced by the basic nature of this industry, which in important ways is different from that of other internationally operating industries. There are also a number of more immediate internal and external factors which affect companies' decisions on international policy. Thirdly, problems of the organisational structures adopted by multinational pharmaceutical firms to control their world-wide activities are examined.

## Corporate objectives

Economists have always been prone to trying to trace corporate behaviour back to a fundamental company objective. Traditionally, this has been assumed to be profit maximisation, but in more recent years turnover growth, brand share increase or rate of new product introduction have been postulated as alternatives. In fact, ultimate corporate objectives are difficult to define and may differ from company to company, or even from point to point within a company. Our study did not attempt to tackle this conundrum and was content to regard the basic corporate objectives as given. What was clear, however, was that in multinational firms the achievement of a multinational structure or international representation *per se* was not one of these.

In the shorter term there are a number of very cogent reasons why pharmaceutical firms wish to develop overseas sales, for example the limitation of product life in pharmaceuticals. Patented products almost certainly constitute the major element of pharmaceutical sales for any company, and generate the majority of growth. But the period of a patent sets a limit to profitable product life. Since part of the patent life is absorbed in technical development, clinical trials, and product registration with national control authorities, profitable product life is unlikely to exceed ten to twelve years. Moreover it is common for pharmaceuticals to be superseded



technically by competitive development prior to patent expiry and this may further reduce effective product life. Because the approach of patent expiry and the threat of competitive obsolescence are quite exogenous to the firm, a premium is put on speedy generation of maximum sales volume. To have a developed world-wide sales network clearly improves the potential profitability of a given product within its limited life-span.

Another factor lies in the changing nature of pharmaceutical business. Over the last twenty years companies have tended to specialise more within particular product areas. This in itself has limited the size of home markets and together with increasing research costs has heightened the importance of overseas sales. Companies now deliberately seek new products within their defined therapeutic area which can be patented and marketed in a number of national markets. As one company president has expressed it: 'the effect of this international specialisation is for us to switch shares on one another's markets'.

For reasons like these, the pharmaceutical industry today is very different from what it was at the end of the 1930s. At that time, experiencing for the first time the rapid growth in demand for the new products of the therapeutic revolution, companies tended to think first in terms of direct export and had little concept of an explicit international corporate policy. The actual establishment of foreign subsidiaries usually resulted from the initiative of individuals or clear evidence of real cost savings. Since then, pharmaceutical subsidiaries have proliferated and by now overseas business for many multinational firms exceeds domestic business. Overseas business is no longer a surplus to be tacked on to the basic domestic activity: it is an integral and possibly a major part of a world-wide activity, and corporate policy is structured in recognition of this.

### **The development of multinational operations**

The historical development of a multinational activity is generally assumed to begin with export or licensing followed by the gradual establishment of overseas subsidiaries. Similarly it is sometimes assumed that in considering a particular overseas business opportunity a company is faced with clear alternative methods of overseas marketing – exporting, licensing, or manufacturing through subsidiaries – and that a decision must be taken between these alternatives.

These assumptions do, however, over-simplify the real situation. They do not make explicit that the multinational enterprise, with subsidiaries in certain markets, will usually also remain an exporter to other markets – and indeed to its own subsidiaries. Local manufacture even in the largest firms never completely replaces exports, and most companies, whatever the sophistication of their subsidiary networks, ship considerable quantities of pharmaceutical goods around the world. Because of the nature of the

industry's production – which I will mention again later – the precise 'mix' of exports and local manufacture is usually more influenced by factors external to the firm than internal to it: for instance the different levels of tariffs which a company faces in its world markets. The assumption of three basic choices of method ignores the possibility of hybrid situations such as that in which a company carries out its own overseas marketing yet uses a local agent for distribution, or in which a subsidiary pays a production royalty to its own parent.

Nevertheless, the companies interviewed in the survey generally agreed that their methods of international activity do evolve over time in the sort of sequence mentioned above. The reason for this is that in achieving its fundamental objective – whatever that is – the immediate task of a company in developing its overseas markets is usually the acquisition of direct marketing control by the company itself: that is, managerial control by the company over the direction, emphasis and timing of product launches, sales programmes and budgets, promotional campaigns and so on. This cannot be achieved so effectively when exports are distributed by an agent as when the company handles its own distribution by establishing a marketing subsidiary. Thus there is a strong incentive for a company to develop in a sequential form, from a simple export situation to an enterprise with multinational investment. But it is important to emphasise that there may be limits to this sort of evolutionary development. The company's objective is, say, to achieve maximum profits, not to develop local subsidiaries: there may be certain markets in which the establishment of a subsidiary is not the right means to that end. Alternatively, the formation of a marketing subsidiary may be all that is required and in such a market the sequence of development will stop short of investment in productive capacity.

### **Exporting**

This operational principle – the drive towards greater marketing control – can be seen in examining exporting alone. Here, the 'weakest' position, usually only adopted in the introductory phase of entry to a new market, is to employ a speciality agent who acts as distributor and provides marketing and promotional services for the product within his territory. Relinquishing control of promotion and representation, this situation also means that the company's product might become one of a number of products handled by the agent which, while not in direct market rivalry, do 'compete' for the agent's time and promotional efforts. To improve on this situation, the agent may be encouraged to limit the number of products handled by each of his representatives – if possible to the company's range alone. A further step is for the company to finance directly the employment of representatives by the agent. Technically these remain the agent's employees but their direct costs are borne by the exporting company.

The representatives will then handle solely the products of the exporter. Alternatively, the company may be able to inject an element of control into an export situation through the appointment of territory sales managers, who supervise operations even though the company itself is not handling the activity. These managers act in an advisory capacity, working in close contact with the agent, and can provide a regular channel of communication between the day-to-day selling and the exporter. Possibly the most developed export situation is that in which the agent provides an operating headquarters and support facilities for representatives who are in fact employees of the exporting company. This greatly tightens up control of marketing, since it is now the responsibility of the exporter's own employees. However, the situation stops short of the actual establishment and equipping of a local sales office and it is not therefore a fully independent position.

### **Licensing**

Licensing involves the granting of the right to manufacture a product together with the relevant know-how. In a marketing sense its most important advantages are that it can provide a means of entry to a market which would not be easily penetrable by other methods, or an opportunity to gain experience of the new market and to begin to develop some market share prior to the establishment of a direct presence in the market. It is in principle a flexible technique and a licence agreement is one most aspects of which are open to negotiation. As long as the product is covered by patent the licensor has considerable control over the way in which his product can be handled. He can restrict the licensee's manufacturing or exporting freedom, and retain certain territories for himself. Or he can allow non-exclusive licensees to compete in the same territory. He can provide that the licence may be modified or rescinded on conditions defined by himself. The only limitations are that his terms must not be so extreme to be unacceptable to a suitable partner, and they must conform to local statutory regulations (which in some countries might, for example, impose a ceiling on royalty rates).

The main disadvantage of licensing – although we were not able to collect data on this – appears to be that, where alternative methods are available, it constitutes the least profitable method of overseas marketing. But it can also have other drawbacks. Companies have to exercise care if the terms set are not to lead to a disadvantageous situation which reveals itself too late. There may be a risk that pharmaceutical quality of a standard acceptable to the licensor will not be maintained. The licensor may lose direct control over his marketing, which could damage market prospects in another market. Thirdly, it is possible that the licensee will have a less motivated interest in the licensed product than in his own. His represen-

tatives may detail their own products first and licensed products second which may not yield what the licensor would regard as an equitable share of the effort. There is indeed no guarantee that the licensee will work the licence at all and although this contingency can have been allowed for by escape clauses in the agreement, nothing can retrieve the time lost. Then, if the licensor does decide to enter the market himself later, he may find that his agreement does not leave him free to sell his product in the way in which he wants. Finally, both parties to a licence can run into legal problems if the agreement, as worded, appears to conflict with national restraint of trade regulations.

Thus the impression we gathered was that licensing was thought to be a technique which offered unique advantages in certain situations and in the short term, but which suffered from too many disadvantages to be in the front rank of the company's policies for overseas marketing – it is a limited tactical weapon rather than a strategic one.

### **The marketing agreement**

An alternative to using exports or licensing to develop overseas sales, yet which does not involve the immediate commitment of overseas subsidiary, is to undertake a marketing agreement with a fellow pharmaceutical firm. This can be particularly appropriate in countries where no specialist pharmaceutical agent is available; it is also an arrangement which lends itself to reciprocal agreements between companies in different markets. It involves the 'host' company taking on the sales management of the products of the 'initiator' – that is the company new to the market. It is not a licence agreement since the host is not given rights to patented know-how, nor is it a joint venture in that it does not involve a capital agreement or the creation of a jointly owned subsidiary company. Because of its flexibility it is a widely used method in this industry.

Under a marketing agreement, the product is usually, though not always, supplied by export by the initiator and sold under its own brand name. The object of such agreements is normally the establishment of the new company name in the market and the development of revenue on which future growth can be based. In the marketing agreement, the initiating company makes use of its partner's developed marketing or distributional abilities in the market concerned, and supplies the marketable new product; while the partner benefits from commission, royalties and/or service fees for his assistance.

### **Joint ventures**

Many marketing agreements are difficult to distinguish from joint ventures since, as operated, they may give the appearance of a separate corporate activity. However, the characteristic of the true joint venture is that it

involves the legal establishment of a jointly-owned subsidiary undertaking. The joint venture is often found in industrial undertakings which involve heavy capital investment – for example civil engineering or mining – when an overseas firm which can supply, say, advanced technological expertise, may set up a joint venture with a local company providing manpower and planning know-how. But because pharmaceuticals is a relatively low capital industry, joint ventures are not widely utilised. The non-capital advantages they confer can usually be obtained through a marketing agreement. Nevertheless, they do exist. Joint ventures are rarely intended as other than temporary. Even in other industries they may be entirely *ad hoc*, e.g. for the building of a dam or the construction of a chemical plant, and will be dissolved on completion of the project. In pharmaceuticals they may be conceived, like other methods of market entry, as a stage on the way to the eventual full representation by the newcomer through a wholly-owned subsidiary. Only when this can be catered for in the agreement are joint ventures likely to occur.

#### **Overseas subsidiaries**

Lastly in the 'sequence' we have what is commonly assumed to be the final stage in development of a multinational activity, the establishment of subsidiary companies overseas. On examination this also proves to be rather less simply described than might be supposed. As we have noted, the goal of a company's overseas development is usually the establishment of a marketing capability, and this may or may not involve the need for production capability. Therefore, the stage of direct investment, at which the company becomes truly multinational, may still only involve the establishment of a local sales office. As one company put it 'one becomes one's own distributor', and in terms of assets the company's involvement in the market may be small. In other cases there may be just a part-production undertaking in the market, imported bulk chemicals or finished preparations being further processed or packed in the market. Only occasionally does the company go as far as investing in a subsidiary a full capability for the manufacture of the company products, and even then it is rare for a subsidiary's production to be totally independent of parent or associated companies.

Thus, it is not accurate to regard even the most mature multinational company as one with productively self-sufficient subsidiaries spread across the globe. Not all of the company's various markets will have reached an identical stage of development; but more importantly, in some markets it will never be appropriate for there to be a full production presence. To understand precisely why this is so requires a closer look at the peculiar nature of the pharmaceutical industry's production – peculiar in its relation to other corporate functions.

### **The nature of pharmaceutical production**

The text book interpretation of a multinational activity emphasises the relative production costs of which the multinational firm can take advantage in siting its production activities. For example, raw material availability and the costs of labour can be important factors, and the latter explains much of the expansion of production facilities in Europe by American electronic and engineering firms. Transport costs are another factor: where these are high, there is an additional incentive towards local production.

The survey found that in general within the pharmaceutical industry neither transport nor direct production costs have a central effect on the location of production. Several companies in the sample emphasised that the activities of the pharmaceutical firm were orientated towards the development of new products and their marketing, with production being a subordinate function. As an extreme view it was stated to be 'irrelevant'. Transport costs of pharmaceuticals are low, and thus can be discounted as a factor significantly influencing locational decisions. Thus, while the form of the company's representation in an individual market will depend to a considerable extent upon factors external to the company – e.g. market size, trade conditions, and factors relating to market infra-structure such as registration requirements and political attitudes – these factors do not normally include some which in other industries can be of paramount importance. The reasons lie in the nature of pharmaceutical production.

Manufacture of pharmaceuticals can be viewed in two stages: first the chemical production of the active pharmaceutical ingredient, and secondly the processing of that ingredient into finished product form – whether capsule, tablet or injection. The first part, chemical production, may be technically complex and require considerable capital investment. In such cases this can lead to economies of scale from centralisation of production and, combined with relatively low transportation costs, provide an incentive for a company to concentrate its chemical manufacture.

The second part, pharmaceutical processing, finishing and packaging, is for most firms standard and technically straightforward. The capital required is relatively small. This is therefore the more 'mobile' aspect of the production process and a limited investment in processing facility is often the first, and sometimes the only, type of production investment undertaken by companies in overseas countries. Even where processing is carried out in the local market this need not be done by the subsidiary itself. The work may quite well be subcontracted, if the industrial infra-structure of the host country is sufficiently developed.

These characteristics give a flexibility to the physical supply of pharmaceuticals. A product can generally be exported at different stages of the production process – as a chemical intermediate, a bulk pharmaceutical

chemical, tablets or capsules in bulk, or a finished packed product. As I have mentioned, the stage at which the product will be shipped usually depends upon conditions in the recipient market – for example the tariff structure may make importation of finished goods prohibitively expensive; or a limitation by government on earnings from local production may encourage shipment of finished products; alternatively an element of local production may offer marketing advantages. So one company is likely to be faced with many different production requirements among its different overseas markets, with its subsidiaries undertaking correspondingly different amounts of the production process themselves – or even none at all. This production flexibility also means that in response to changing external factors the developed pharmaceutical multinational firm may be able to transfer production from one source to another to take advantage of preferential conditions. The source of a market's physical supply of products is not normally critical to a company's success in that market. To a large extent the scatter of pharmaceutical production which does exist is a response to external barriers and opportunities rather than to conventional factors of relative costs and resource availability. The multinational pharmaceutical firm is therefore typically a marketing rather than a production system and the subordinate role of production in this industry certainly means that, in contrast to industries like motor cars or oil, the main determinants of multinational growth patterns must be sought in non-production factors.

The factors which do operate to influence the firm's international sales patterns can be grouped under two headings: internal, or industrial, and external. I will mention briefly just the main factors which the survey disclosed under each head.

#### **Internal factors affecting multinational operations**

An important internal factor is the availability of manpower. The pharmaceutical firm moving for the first time into overseas markets is not faced with significant manpower problems until it reaches the point at which it needs direct representation abroad. This is most likely to relate to the marketing function, with manpower for production, and certainly R and D, following only later. Marketing employees 'in the field' are usually nationals of the country concerned. But the company normally has a choice over senior management. It can either attempt to recruit locally or transfer people from another country. While the importance of giving responsibility to indigenous managers is undeniable, it will not always be possible to staff a new subsidiary from the start with them. And it is always possible for a firm wishing to establish a marketing subsidiary to be inhibited by a shortage of appropriate manpower. This may have the effect of prolonging the period during which the market is served by exports.

Another important factor is product range. It is expensive to establish a marketing organisation in an overseas market and, to justify the expenditure and risk, a good product range yielding an adequate level of revenue to bear the overheads is essential. It is usually too expensive to have a representative team engaged in selling just one product, apart from resulting in lower job satisfaction. The obvious solution is for the company to serve the market through exports or through a marketing agreement until its own product range or sales volume has developed sufficiently to bear the costs of a marketing subsidiary. The main disadvantage of waiting for the development of a wider product range is that it accepts the lengthy time scales of R and D and places the establishment of a marketing subsidiary some way in the future. An alternative solution may therefore be to look for good products to license in. This may not be very profitable in itself but for a company with limited product range and multinational ambitions, it may provide the opportunity to establish an otherwise un-supportable overseas activity.

### **External factors**

Turning to those factors which are exogenous to the firm, yet which affect the kinds of decisions it will take in developing overseas sales, the one mentioned most frequently by companies was the widening requirement among countries that pharmaceutical products be registered with and approved by a national drugs authority. Many countries now employ safety and marketing control procedures and a considerable increase in the number of national registration agencies has occurred over the last decade. Many of these are modelled on the Scowen Committee in the UK or the Food and Drug Administration in the USA. None of the companies dissented from the basic justification for such controls, but many found individual control agencies tiresome in the procedures required, and unnecessarily slow in giving marketing approval. The delays involved may typically be between eighteen months to two years, with greater lengths of time not unknown. Such periods can occupy considerable proportions of the limited profitable life of many products. Product registration is thus a factor which affects the rate at which a company can develop its overseas business. It also injects an element of uncertainty into the company's planning process which it finds difficult to absorb. In the long run it would seem that a wider harmonisation of the requirements of registration agencies is required. Drug control systems have so far failed to parallel the international structure of the industry.

A second factor also related to the relationship between the industry and national agencies, in this case on the question of price. A growing reference by governments to prices of products in other markets is today becoming a factor that can influence the form of company marketing. Several com-



panies claimed that, whatever their internal philosophy of pricing, their ability to price solely on economic factors is limited by the growing cross reference between countries. It was also noted that the production flexibility of the developed multinational pharmaceutical firm may provide it with responses to external price pressures. In Belgium, for example, price ceilings for some imported pharmaceuticals are set by a formula reference to prices in the country of source. There is an incentive here for the multinational to supply the Belgian market from the highest priced country in which it has production plant. The French price regulation scheme is more complex, stipulating that price must be within a certain percentage range of direct costs. Again, it is open to the developed multinational to work up what it regards as a realistic end-price by transfer shipments at various stages of production.

A third factor is the operation of instruments common to all industries, trade controls – tariffs, quotas and currency exchange limits. These again can influence the form of marketing. Some countries will not allow the importation of finished and packaged products, but will admit part-processed produce. Others will give purchasing preferences to products with a local element in their manufacture. Such factors may encourage a company to undertake at least a limited local production operation earlier than might otherwise be economic, or even where otherwise uneconomic. In pharmaceuticals, in some cases a greater freeing of trade might lead to the disappearance of some local production so that the advantages of greater production centralisation could be obtained. Trade control instruments can, however, operate in unexpected ways. The encouragement of local manufacture by these means will serve only to restrict the supply of product if other (e.g. political) factors are acting to discourage investment. And while encouragement of local activity is one thing, the ability of particularly the smaller company to respond is another.

Other external factors mentioned by the companies included the social and political stability of the countries concerned and the possibility – particularly significant in pharmaceuticals – of technical piracy. In some countries purchasing agencies are not over-scrupulous whether the product comes from the legal owner of the product know-how or from a cut-price local ‘pirate’ competitor. And a final factor – which is so obvious that it is particularly worth mentioning – is the differing medical and economic character of national markets. Putting it simply, these mean that there is small prospect for an anti-malarial product in a temperate climate market; and companies specialising in so-called developed economy diseases such as hypertension or anxiety/depressive neuroses will rarely look to the developing countries for market expansion. The direction of a firm’s overseas expansion is therefore limited by its basic specialisation.

### **The organisation of multinational operations**

Having discussed briefly the methods used to generate overseas sales and some of the factors which can influence policy decisions on these, I would like now to give some attention to the organisational structures which companies adopt to manage their world-wide activities. Recently this question has been receiving a good deal of attention from academic researchers and management scientists. One of the British specialists in this field is Michael Brooke, at Manchester University, and some of his observations on this subject provide a good background.<sup>(2)</sup> He notes that in a multinational firm there are four areas of decision within which management decisions may be taken: at overall group level (i.e. chief executive or board); at central services level (i.e. with an advisory line to operating companies); within a product group or division; and within a geographical division of the company's activities. These four do not of course exist in all companies and it seems plausible that the present structure of a company is related to its stage of growth. Thus the small firm will have only the overall projection of unified company activities headed up by a number of senior functional managers. As the firm grows, any export business may become the responsibility of an export manager and department – and here is the beginning of a geographical split. Alternatively, as a firm grows it may elect to organise itself on a product division basis – a system widely adopted today. In either case, growth will usually bring the addition of a central services activity.

It is a natural inclination to regard overseas sales as a separate compartment of activity from home sales; and this can produce problems of communication in a company adopting a product division structure. For Product Division A overseas will report to the export or international director and not to Product Division A at home. This communication problem is in practice solved by the appearance of sensible 'dotted' lines of communication, but nevertheless the basic flaw in the structure can lead to strains as the company continues to grow. The logical next step is the rigorous application of the product division structure, and the abolition of the distinction between home and overseas sales. But this too can lead to stress, as managers of overseas subsidiaries have to respond to the split imposition of command from the various product divisions at home. As long as the company is growing, any particular structure of world-wide activities should probably only be regarded as temporary, and the problem of matching structure to the company's stage of multinational growth is by no means easy.

### **Organisational case studies**

The international structures of the three British pharmaceutical companies who participated in the survey illustrate well some approaches

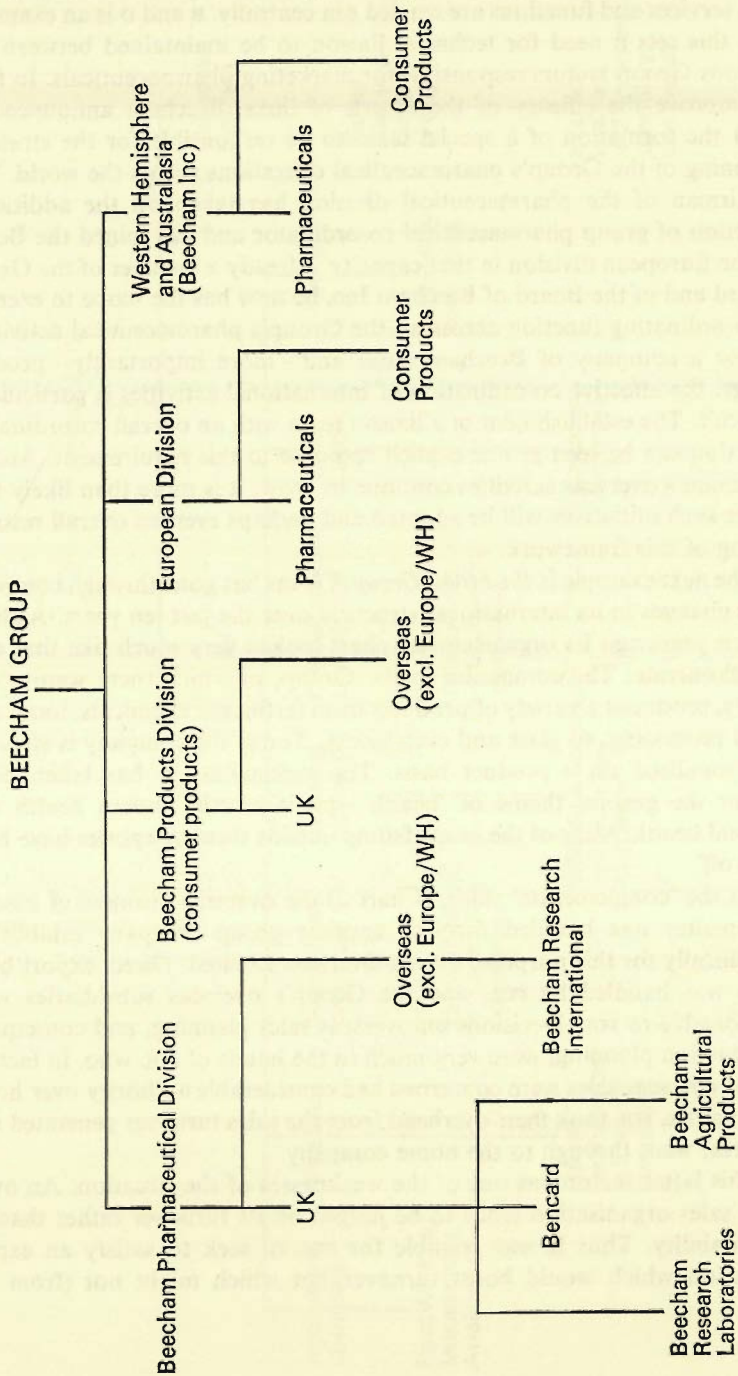
adopted by actual firms to these sorts of problems. Their permission to utilise the case-study material here is gratefully acknowledged.

Firstly, *the Beecham Group*. Beecham's activities can be viewed in two major parts, pharmaceuticals and consumer products. The company has had a prescription pharmaceuticals interest for longer than is often recognised, since it purchased C L Bencard in 1948. This company itself had a rudimentary export department which Beecham retained. In the early days of Beecham's own major pharmaceutical activity (the early 1960s) it was in fact through an expanded version of this export department that the main overseas markets were served. While Beecham's pharmaceutical activity was treated as separate from consumer products, its early export sales were, then, handled on a traditional 'geographical' basis, being channelled through an export department. As the pharmaceutical business grew in importance, and as a greater proportion of Beecham's profits became earned overseas, a new company structure was developed. Chart 1 gives a representation of the Group's activities today. (This is not the company's formal organisation chart but simply a visual aid prepared to support the discussion.)

Particular areas of growth for Beecham's activities, both in pharmaceuticals and in consumer products, were identified as Europe and the USA. Clear cut areas geographically, these were each susceptible to a more unified marketing approach than other geographical areas of the world. So the Beecham European division was established and Beecham Incorporated, in the USA, was given wider responsibility for business development in 'the western hemisphere' (i.e. the Americas and Australasia). Back at home the old export division was translated to Beecham Research International, and became the company within the Beecham pharmaceutical division responsible for handling overseas business other than in the two geographically separated areas. In effect, the old export division has now become an explicit operating company, but it has also lost some of its old geographical extension, following the establishment of the European division and growth in scope of the American company. Thus, the present structure of the Group is on the face of it something of a hybrid. Two of the divisions are, at first level, product divisions, and two are geographical. But in fact the geographical ones break down to product divisions at secondary level, so that by the second level the structure is explicitly product divisional. Nevertheless, overall there are elements both of geographical divisionalisation and product divisionalisation. This present structure is a response to the need to devote special attention to particular markets, and at the same time to give specialised management attention to the very different products within the Group's wide range.

The main question in this sort of structure must be one of achieving effective overall group communications. There is a pharmaceutical activity in Beecham Incorporated, and in the Beecham European division. These

**Chart 1** Diagrammatic representation of the Beecham Group's international activities (not an official or formal organisation chart)



are separated from the Beecham pharmaceutical division itself, in whose orbit lie UK sales of pharmaceuticals and remaining overseas sales. Certain services and functions are carried out centrally. R and D is an example, and this sets a need for technical liaison to be maintained between the various Group sectors responsible for marketing pharmaceuticals. In fact, to improve the efficacy of these sorts of links, Beecham announced in 1971 the formation of a special team to be responsible for the strategic planning of the Group's pharmaceutical operations across the world. The Chairman of the pharmaceutical division has taken on the additional function of group pharmaceutical co-ordinator and has joined the Board of the European division in that capacity. Already a member of the Group Board and of the Board of Beecham Inc, he now has the scope to exercise a co-ordinating function across all the Group's pharmaceutical activities.

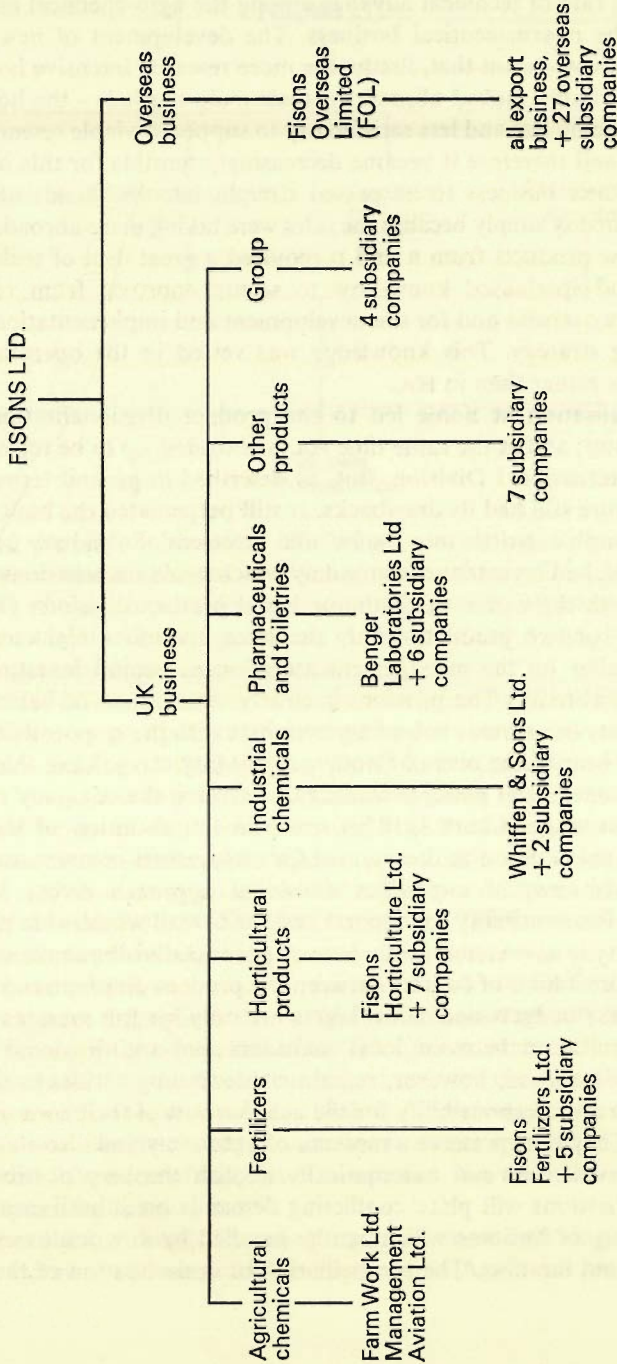
For a company of Beecham's size and – more importantly – product range, the effective co-ordination of international activities is particularly difficult. The establishment of a liaison team with an overall co-ordinative function can be seen as one explicit response to this requirement. And as Beecham's overseas activities continue to grow, it is more than likely that other such initiatives will be adopted and perhaps even an overall restructuring of this framework.

The next example is *the Fisons Group*. Fisons has gone through considerable changes in its international structure over the last ten years. As little as ten years ago its organisational chart looked very much like that of a conglomerate. The companies in the Group, of which there were about thirty, produced a variety of products from fertilizers, chemicals, foods and food processing, to glass and even bricks. Today the company is strongly divisionalised on a product basis. The rationalisation has taken place under the general theme of 'health' – plant health, human health and animal health. Most of the assets falling outside these categories have been sold off.

At the 'conglomerate' stage, (Chart 2) the overseas business of Fisons' companies was handled through another group company established specifically for this purpose, Fisons Overseas Limited. Direct export business was handled by FOL, and the Group's overseas subsidiaries were responsible to FOL. Decisions on overseas sales planning, and consequent production planning, were very much in the hands of FOL who, in fact, as far as overseas sales were concerned had considerable authority over home companies. FOL took their overhead from the sales turnover generated and the rest went through to the home company.

This latter factor was one of the weaknesses of the situation. An overseas sales organisation tends to be judged on its turnover rather than its profitability. Thus it was possible for FOL to seek to satisfy an export situation which would boost turnover but which might not (from the

**Chart 2** Early 1960s: diagrammatic representation of the Fison company's structure (not an official or formal organisation chart)

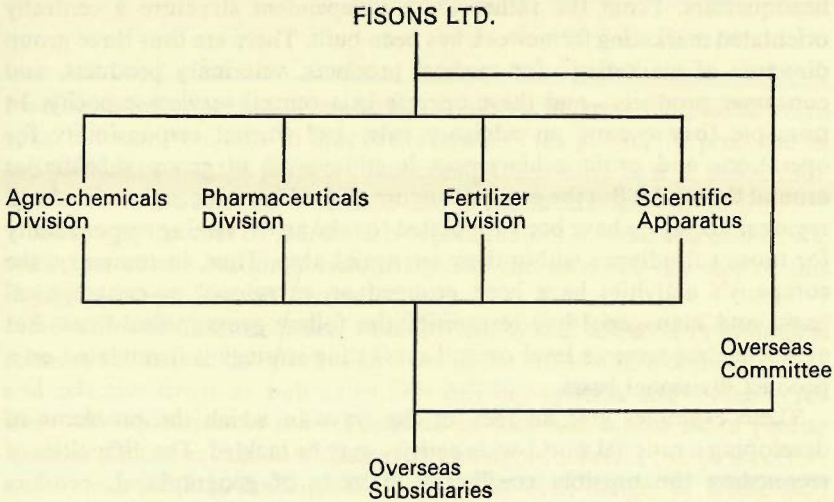


point of view of the home supplying company) be particularly profitable. But more important than this in the eventual replacement of FOL was the increasing rate of technical advance among the agro-chemical and, particularly, the pharmaceutical business. The development of new science-based products meant that, firstly, the more research intensive home companies inevitably looked abroad for their main markets – the home market alone being less and less satisfactory to support a viable research-based activity – and therefore it became decreasingly sensible for this important share of their business to be passed straight into the hands of another group company simply because the sales were taking place abroad. Secondly, the new products from R and D required a great deal of technical expertise and specialised know-how to secure approval from regulatory authorities overseas and for the development and implementation of their marketing strategy. This knowledge was vested in the operating home companies rather than in FOL.

Rationalisation at home led to the product divisionalisation of the whole group; and at the same time FOL was wound up to be replaced by a Fisons International Division. But, as described in general terms earlier, this structure still had its drawbacks. It still perpetuated the basic division of the group's activities into 'home' and 'overseas'. Subsidiary companies abroad still had an extent of autonomy which could on occasions result in conflict with the wishes of the home based product divisions. (Thus two divisions – or two products within the same division – might make conflicting claims on the management attention or capital investment of a subsidiary abroad.) The problem is clearly seen as one of balancing the individuality of overseas subsidiary activities with the responsibility which they each bear to the overall Group profitability. To achieve this balance and to reconcile any possible conflict of interests, the company moved to the present stage (Chart 3). This involved the abolition of the Fisons International Division as the channel for UK/overseas communication and the establishment of a product divisional approach across all world activities. Responsibility for exports and for overall world-wide profit and profitability is now vested firmly in each product division in the UK. There are now direct lines of contact between the product divisions and overseas subsidiaries; budgets and sales targets are only set for overseas markets after consultation between local managers and UK divisional control. Subsidiaries abroad, however, remain viable trading entities in their own right and retain responsibility for the achievement of their own individual budgets. They thus preserve a measure of autonomy and also status.

This system does not automatically abolish the very possibility that product divisions will place conflicting demands on subsidiaries abroad; the quantity of business which can be handled by any one overseas subsidiary is not limitless. The reconciliation or consolidation of the various

**Chart 3** 1971: diagrammatic representation of the Fison company's structure (not official or formal organisation chart)



divisional demands is therefore effected at a newly established Overseas Committee, which operates at chief executive level. This includes the chairman of each UK division and the management of group functions relevant to international operations. A Main Board director represents the interests of the overseas companies.

So here is an example of a company which has in effect brought back some control to group level from what used to be a fairly autonomous world-wide activity. Autonomy is still retained in principle for the subsidiaries, but it is now subject to clearly stated limits. In this case a measure of 'centralisation' of a previously existing structure was deemed necessary in order to take maximum advantage of opportunities presented by the new products and the new types of market which the company was entering.

The third example is *the Wellcome Foundation*. This is one of the longest-established manufacturing pharmaceutical companies in the world and must be one of the very earliest pharmaceutical multinationals, having had subsidiaries throughout the world for more than seventy years. Until relatively recently the companies of the Group were run on a largely autonomous basis and, as the Group developed over the decades, the tradition of separate entity became well established. There was little concept of a structured world-wide activity, controlled from the centre. It was rather a loosely-knit federation of associated companies. Nor was this necessarily a bad thing for the times.

But over the last decade the company has been undertaking a considerable restructuring of its international operations. Again this has essentially



involved the pulling back of some of the autonomy which international subsidiaries had, and subjecting them now to overall limits set by Group headquarters. From the rather loose independent structure a centrally orientated marketing framework has been built. There are thus three group directors of marketing – for medical products, veterinary products, and consumer products – and these operate in a central services capacity. In principle they occupy an advisory role, and formal responsibility for operations and profit achievement is still vested in group subsidiaries around the world. But the group structure abroad has been regionalised and regional managers have been appointed to take an overseeing responsibility for those subsidiaries within their territorial area. Thus, in summary, the company's activities have been grouped on a regional or geographical basis, and managerial line responsibilities follow geographical lines. But at the central services level overall marketing strategy is formulated on a product divisional basis.

These examples give an idea of the ways in which the problems of developing a rational world-wide activity may be tackled. The difficulties of reconciling the possibly conflicting interests of geographical, product divisional, or head-office orientated activities are considerable. In Brooke's analysis it was found that there can be formal, structural ways round these dilemmas in the institution of highly sophisticated group structures with double or even treble lines of explicit communication between subsidiaries and head office to cater for the necessary contacts at product divisional level, international operations level, and central services level. But such a system is very cumbersome and, as Brooke admits, very few companies have in fact got as far as this. Moreover, this type of answer does rather have the air of a contrived solution to a particularly knotty problem, and it seems to me that the more likely evolutionary pattern will be for companies more and more to abolish any distinction between home and overseas sales – thus cutting out one intermediary, the international division – to limit the autonomy of overseas subsidiaries by subjecting them primarily to overall product divisional control, and to provide central or regional services at strategic points throughout the world activity in the same way as service stations may be placed along a motorway. However, this is still speculation; and in any case such a development would bring its own problems, particularly national political ones as the supra-nationality of the multinational corporation and its potential conflicts with national interests became increasingly appreciated.

#### References

1. 'Reaching World Markets'. National Economic Development Office, November 1971.
2. Brooke M Z and Remmers H L, 'The Strategy of the Multinational Enterprise'. Longman, 1970.

# The cost of safety in medicines

Arnold H Beckett

I welcome the opportunity to attempt to dispel the misconceptions which seem to occur from time to time in the minds of the public, the professions, the politicians and the planners concerning the relative cost of medication in the modern treatment of disease and in the maintenance of health.

Although the cost of medication represents but a small fraction of the total cost of the National Health Service, the need for the size of this fraction is sometimes challenged.

Advances in pharmaceutical sciences, in physical sciences, in biological sciences and in medical sciences have led to the introduction of more potent and selective drugs as well as to new delivery systems and methods for their administration to man. Precision in their use means more precise medical treatment than in a decade or two ago. Incorrect use or incorrect quality can result in inadequate treatment or even danger in medication with modern medicines. As the search to combat diseases not yet conquered by medical agents becomes more complex, as the drugs designed become more potent and specific and their delivery systems more sophisticated, inevitably the cost of the search, development and control becomes greater. In this presentation an attempt is made to indicate the various reasons underlying the present cost of medicines if adequate efficiency and safety of medication is to be ensured and also to indicate that medicines must not be regarded as 'ordinary articles of commerce'.

The speaker considers that safety and efficacy should be considered as indivisible in the context of medication despite the contrary view held by some authorities.

It is important in these considerations to distinguish between the drug i.e. active principle, and the drug preparation (drug formulation, pharmaceutical product or medicine) containing it.

Although in the last few years, many new drug products have been introduced onto the market, very few new drugs have been introduced. In Table 1 is given some indication of the costs of the introduction of new drugs to the USA market by UK and USA companies. Although the assumption that half the research and development costs of companies is involved in the search and development of new drugs may be questioned, and the influence of the introduction of new drugs by the companies to markets other than the USA market may reduce the cost per new drug introduced on to the USA market, the figure of £3 to 4 million per UK and £6 to 9 million per USA company for a new drug on the USA market must be considered as a not unreasonable estimate.

**Table 1** *Cost of introduction of new drugs on to the USA market***Assumption**

Half research and development costs involved in new drugs and half upon new products of existing drugs.

**UK Companies**

R and D expenditure 1965-70	=	£95 million (approx.)
Approx. for new drugs	=	£50 million
New drugs introduced 1965-70	=	9
∴ Cost per new drug (no lag)	=	£5 million*

Assume a lag of 3 years before the introduction of the new drug

R and D total 1962-67	=	£67 million
Approx. for new drugs	=	£34 million
New drugs introduced 1965-70	=	9
∴ Cost per new drug (3 year lag)	=	£4 million*

\*Note Figure high because some drugs from UK companies get on to the USA market.

**USA Companies**

R and D Global Expenditure 1967-70	=	£840 million (approx)
Approx. for new drugs	=	£420 million
New drugs introduced 1967-70	=	33
Cost per new drug (no lag)	=	£13 million
Cost per new drug (3 year lag)	=	£9 million*

\*Note Figure high because some drugs are marketed in countries other than the USA.

**Table 2** *Various features of 'Safety in Medicines'*

Drug Search and Development
Drug-Delivery System Development (Medicine Development)
Drug Production and Quality Control
Medicine Production and Quality Control
Prescriber Information and Protection
Medicine Distribution and Control
Patient Protection

Why are these costs so high? Are these costs necessary to produce efficacious and safe medicines and to produce correct drug treatment with the minimum of safety hazards for the patient? To attempt to answer these questions, the steps required in the introduction and control of drugs and medicines to ensure safety in medication will now be considered; in Table 2 these are summarised.

### Drug search and development

It is well known that in the search for new drugs, many thousands of compounds are synthesised or examined and screened for biological activity to produce a few candidates worthy of more detailed pharmacological tests and subsequent toxicity tests. For instance, one UK company examines annually some 6,000 chemical compounds to provide the one or two compounds which constitute new drugs for release into clinical use.

Many scientists from different disciplines are involved in the investigations. The physical scientists (i.e. chemists, pharmacists and physicists) deal with the synthesis of the compounds, their analysis, the purity of the compounds and their impurities and methods of analysis while the pharmacologist, biochemist, toxicologist, physiologist deal with establishing the action, distribution, metabolism and toxicology etc. of the compounds. The depth of the study obviously depends upon the result of the pharmacological screening tests. The principles for pre-clinical testing of drug safety have been outlined in a report of the WHO Scientific Group (Table 3a, 3b and 3c).(1)

**Table 3a** *Principles for pre-clinical testing of drug safety*

(From Report of a WHO Scientific Group 1967, No. 341)

Biochemical Studies	Apparatus
Absorption	Spectrophotometry
Distribution	Spectrofluorimetry
Excretion	Chromatography
Metabolism	Mass spectrometry
	Tracer techniques
	Polarography
	Immuno-assay
	Counter-current distribution etc.

**Table 3b** *Factors controlling drug metabolism*

(From WHO Report 1967, No. 341)

Species and Individual Differences

Enzyme Induction

Age of the Animal

Sex of the Animal

Pathological State of the Animal

*Recommendations*

(a) To determine those parameters i.e. plasma concentrations, biological half-life, drug distribution and metabolism that have an important relationship to drug effect.

(b) The type of study will depend on the drug and on the nature and stage of the investigation.

(c) Studies should be closely related to, and integrated with, all other phases of drug safety evaluation.

(d) Studies require investigators experienced in the work and well aware of their relevance and limitations.

**Table 3c** *Relationship between animal and human studies*

(From WHO Report 1967, No. 341)

- 
- 1 Some animal studies before knowledge of absorption, distribution and metabolism of the drug in man.
  - 2 Before laboratory studies are completed, some studies of drug absorption, distribution and metabolism in man – facilitates choice of best animal species.
  - 3 Before (2) preliminary study to ensure that risk to humans receiving drug is minimised – small doses at first.
    - (a) methods for the determination of the drug and possibly its metabolites in blood and urine.
    - (b) full pharmacological study of the drug and acute and subacute toxicities and histopathological evaluation: the latter to involve at least two species, one of which should not be a rodent.
  - 4 Drug to patient – illness or other treatment may interfere with the absorption, metabolism or effect of the drug.
  - 5 Feedback of information on adverse reactions – applies to drug but in the particular formulation used.
- The use of any new drug product (medicine) should be monitored for two or three years after it has been placed on the market.
- 

The costs involved in these studies are great and inevitable when the need for the experts and their supporting staff from a variety of disciplines, the need for complex and expensive equipment and the need for extensive animal studies over long periods are accepted as essential.

#### **Drug delivery system development**

In general, the drug itself is not used as medication in man, but a pharmaceutical product i.e. medicine, is used as the drug delivery system to man. Factors such as particle size of the drug, salt form, diluent, lubricant, compression of tablet, type of capsule etc. can alter the rate at which the drug becomes available for absorption in man. When more sophisticated formulations are used, as in sustained release preparations or enteric coated forms, further variables may be introduced into the rate at which the drug is absorbed.

Detailed investigations are necessary to establish the type of drug which is required. Storage of the product may influence the date of drug release. Different excipients may alter the rate of decomposition of the drug.

The costs have to be borne in each project although the majority of projects will be aborted before the clinical trial stages on a very few products of the research.

Studies to deal with these points must be pursued even though toxicity results at a later stage may result in discontinuation of the plan to proceed to clinical trials. The cost of safety in medicines is involved in failures as well as in the medicines finally marketed.

**Drug production and quality control**

The compliance with official standards is merely sufficient to guarantee the quality and safety of the drug. The scaling up from laboratory to bulk preparation may introduce new factors and necessitate further investigation of impurities. To ensure precise specifications for the drug, increasing use is being made of more sophisticated and expensive instrumentation.

**Medicine production and quality control**

Some of the causes of lack of quality in medicine are listed in Table 4a (Chemical Aspects) and Table 4b (Biological Aspects). These aspects must receive attention to ensure the quality of the product.

In 1969 a WHO Expert Committee issued a report (No. 418)(2) on 'Specifications for Pharmaceutical Preparations' i.e. medicines. Some of these recommendations for good practices in the manufacture of drugs and medicine are summarised on Table 5. The principles of quality control are summarised on Table 6.

**Table 4** *Causes of lack of quality in medicines (preparations)*

---

**a Chemical aspects**

- Unsuitable drug quality
  - Unsuitable drug physical form
  - Unsuitable quality of adjuvants
  - Interaction of drug with adjuvants
  - Manufacturing hazards
    - Partial decomposition during compounding
    - Inaccurate compounding
    - Incomplete mixing
    - Chemical cross contamination
    - Process errors
    - Microbial contamination
    - Packing errors
  - Impurities from containers
  - Uptake by containers
- 

**b Drug availability and biological aspects**

- Unsuitable drug particle size
  - Unsuitable drug physical form
  - Unsuitable salt of drug
  - Unsuitable capsule contents for capsule form
  - Unsuitable adjuvants for drug in capsule or tablet
  - Unsuitable product coatings
  - Unsuitable enteric coating
  - Unsuitable base for drug in ointment or suppository
  - Powder compaction in capsules
  - Microbial contamination in non sterile product
  - Non sterility in sterile product
-

**Table 5** *Good practices in the manufacture and quality control of drugs and medicines*

---

Attention should be given to the following:

- 1 Personnel
  - 2 Premises
  - 3 Equipment
  - 4 Sanitation
  - 5 Starting materials
  - 6 Manufacturing operations
    - (a) cleanliness
    - (b) equipment and containers
    - (c) precautions against contamination
    - (d) manufacturing personnel
    - (e) manufacturing procedures and written instructions
    - (f) batch manufacturing records
  - 7 Labelling and packaging
  - 8 Quality control system
  - 9 Self inspection
  - 10 Distribution records
  - 11 Complaints and reports of adverse reactions
- 

**Table 6** *Principles of pharmaceutical quality control*

---

**a Product quality specifications**

*Starting material* (Drugs and Adjuvants)

- (a) Physical characteristics
- (b) Specific identification tests
- (c) Purity tests
- (d) Assay method

*Half finished product*

- (a) Suitability for further manufacturing operations
- (b) Acceptability for manufacture of medicines

*Finished product (medicine)*

Precise details for acceptability of the medicine – during contact, etc.

---

**b Production control**

*Environmental control*

Suitability of premises, equipment and staff

*Manufacturing control*

- (a) Factors in the processes
- (b) Adverse extraneous factors such as:  
contamination of starting materials, 'half-finished' products and end products.

*Final control of end products (medicine)*

To ensure:

- (a) Compliance with established specifications.
  - (b) Products have been manufactured by the prescribed procedures.
-

**Table 7** *Formulation effects in drugs leading to therapeutic non-equivalency of drug product (medicine)*

<i>Drug</i>	<i>Formulation variable</i>	<i>Assessment or observation</i>
<b>Antibiotics</b>		
Chloramphenicol	Different brands – particle size, polymorphic forms, formulation	Some products showed poor biological availability. FDA 1968 – cancelled certifications of three manufacturers and five repackers of capsules because ‘substantial doubt about the safety and efficacy’ of the products.
Tetracycline	Capsules – different sources	Differences in dissolution rates and blood levels.
Oxytetracycline	Formulation in capsules, different brands – particle size and formulation	Seven out of sixteen commercial series gave serum levels below accepted minimum therapeutic levels. Seven out of eleven brands gave lower and more variable blood level than the original brand capsules.
Penicillin V	Different brands; formulated differences giving different disintegration times	Different serum levels.
<b>Hypoglycemic agents</b>		
Tolbutamide	Reports that some patients whose hyperglycemia had been controlled by a product, went out of control when another brand was substituted. Differences in formulation involving the salt form used and the excipients can cause differences in biological availability.	
<b>Antifungal agents</b>		
Griseofulvin	Differences in plasma levels obtained with different products – particle size and formulation factors involved.	
<b>Anti-inflammatory agents</b>		
Phenylbutazone	Big differences in absorption characteristics in many commercial brands – differences in formulation leading to differences in disintegration and dissolution of tablets.	
<b>Anticoagulants</b>		
Phenindione	Different commercial brands giving different systemic availability – formulation differences leading to different dissolution rates.	
<b>Steroids</b>		
Prednisone	Chemical failure with some products – difference in dissolution rates.	
<b>Sulphanamides</b>		
Sulfisoxazole	Different preparations gave different systemic availability.	



**Table 8** *Lack of safety produced by changes in drug formulation*

<i>Drug</i>	<i>Toxic symptoms upon change of formulation but same dose</i>
Aspirin (enteric coated)	<i>Product A</i> – little success in treating rheumatoid arthritis <i>Product B</i> – toxic systems; reduction of dose required.
Diphenylhydantoin capsules	<i>Capsule</i> – <i>Calcium sulphate diluent</i> – patients controlled adequately. <i>Capsule</i> – <i>lactose diluent</i> – ‘epidemic’ of toxic symptoms in Australia.
Chlorthiazide-potassium chloride tablets	Some formulations but not others caused numerous intestinal perforations, some of them fatal.

It is becoming realised increasingly that chemical equivalency of a drug in a medicine is not synonymous with therapeutic equivalency or relative freedom from toxicity.(3) Some of the examples which have led to this are shown on Table 7. Not only can there be differences in efficacy in the products containing the right amount of drug of the correct quality, but lack of safety can be produced by differences in formulation (Table 8).

In the USA this led to a White Paper in 1969 by a Sub-Committee of the Policy Advisory Committee, on the problems of ‘Therapeutic equivalence of chemically equivalent drugs’ (really of medicines) from which I quote: ‘Recent reports of considerable variation in the serum levels, and therefore in the probable biological activities, of equal doses of certain drugs marketed by different manufacturers, focus attention upon an important determinant of drug efficacy, These variations indicate that therapeutic equivalence, or equal biological activity, cannot necessarily be inferred from equivalency in the chemical constitution of different formulations of the same drug.

‘It would seem reasonable for the FDA to require that the generic manufacturer submit, in addition to evidence of chemical equivalence and purity, data on dissolution rate and data from other *in vitro* tests demonstrating equivalency. However, if there is evidence that *in vitro* evaluation or animal tests do not correlate well with pharmacodynamic effects in man, there may be need to resort to clinical tests. In this way, the principle of generic prescribing based on therapeutic equivalence may become acceptable to the medical profession and be supported by the pharmaceutical industry.’

Also the Academy of Pharmaceutical Science adopted a declaration on Biological Availability in 1968 (Table 9).

**Table 9** *'Biological Availability' – the Academy of Pharmaceutical Sciences declaration adopted 1948*

---

Prior to the initial distribution of a drug product or modifications of an existing product, every manufacturer should be obligated to perform tests which are appropriate and sufficient to demonstrate the clinical safety and efficacy claimed for that manufacturer's product. In particular, in the absence of such tests, it cannot be assumed that the product will exhibit clinical acceptability simply because an apparently identical product is already marketed.

---

Some of the critics of the cost of medicine quote that generic manufacturers can produce medicines which comply with official chemical standards for the product more cheaply than the medicine originators. However, these standards alone do not ensure the efficacy or safety of the product as indicated above.

Now that these facts have been established, what are the medicolegal responsibilities of medical practitioners with regard to medicine safety and the costs involved? These problems are causing concern; I quote from an article by Professor D H Mills, Clinical Professor of Forensic Medicine and Pathology, University of Southern California.(4)

*'Medical judgement issues in choosing one of several "equivalent" drugs'*  
 'Until recently many have presumed that generic or chemical equivalency is synonymous with therapeutic equivalency. Why and how such a presumption has developed is quite complex and beyond the purview of my presentation. However, this presumption has been enough until recently to allow physicians the legal right to permit generic substitution or to prescribe generically without specific concern of medical or legal repercussions. In medicine, as elsewhere, ignorance is bliss and the commonly accepted proposition of chemical equivalency as being related to therapeutic equivalency has prevented physicians from being examined in court on this particular type of judgement decision.

'In view of recent studies, however, the protective presumption referred to above is on extremely shaky ground, and the presumption may be reversed completely. That is within the very foreseeable future, the relationship between physicians and their patients may prevent doctors from prescribing generically at all, unless they are capable of offering authoritative proof, that, in any specific instance, chemical and therapeutic equivalency are synonymous. In effect as scientific evidence becomes more available to the medical profession, a presumption *against* equivalency will become the medical and legal basis of the physician's prescription responsibility.

'From a legal standpoint there are those who would argue that the difference between chemical and therapeutic equivalency is academic. On an individual basis how would any patient be able to prove that he was damaged because of a physician's improper choice of a chemically, but not therapeutically, equivalent drug? For instance, let us assume that a physician prescribed phenylbutazone, generically, for a patient with arthritis. Let us also assume that this drug proved ineffective, whereupon the physician then prescribed steroid therapy which ultimately induced aseptic necrosis of one or both femoral and/or humeral heads. That the patient has suffered damage is obvious. Whether the patient will be able to show that the physician was negligent in his judgement decision to prescribe phenylbutazone generically is much less obvious. However, in a court of law, if the patient is able to produce any studies through expert testimony showing that the specific drug involved exhibited therapeutic non equivalence between some of the chemically equivalent products, he will have gone a long way in being able to prove his case against a physician. Remember, the physician's duty to his patient to prescribe reliable drugs is an affirmative one. When he loses the presumption that chemical equivalency is synonymous with therapeutic equivalence, he then must rely on specific studies of therapeutic equivalency alone (or at least upon the next best evidence: biologic availability). Of course, such lawsuits are not yet in existence, probably because few patients or their attorneys are capable of or willing to take the time and energy to resolve this issue in court. However, the present lack of activity constitutes only a breathing spell. If present trends continue, I anticipate such legal attacks.

'Are there any alternatives? One is to limit the physician's prescription to drugs with evidence of proven efficacy. This would, of course, eliminate many generic prescriptions in the absence of affirmative studies. Except for questions of cost, this alternative is clearly best for patients and their doctors.'

### **Prescriber information and protection**

If the medical practitioner is to use the correct medicine of the appropriate quality in the correct manner, the need for information becomes obvious.

The complexity of the problem necessitates the use of well trained scientific personnel to be in contact with doctor and industry. A feed-back route of information on side effects, drug interactions, drug-food interactions on the *particular product* of the drug and not just the generically named drug is essential.

This must be a cost built into this control of safety and efficacy of the particular product.

### **Medicine distribution and control**

The introduction of many of the modern medicines has led to great benefit to mankind. However, the misuse of drugs is causing increasing concern.

The normal laws of the market place cannot be accepted if one is concerned about the safety of medicines. Increasing legislation has to control the manufacture of drugs and medicines and their distribution. These requirements, because medicines must not be considered as ordinary articles of commerce, add to the cost of medicines.

### **Patient protection**

The increasingly potent drugs and their interactions, and the complexities of evaluating and considering the efficacy and safety of alternative forms of medication, results in the need for a well trained person to act as a buffer between doctors and patients. The modern well trained pharmacist constitutes this last bastion of safety. He must be granted the appropriate salary for this important work as a professional man without having to subsidise the service by undue dilution of the work with trading activities.

In my opinion this final step in the safety of medicines has not received adequate attention. Thus the public in general and many politicians have failed to understand that medicines are not ordinary articles of commerce and are contributing indirectly to drug misuse problems amongst our youth who have not been taught by example the true role of medicines in our society.

I trust this account has indicated that efficacy and safety in medicines cannot be bought cheaply. In the Sainsbury report it is stated 'There would be little inducement for firms to take on the specially high risk of searching for the particular medicines which may be eagerly desired in medical practice if there were to be no possibility of unusual profit, and a high possibility of failure after considerable costs had been incurred'. I accept this statement but commend the responsibility of pharmaceutical companies who have played a leading role in ensuring the establishment of quality control techniques and research techniques which not only have led to a therapeutic revolution but also one achieved with the maximum of safety to the recipients.

### **References**

1. Principles for Pre-clinical Testing of Drug Safety. Report of a WHO Scientific Group, 1966. Technical Report No. 341.
2. WHO Expert Committee on Specifications for Pharmaceutical Preparations 1969. Technical Report No. 418.
3. See Articles in Drug Inf. Bulletin, 1969, 3, page 6-118. Drug and Therapeutic Bulletin 1971, 9, 65-68. Prescribers Journal, 1971, II, 48-52.
4. Mills D H, Drug Inf. Bulletin, 1969, 3, 92.

# The cost of compliance with international regulations

Gordon C Hellyer

## The increase in registration requirements

The tremendous increase in legislation controlling medicine since the early 1960s prompts the need to consider whether all the requirements are strictly necessary, and to examine the cost to the pharmaceutical industry. Consideration will, in the main part, be restricted to the regulations for registration of ethical pharmaceuticals, which, because of the manner of their promotion, are in the main, only available on prescription. I will also be looking at the regulations from the point of view of an international pharmaceutical company based in the United Kingdom.

In the early 1960s most countries had laws for narcotics, for example, in this country certain ethicals were covered by the poisons' rules, Therapeutic Substances Act, and the Dangerous Drugs Act, but procedures for registration were still relatively simple. There were no registration formalities, and it was not until the first script written by a GP had reached the Pricing Bureau, that the Ministry of Health took any action. The action from the Ministry was to request information on the medicine, in particular, clinical information which was then considered by the Committee on the Classification of Proprietary Pharmaceutical Products. This committee awarded the product one of several categories. If you were fortunate enough to receive a favourable category, then your product was freely prescribable; if the category was unfavourable, then your product was still prescribable but with restrictions on the frequency of prescription. In fact, unfavourably classified products were rarely successful although there were some notable exceptions.

The advances in medical chemistry during the 1960s meant that much more potent medicines were available which, if incorrectly used, could result in untoward side effects. The legislation which grew up was directed primarily to safety, but this was also often coupled with efficacy, and control in many countries also extended to include promotion and pricing.

In the UK Sir Derrick Dunlop as Chairman of the Committee on Safety of Drugs stated that 'the Committee's remit does not impose upon it any responsibility to consider the efficacy of drugs except in so far as their safety is concerned'. (1) It is never possible to completely separate safety and efficacy so that toxicological findings must always be considered in relation to the intended use of the product. This does illustrate a fundamental

need for flexibility in any system of control. Such flexibility is essential to harmonious relationships between government and industry.

In the United States the procedures developed are rigid and detailed and contrast most markedly with the system in this country. The Committee on Safety of Drugs depended on a voluntary collaboration with industry, and a promise was obtained by the ABPI and the PAGB that their members would not submit for clinical trial or market any new medicine against the Committee's advice. This promise was loyally observed.<sup>(2)</sup> It is very important that the dialogue which has grown up between the Committee on Safety of Drugs, the equivalent Committee for Agricultural Products (Veterinary Products Safety Precautions Scheme) and the pharmaceutical industry should continue under the legislation which has followed the Medicines Act.

In 1971 at the annual dinner of the ABPI the retiring President and Chairman of Beecham Pharmaceutical Division, Mr G J Wilkins, stressed the need to preserve the informal and flexible approach which has made the Committee on Safety of Drugs the object of admiration and envy in other parts of the world. In reply, Lord Aberdare, Minister of State at the Department of Health and Social Security said that 'We have every intention of retaining the greatest possible degree of flexibility in the operation of the Act and we believe that you will find that the system will work very much in the way that the voluntary system has worked in the past. I would like publicly to pay tribute to the way in which your association and the Proprietary Association of Great Britain, and the individual member firms of both organisations, have co-operated so fully and completely with the Committee on Safety of Drugs since its inception in 1963. Not only has the partnership provided a firm foundation on which to build for the future, but it has been of inestimable value in ensuring that the people of this country receive only medicines of the highest quality and the greatest possible degree of safety. I feel sure that in the new system this happy combination of responsibility and expert knowledge will continue'.<sup>(3)</sup> This assurance augurs well for the pharmaceutical industry in this country. There have, however, been less happy predictions made as a result of new regulations in other countries.

### **Registration systems throughout the world**

One way to approach this formidable subject is to consider how registration requirements throughout the world will affect the programme that must be drawn up by a pharmaceutical company for the development of a new ethical medicine. The work carried out by the new product development department of an international pharmaceutical company must be geared to marketing on a world-wide basis. In Beecham Research Laboratories we compare the regulations overseas with UK requirements, and the

requirements of the Food and Drug Administration in the United States. Generally, if we meet the requirements of these two authorities, then we will not be unprepared for requirements elsewhere. Nevertheless, many nations are now in the process of setting up their own regulatory bodies, and there is always the danger that they may introduce unforeseen requirements. A close watch on drug legislation is essential for companies exporting pharmaceutical goods.

I will make the following division of control systems into three groups:

- 1 New drug submission
- 2 Product registration
- 3 A visa system.

France is the only country to have a visa system, and the essential characteristic is that listed experts are employed to carry out tests on all products submitted for a visa. The extent of work checked by the expert is not defined and is usually determined in collaboration with the manufacturer who will have submitted all his information for the speciality. When all the information has been assembled by the manufacturer, including the results from the experts, it is set out in an approved form and submitted direct. Our experience has been that toxicity studies of up to six weeks' duration in two species, pharmacological and clinical studies may be repeated, in addition to a check on the manufacturer's control procedures for the speciality and the raw material used.

With the exception of France, in all other countries the responsibility for the new medicine lies fully with the manufacturer or, if more applicable, the importer or agent in that country.

The basic principle of the product registration system is that a legal form containing information on the new product must be approved by the authorities before the product is offered for sale. About seventy-six countries including Japan, Spain, Italy, Germany, Holland, Austria, Belgium, Greece, Scandinavia and Latin America, enforce product registration. The requirements are very variable, but may approach the FDA standards, particularly in the Scandinavian countries. In Sweden proof of both efficacy and safety of new drugs has been required since 1944. Samples of the product are often required and attention is paid to labelling and methods of analysis for active ingredients and excipients. Often these methods of analysis are checked in government laboratories, e.g. Venezuela. In Belgium the manufacturer is required to file methods of analysis for the dyes used in the gelatin capsule. A declaration of these dyes is then required on all labels and package inserts.

Negotiation on price is also required in Belgium and the price agreed will not be greater than the country of origin.

A further requirement peculiar to the Belgian market is the need for all

formulations to be at 100 per cent potency at the end of shelf-life. This is quite unlike the usual requirement, for example, in the British Pharmacopoeia that potency should be within the published limits. This often necessitates adding an overage at the time of manufacture for products sold in Belgium. Many countries, for instance Germany, insist on local clinical trials in addition to studies carried out in the country of origin. It is not unreasonable to ask for additional clinical work under local conditions, and companies will often require these studies for promotional purposes. For many countries, Venezuela and other Latin American countries, a certificate of free sale in the country of origin is required. This means that a product must have been approved and offered for sale in the country of origin before it can be registered overseas. Rigid adherence to this requirement is, of course, ridiculous in the case of drugs that are only developed for one particular market, e.g. antimalarial drugs. There are also other more subtle complications of marketing and licence that may limit the countries available for a new product. For a British company wishing to export, the problem remained relatively easy provided that the product is marketed in the UK and certificates of free sale are readily available. However, the Medicines Act 1968 as presently constituted does not apply to products for export and overseas governments may demand proof of licence rather than certificates of free sale. There is, however, provision within the Act for the licensing authority to issue an appropriate certificate. It does, however, appear that a British company must obtain a licence for the UK before exporting the product and that there will be instances when a licence will have to be obtained solely for a product intended for export. Discussions are at present under way between the ABPI and the Ministry to resolve this problem which has an important bearing on British companies that sell a large part of their output overseas. For example, Beecham Group won the Queen's Award this year, for the third time, for the export of human and veterinary prescription medicines to more than a hundred countries. In the year ending 31st March 1970, the pharmaceutical division's exports amounted to 58 per cent of total sales.

In Japan, clinical trials can usually be started on the basis of studies carried out in the country of origin, but before marketing, it is necessary to carry out much of the work required for registration on Japanese soil. Acute, subacute and chronic toxicity studies, pharmacological work and teratogenicity studies must be repeated. Stability studies must also be repeated in Japan and will be continued to the duration of the shelf-life regardless of the fact that these time-consuming studies have already been fully documented in the country of origin. The clinical requirements in Japan are also defined in terms of the number of cases to be submitted. With antibiotics, the minimum number of cases for each indication is defined, and in these cases a certain percentage are required where the



bacterial organism responsible has been identified. For example, in bronchitis forty cases are required, and in half the organism must be identified. This means that for an oral presentation of a new antibiotic, several hundred cases must be submitted. This may present no great problem for an oral presentation, but it is also required for a parenteral presentation where it takes a long time to collect together this number of cases. The use of antibiotics by the intravenous route is obviously limited, nevertheless the same requirements apply. In Japan the price of new drugs is controlled and a new drug should have an advantage over an existing drug. In the case of antibiotics, if, as a result of either increased activity or better absorption, a lower total daily dose can be used, then in order to obtain even the same pricing structure for the new compound, one must show that at half the dosage or less, the compound is as effective as the higher dose of the established compound. This policy means that there is little point in trying to market a product with only a small advance over an existing product since only clear cut advantages such as twice the efficacy will qualify for an acceptable price structure. Even when the registration application is made, there is still a requirement for listing, and negotiation of price, so that the final launch may only be possible three or four years after the product was approved for marketing in the country of origin. The loss of sales over this period, and the cost of repeat studies (about £75,000 per product) make registration of new products in Japan extremely costly.

New drug submissions are required in the UK, and USA, and such countries as Canada, Australia, India and Ireland. Essentially this system relies on adequate documentation, in many cases an inspection of the premises and an expert assessment of the evidence submitted. Although these systems were originally agreed for new products, they have tended to approach the registration system and now extend to all new products. Evidence is usually submitted at two stages in the development of a medicine – firstly, to allow clinical trials, and, secondly, to give approval for marketing. Information provided by the manufacturer at the first stage will include such details as the method of manufacture, the formulation, the specifications, and quality control of the active ingredients and the final formulations, stability studies, acute, subacute and chronic toxicity studies. The duration of the toxicity studies will be related to the duration of proposed clinical use. In the case of an application for an antibiotic, three months' chronic toxicity data in two species will probably be sufficient. For medicinal compounds that are administered to man for longer periods, then six months' toxicity studies would probably be required.

Studies are also necessary on teratogenicity if the drug is to be given to women of child-bearing age and the submission will also contain a report on the pharmacological, metabolic, and biochemical studies. An outline will also be required of the proposed clinical trials.

A further application is prepared on completion of the clinical trials and will contain the results of these trials together with an up-dating of the information previously supplied. For example, the chronic toxicity studies may have reached twelve or eighteen months' duration and if appropriate, results may be available from long-term carcinogenicity studies.

In this country, under the Medicines Act of 1968, the Secretary of State for Social Services and the Minister of Agriculture were required to act as a licensing authority to issue licences governing the marketing, importation and manufacture of medicines for human and veterinary use. From 1st September 1971 new products in the UK have been subject to a licensing system. The Committee on Safety of Drugs remains, but is now referred to as the Committee on Safety of Medicines. Certificates are required before manufacturers can undertake clinical trials, and licences are required before products can be marketed. Certificates will be granted for a period of two years, and product licences will be renewable after five years. A scale of fees for licences and certificates has recently been issued by the Department of Health and Social Security. Licences are also required by manufacturers related to the class of products that they intend to manufacture.

Products already under clinical trial and products already on the market are entitled to certificates and licences of right. In order to qualify, pharmaceutical companies are required to submit particulars on each product in their present range.

The Act includes ethical drugs, proprietary drugs, (products sold over the counter), and veterinary products for sale to the profession as well as direct to the farmer. Veterinary products were previously governed by the Veterinary Product Safety Precautions Scheme which applied only to products sold direct to the farmer. The new Act will cover all products for agricultural use and, further, test certificates must be filed before field trials can be started. There are important differences in emphasis between the development work necessary for human and agricultural products. The purpose of the Veterinary Products Safety Precautions Scheme was to safeguard human beings (whether they be users, consumers of food substances from treated animals, or other members of the public), livestock, domestic animals, and wild life, against risks from veterinary products. The scheme was not concerned with the efficacy of veterinary chemicals but only to provide for the safe use of such products.

In effect, the studies undertaken are orientated more towards residue studies than long term toxicity studies. Tests in the definitive species could usually be undertaken at a fairly early stage and help establish the most suitable formulation for marketing. In the Act there are exemptions in respect of medicinal tests on animals but these will only apply to preliminary studies where the benefit of the treatment is unknown.

The information required for the registration of veterinary products is now very similar to new medicinal products, and I suspect that many companies will look closely at the economics of developing new agricultural products.

These new regulations bring us a little closer to the system which is operated in the USA under the Food and Drug Administration. Information is filed with the FDA by the pharmaceutical company as notice of claimed investigational exemption for a new drug, usually referred to as an IND. An IND is usually filed at three phases during the development of the drug. An IND phase I allows several days administration to man, and can be filed on a repeated dose study in two species of two weeks' duration. As the toxicity studies continue, so the IND phases II and III can be filed, and an extension permitted to the duration of clinical usage. At the phase III level, full scale clinical trials can be carried out. It now appears that these clinical trials have to be carried out in accordance with guidelines laid down by the FDA. Upon completion, a 'new drug application' is filed and a request is made to market the new medicine.

The pronouncements made by the FDA have had an influence on the requirements for registration that have been adopted throughout the world. Obviously statements made by the FDA on such subjects as biological availability and metabolic studies influence the development programme planned by pharmaceutical companies for new products.

One example of the FDA's recent activity was the Drug Efficacy Review. In 1966 the FDA asked the National Academy of Sciences and the National Research Council to set up a panel to evaluate more than 3,000 marketed preparations approved by the FDA between 1938 and 1962. The FDA claim that these drugs were marketed on proof of safety only, and as a result of a report by the panel, manufacturers are asked in many cases to provide new evidence of efficacy as well. It should also be emphasised that the NAS/NRC review includes 'related drugs' i.e. drugs that are the same as those which have NDA's but marketed by other manufacturers without an NDA. It was stated recently that 20,000-40,000 products could be affected. The most distressing aspect I believe, is that it was necessary for the list to be published at all. So much better for both sides concerned if there could have been collaboration outside the public arena.

Combination drugs account for about 50 per cent of the products that were involved in the NAS/NRC reviews. The reviews were particularly critical of these fixed dose combination drugs and at one stage there was a danger that the FDA would remove from the market all but a handful of these combination drugs. The FDA Commissioner has, however, recently stated that no massive recall is planned. Nevertheless, the importance of the issue is evident when it is considered that 40 per cent of America's best selling drugs are fixed dose combinations. One American pharmaceutical

company has recently stated that as a result of the NAS/NRC reviews the cost of supporting their marketed products has risen to about 30 per cent of their budget.

The publication of these reviews has not surprisingly produced a strong protest from the pharmaceutical industry. The Pharmaceutical Manufacturers Association feels that the FDA apparently intends to go beyond the law's requirements that drugs be safe and effective to ensure that they can be used rationally. The FDA have, however, recently stated that they are concerned with all phases of the drug business. The FDA Commissioner recently stated his concern –

- with all manufacturers large and small;
- with the discovery and investigational use and development of all new drugs;
- with the evaluation of safety and efficacy of new products offered to the profession;
- with the quality controls that assure the identity, strength, quality, purity, and reliability of the product that comes off the production line and into the hospital, and the community pharmacy;
- with the labelling and promotions of these products;
- with the experience of these drugs in the hands of the practising physicians and indirectly with the costs of these products.

There is a need, as the President of the Pharmaceutical Manufacturing Association recently stated, for the pharmaceutical industry to improve its relations with the Food and Drug Administration.

There is also a need for harmonisation of the laws affecting registration in different countries. It is becoming increasingly time consuming for the pharmaceutical manufacturer to provide the differing sets of data required by the various countries. For example, one would hope that all countries would accept the same species for teratogenic studies, or alternatively would leave the selection of the species to the discretion of the pharmaceutical company. Again, scientific work should be accepted regardless of the country of origin provided that the work is up to a generally agreed standard, this would avoid the repeat studies that are so costly and time consuming and cannot really be claimed to have any purpose except to delay the approval of a new product.

The European Economic Community recognises the need for harmonisation, and looks forward to a final goal when there will be a free flow of pharmaceutical products without import and price restrictions. Progress in Brussels has been slow, and so far only one directive of consequence to the pharmaceutical industry has been adopted. This directive adopted in January 1965 relates to national licensing systems and the marketing of pharmaceutical products for human use.

The new regulations for the testing of pharmaceuticals which came into force in Germany in June 1971 were based on a draft EEC directive covering analytical, pharmaco-toxicological and clinical standards and procedures. The amendment of the German Drug Law existing in draft form at present is in line with the EEC directive of 1965.

A draft second council directive on the harmonisation of legislative and administrative provisions relating to pharmaceutical specialities has also been seen.

The progress towards harmonisation being made in Brussels will have important implications for the British pharmaceutical industry and as we enter into Europe, it is essential for our representatives to enter into these discussions as soon as possible.

We have also seen reports from the study group set up by the European Free Trade Association.(4) The World Health Organisation and the United Nations are also known to be actively considering these matters and will perhaps be able to use their authority to influence world attitudes. It is most essential that emerging nations pay attention to existing procedures and receive guidance on setting up their own legislation rather than creating new organisations of their own design.

Specifications, processes of manufacture, analytical methods and formulations of pharmaceutical products are under constant review and any registration system must allow for improvements to be notified and approved with the minimum of effort. Registration procedures must lengthen the development programme for new products and companies are conscious of the time taken by some authorities to approve submissions and we would always hope that government regulatory agencies will retain sufficient technical staff to deal with submissions as quickly as possible.

I would say, however, that in this country we are fortunate that submissions have always been dealt with rapidly and within a predictable time that can be built into the development programme.

Basic and sometimes extreme differences in medical tradition, drug usage, industry controls and political and economic thinking in general between one country and another are largely responsible for developing government regulations and practices.(5) Those of us in the industry who have looked at the products successfully marketed by companies in other countries have often had cause to reflect on the differing medical practices from country to country. To retain the traditions of medicine, trade and government within individual countries will always raise difficulties for the harmonisation for drug legislation. I would, however, hope that at least on scientific requirements we might have agreement within the next few years.

### **Compliance with registration requirements**

Pharmaceutical companies must provide the expert staff and facilities to

carry out the specialist studies required for registration and to deal with the legal and editorial aspects of drug documentation and registration. There are several ways that a pharmaceutical company can approach the organisation of the development work required to comply with registration requirements.

I will illustrate the type of approach that has been adopted within Beecham Research Laboratories.

In June 1969 a decision was made to establish a single department which would contain all the new product development activity, an organisation structure for the new department was produced, and a system for controlling projects that are undertaken within the department. It was recognised that in the development of a new product, co-ordination between the new product development and other parts of the pharmaceutical division was essential. A liaison department was created to provide this co-ordination function, and members of the department maintain links with marketing, production and within the various parts of new product development.

New work within development can only be initiated by a formal request made to the liaison department and all work undertaken in new product development is allocated a code number. This number is recorded on diary sheets kept by scientists so that subsequently cost can be established for work carried out. The department is also responsible for drawing up networks for products under development, and we are at present evaluating a PERT system which schedules, co-ordinates and disseminates information on development compounds.

The department also has a documentation unit which is responsible for preparing submissions on new products for this country and overseas. Submission dates are key events on the development networks drawn up for a new product. The network also indicates the completion dates for the various studies required for filing on a new product. We are, therefore, able to predict accurately the earliest date that documentation can be prepared for registration of a new product. The documentation unit is responsible for registration in this country and for supplying the information required for registration by the marketing companies overseas. Local registrations are the responsibility of the individual markets since they have the detailed knowledge required for registration, but the New Product Liaison Department is involved to make sure that filings are consistent in the various countries and that any relevant information is supplied. The department needs to be aware of international regulations, and advises on the standards required to meet these requirements.

The overall responsibility of the department is to ensure that registration programmes are kept to schedule and that products reach the market in the minimum time.

We are very much aware that improving technology leads to a multiplicity of results which must be carefully appraised for their true utility. Generally speaking, in a large pharmaceutical company, the internal standards must be set higher than the current registration requirements. The actual information supplied must in its turn, be tailored to the requirements of each individual country. Unnecessary information can so easily be supplied and can become an obligation for future registration, either at the request of the authorities or because of a company's natural tendency to try again what was successful the first time.

Concern has been expressed in the past at the overall effect of new regulations on the pharmaceutical industry. Will pharmaceutical innovation be reduced? Will the increasing cost of development eliminate the smaller companies and cause the remaining companies to amalgamate into larger units? The ever increasing cost of development is undoubtedly one of the reasons for the reduction in the number of new products available, and in some fields where the demands of the registration authorities are particularly onerous may make a pharmaceutical company consider very carefully whether it can afford the time and costs involved. Some of these aspects were considered by Djerasi with specific reference to the requirements for new oral contraceptives.<sup>(6)</sup> Djerasi considered the different FDA requirements for new fertility control agents. For example, the FDA require two-year toxicity studies in rats, seven-year studies in dogs and ten-year studies in monkeys. Contraceptives are exceptional in that the FDA define the animal species necessary for toxicity tests. The stipulation of the animal species to be used in any toxicity studies is always a difficulty, since the species should be selected which most resembles man in the metabolic handling of the drug. The FDA also defines 1,000 women studies for 10,000 cycles as a requirement for clinical trials on a new contraceptive. No company needs reminding that any increase in duration of drug development reduces the period of patent life that is available to recoup costs before the patent life expires. This is a good case for extending the patent life of pharmaceutical products.

Returning to Djerasi, he believed that the costs of development have escalated to such an extent that the creation of fundamentally new fertility control agents is unlikely. Similar conclusions can also be reached for other drugs which need to be administered to normal populations for long periods to establish their efficacy. I cannot really accept these pessimistic judgements based on present knowledge, since they do not allow for new discoveries that may be made in the future. Preparing quantitative estimates of the return in a particular field is impracticable without knowing in advance the breakthrough that one hopes to make.

With the job control system at present in operation within our laboratories, we can apportion costs directly to independent developments, and

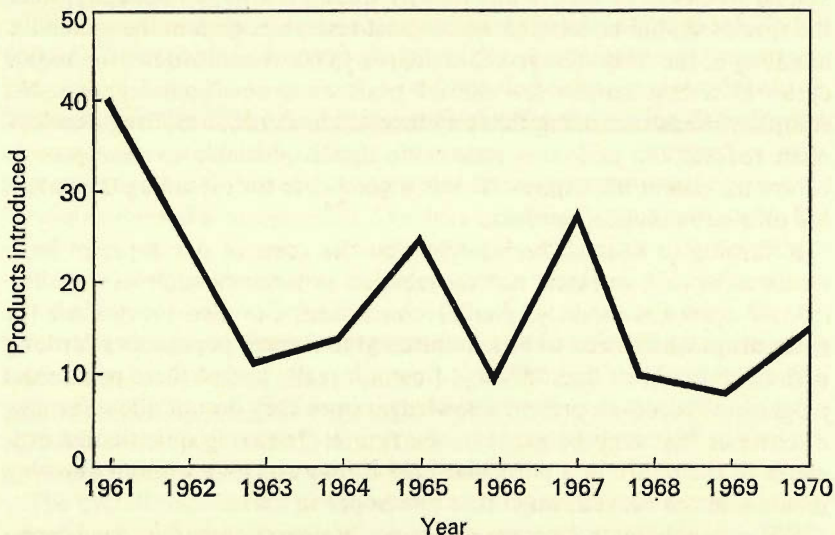
consequently we will have very accurate historical costs emerging over the next few years.

However, we are unable to forecast the failure rate of drugs in research and development as in general there is no previous experience and consequently the full development costs involved in launching a new drug entity are extremely speculative. Over the last five years as our research and development costs increase so we find that development is taking a greater percentage of the total. A further reflection of the increasing costs of drug development can be seen from some recently published figures(7) showing the number of new single chemicals introduced in the United States over the last ten years (see Fig. 1). The downward trend is also seen in Fig. 2 which also shows, perhaps predictably, the dramatic reduction in the number of combination products.

You will also notice a rise in the number of duplicate drugs introduced in 1970, this is partly due to cross licensing between manufacturers. This trend will probably continue as manufacturers try to increase their return on the higher development costs.

The reason for the fall in new products is undoubtedly the cost of compliance with registration requirements. The safety of the medicine to the patient should always be the main objective and no company can

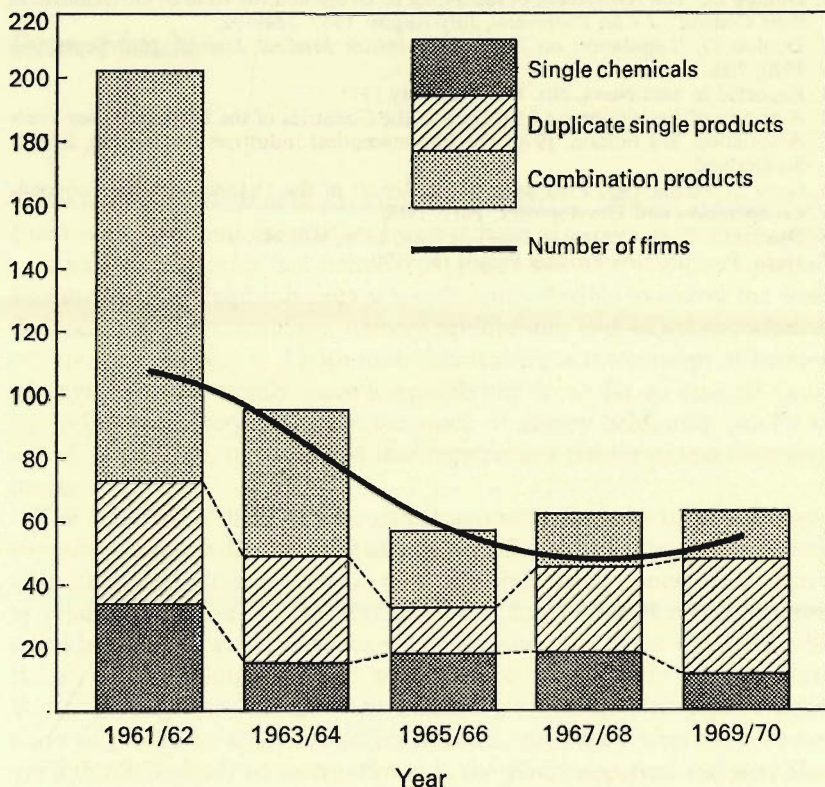
**Figure 1** *New single chemicals introduced in the United States 1961–1970*



Adapted from De Haen's New Product Parade 1970



Figure 2



Adapted from De Haen's New Product Parade 1970

neglect the development work that is considered necessary to predict the safety of a new drug in man. My main point is to question whether it is necessary to spend money on repeat studies that have already been fully documented in the country of origin.

The standards adopted by a pharmaceutical company will never be less than the most stringent requirements of any registration authority. Registration authorities should recognise a company's expertise to select those studies which it considers essential, and to submit those findings which it considers relevant. There are areas where registration can become a costly and time consuming exercise for the pharmaceutical company without any direct advantage to the patient who will eventually benefit from the medicine.

I ask that registration authorities apply scientific judgement rather than rules, flexibility rather than bureaucracy.

**References**

1. Dunlop D, 'The Assessment of the Safety of Drugs and the Role of Government in their Control'. *J Clin Pharmacol*, July-August 1967, 184-192.
2. Dunlop D, 'Legislation on Medicines'. *British Medical Journal*, 26th September 1970, 760.
3. Reported in *ABPI News*, No. 132, 14th May 1971.
4. A Survey of Legislation on Medicines in the Countries of the European Free Trade Association, 3rd Edition, 1970. The Pharmaceutical Industries Association, Zurich, Switzerland.
5. Gaps in Technology, Pharmaceuticals, Report of the Organisation for Economic Co-operation and Development, Paris 1969.
6. Djerasi C, 'Birth Control in 1984'. *Science*, 1970, **169**, 941.
7. Haen, Paul de, New Product Parade for 1970.

# The pharmaceutical industry and the balance of payments

Peter Mould

There is a strong element of paradox about the term 'balance of payments'. Frequently payments in, whether by an individual, a company, an industry or a nation, do not in fact balance payments out over any given period! Fortunately our English language is sufficiently flexible to endow the word 'balance' with two meanings, namely equilibrium, and an excess, whether positive or negative. And both meanings feature in the concept of balance of payments. Put simply there is equilibrium in so far as receipts equal expenditure *plus* any change in the stock of money held, and usually an excess, or balance, to the extent that receipts are greater or less than payments.

The activities of the pharmaceutical industry affect the UK's balance of payments through all the various currency flows that arise from its activities. Thus manufacture of oral contraceptives using imported diosgenin or related derivatives of the Mexican Yam, marketing of cephalosporins made in UK on a world wide scale, construction of a plant equipped with Italian capsule filling machines, manufacture of a drug by a foreign subsidiary developed at that company's central R and D establishment, repatriation of profits by a UK subsidiary in India, all come within the scope of our subject. Indeed, so international is the pharmaceutical industry that this theme could cover a whole series of lectures on the economics of the industry.

But why bother to focus attention on the balance of payments effect of the industry's activities? Given the UK's surplus of almost £1,000 million in 1971 isn't this one of yesterday's problems? Maybe, but it could also be one of tomorrow's. In place of the balance of payments problems of the 1960s, we have had the inflation problem of 1970-71, followed by the unemployment problem of 1971-72. There is a risk that next there could be either, or both, a balance of payments and an inflation problem. Moreover, at an industry level, an industry's balance of payments position can act as a rough and ready barometer of international competitiveness – in particular the relative attractiveness of the UK as a location for that industry – as well as highlighting one aspect of its contribution to the national economy. In this lecture I shall endeavour to set out the pharmaceutical industry's contribution to the UK balance of payments, how it is changing, and also briefly mention some of the main determinants.

Let me emphasise that I am talking about that part of the world pharma-

ceutical industry which operates in the UK to produce ethical and over-the-counter drugs and animal health products. As I am sure many of you are aware, obtaining a completely comprehensive picture of the UK industry's international receipts and payments would require the skills of a statistical Sherlock Holmes. There are no comprehensive statistics. The Sainsbury Committee arrived at a partial picture for the prescription sector using a financial questionnaire to firms producing some 90 per cent of NHS drug purchases. We in the NEDO office carrying out work for the Chemicals EDC's Pharmaceuticals Working Party, have relied on published information, analysis of additional information collected by government but not published, and plain qualitative judgment. At this point I would like to mention that the Working Party has yet to approve its final report and that some of the views expressed in this lecture are my own and may not be shared by the Working Party as a whole.

The picture presented by Sainsbury for 1965 was one of a strongly favourable balance, on a rising trend, in the region of £30 million. This aggregate figure concealed substantial variations in the contribution by firms in different ownership groups. That of the British owned slightly exceeded the aggregate, whilst that of the foreign-owned was broadly neutral. Amongst foreign owned companies there were substantial variations depending mainly on the level of exports from their UK subsidiaries and the extent of imports of semi-manufactured materials. Sainsbury attempted to pass judgement on the effect of foreign-owned firms on the UK economy and whilst acknowledging their role in saving imports and introducing foreign technology and management skills, pointed out that the skilled manpower they employed might have been employed elsewhere, bringing greater benefit to the economy in other firms or industries. At best such a view must be highly speculative and in any case the foreign owned firms are there and, in the short-term at least, likely to remain.

Let us consider the various elements in the balance of payments effects of the industry's operations. But first, by focusing attention on visible trade, the one area where comparable information is available for other countries, we can put the UK's performance into some kind of international perspective.

Per capita expenditure on pharmaceuticals is closely related to levels of income per head, although some countries such as France do seem to display hypochondriac tendencies, and therefore levels of consumption do vary substantially from country to country. Nevertheless, demand has been increasing throughout the world at an average of about 11 per cent per annum in the latter half of the 1960s. Growth has varied from over 16 per cent in Japan, through 12 per cent in Western Europe, and 10 per cent in the UK, to 7 per cent in the USA. (These are at current prices because

of the absence of any adequate indices for pharmaceutical prices, but would be only marginally lower in real terms.)

World trade in pharmaceuticals increased at a slightly faster rate than world demand in the 1960s but accelerated rapidly in the last three years. This was in common with world trade in manufactures as a whole, but largely due to the flow of new drugs and multi-national companies strengthening their international marketing operations.

One of the main characteristics of world trade in pharmaceuticals is the marked and sustained dominance of a small number of exporting countries. Thus West Germany, United States, Switzerland, United Kingdom and France supplied two thirds of all exports at the end of the 1960s. However, their share of total world exports of pharmaceuticals fell from 82 per cent in 1959 to 71 per cent in 1968. This was partly due to increases in the shares held by other industrialised countries such as Netherlands, Italy and Denmark, but more so to the achievements of a number of 'industrialising' countries. In the main these were Spain, Colombia, Brazil, Egypt and South Africa, where advancing export strength was largely due to increased local production by multi-national companies. As to the UK, although exports grew rapidly in the 1960s, some other leading country's exports grew even faster. The UK thus slipped from the position of 2nd to 4th largest exporter between 1960 and 1970, having been overtaken by West Germany and by Switzerland.

Information on the UK's visible trade is not as clear-cut as one might expect. The overseas trade accounts include exports and imports of pharmaceutical preparations, both as finished packaged products or in bulk form, as well as some – and I repeat – some pharmaceutical chemicals, that is the chemical compounds which form the active ingredients of drugs. How we can deal with the chemicals excluded I shall mention later. The broad picture is of the UK's balance of trade in pharmaceuticals having grown rapidly in recent years, particularly since 1967. Whilst imports have been growing relatively the faster of the two, the greater absolute increases in exports have boosted the trade balance. The figures are shown set out in Table 1.

The figures in the columns headed Finished Preparations are those classified to SITC 541.7, Medicaments. Those under the Other columns comprise three elements. Firstly pharmaceutical products in bulk under SITC 541; secondly those pharmaceutical chemicals under 541, that is those which can be readily identified by clerks in Customs and Excise, and thirdly, an estimate of pharmaceutical chemicals, mainly organic in nature, which are excluded. It is important to form an idea of the order of magnitude of trade in these excluded chemicals since it is known to be substantial, increasing, and largely due to the operations of multi-national companies. It was possible to make estimates of imports from a study of special

**Table 1** *UK exports and imports of pharmaceuticals 1963-1971*

	<i>Exports</i>			<i>Imports</i>			<i>Estimate Trade Balance</i>
	<i>Finished Preparations</i>	<i>Other</i>	<i>Total</i>	<i>Finished Preparations</i>	<i>Other</i>	<i>Total</i>	
1963	38.5	14.2	52.7	2.1	9.1	11.2	41.5
1964	41.6	17.1	58.7	3.0	9.7	12.7	46.0
1965	47.5	19.3	66.8	4.2	14.4	18.6	48.2
1966	51.1	23.8	74.9	6.2	17.2	23.4	51.5
1967	55.8	25.6	81.4	6.7	20.0	26.7	54.7
1968	70.7	30.3	101.0	8.5	25.2	33.7	67.3
1969	87.8	33.7	121.5	9.8	31.9	41.7	79.8
1970	104.7	42.5	147.2	13.2	43.3	56.5	90.7
1971	124.2	53.4	177.6	15.0	49.8	64.8	112.8

*Source* Overseas Trade Accounts, DTI, NEDO Estimates

import data for the years 1967-70 which were made available under the provision of Section 3 of the Finance Act (1967), the chemicals being identified by their Approved Names. In 1969 for example such imports, additional to those covered by the routine trade statistics for the industry, totalled over £12 million. No comparable export data are available from statistical sources and the best guess is that whilst appreciable, export business in these chemicals is a few million lower than imports. The estimates of balance of trade in the final column therefore include the estimates of excluded pharmaceutical chemical imports, to which reasonable confidence can be attached, and a 'guesstimate' for comparable exports. Nevertheless, this does give us a more comprehensive picture than the undoctored trade accounts.

Here we have a 170 per cent increase in the trade balance, between 1963 and 1971, and a more than doubling since 1967. In 1970 about 34 per cent of the industry's output was exported compared with about 24 per cent in 1963. This and the level and rate of growth of the balance of trade represent an achievement as good as that of any other major British industry. The activities of British-owned companies, largely through growing product strength, have probably made the major contribution to the rapid growth of exports and the trade balance. This would match their position in the domestic market where their share of the Executive Council Sector - that is National Health medicines less hospital supplies - rose from 27 per cent in 1966 to 33.5 per cent in 1970. Nevertheless, foreign-owned companies could not have been far behind. A survey of published company accounts undertaken for the Pharmaceuticals Working Party shows that, although in 1969 the top three exporters were British companies, no less than 14 of the top 20 were foreign-owned. The survey also

shows that the average proportion of output exported was much the same for the British companies as for the foreign companies. The Sainsbury report on the other hand concluded that, in the prescription medicine sector, foreign companies exported a smaller proportion of their output than the British. But this discrepancy is probably apparent rather than real and explained by the majority of the foreign-owned companies operating in the high exporting prescription sector. Companies included in the study for the Working Party also included smaller and mainly British companies with little export activity.

In turning to the 'invisible' and capital account, as the name implies, the position is more difficult to discern. We are concerned here with international receipts and payments arising from transfer of dividends and interest, payment of royalties and service fees, and movements of capital. These items form an important component of the industry's balance of payments position, because foreign-owned companies account for about two-thirds of the sales of medicines to the National Health Service, and the major British-owned companies have numerous overseas subsidiaries. The Sainsbury Committee's survey of the prescription medicine sector revealed a negative balance on invisible and capital account of £15 million in 1965, made up of a negative contribution of £16 million from the operations of foreign companies, and a positive £1 million from British-owned.

Information on recent trends for the foreign-owned sector is available from a study prepared for the Working Party by the DTI. The results are shown in Table 2.

**Table 2** *'Invisibles' and capital account transactions of selected UK subsidiaries of overseas-owned pharmaceutical companies 1964-1969.*

		1964	1965	1966	1967	1968	1969
<b>American Companies</b>							
Dividends + Interest	(-)	11.3	7.2	6.1	8.7	6.4	7.0
Royalties + Services	(-)	2.7	3.7	4.4	4.8	5.6	6.3
New Investment Inwards	(+)	4.1	0.9	1.2	0.4	0.3	0.9
<b>Total</b>	<b>(-)</b>	<b>9.9</b>	<b>10.0</b>	<b>11.7</b>	<b>13.9</b>	<b>11.7</b>	<b>12.4</b>
<b>European Companies</b>							
Dividends + Interest	(-)	1.1	1.3	1.1	1.4	1.1	1.2
Royalties + Services	(-)	2.1	2.1	2.2	2.9	2.9	2.8
New Investment Inwards	(+)	0.08	0.01	0.5	0.05	0.7	2.4
<b>Total</b>	<b>(-)</b>	<b>3.1</b>	<b>3.4</b>	<b>2.8</b>	<b>4.3</b>	<b>3.3</b>	<b>1.6</b>
<b>American + European</b>							
<b>Total</b>	<b>(-)</b>	<b>13.0</b>	<b>13.4</b>	<b>14.5</b>	<b>18.2</b>	<b>15.0</b>	<b>14.0</b>

Source DTI, NEDO

The data are based on a sample of UK foreign-owned subsidiaries. They can be regarded as giving a fairly reliable indication of the nature of the invisible and capital account contribution of the American-owned sector (the sample includes twelve of the top fourteen American-owned suppliers of drugs to the National Health Service together with the four chief leading American-owned firms in the over-the-counter market). Some major European-owned companies had to be omitted, however, and the results may therefore not be truly representative for this group as a whole.

Dividend and interest remittances by the American companies fluctuated much more widely than those by the European, and it is interesting that in neither case did they correspond closely to after-tax earnings. Royalty and service payments have not shown marked fluctuations from year to year and, in both groups, have been steadily rising, but more rapidly in the American group. Investment inwards includes both long-term and short-term finance, and thus a negative figure implies a net repayment of loans in a given year. Not surprisingly, it is highly variable. For example there is the substantial American investment in 1964, and sharp rise in European investment in 1969.

The broad indication therefore is of little change in the trend between 1964 and 1969, if anything a slight increase in the negative contribution. Inclusion of British-owned companies in the sample was not possible because the major ones were substantially diversified into chemicals, toiletries and other areas, but their net position is unlikely to have undergone major change over the same period. Royalties, dividends and interest almost certainly increased but so did outward investment. If a significant proportion of such investment was financed by money raised overseas and subsidiaries retained earnings, the trend may well have been towards a slight increase in the positive contribution of the British-owned sector.

To complete the picture we need to consider briefly a number of other aspects. There are imports of raw materials, excluding pharmaceutical chemicals of which we have already taken account – all the excipients, such as flavours, binders and colouring. According to the 1968 official statistics the pharmaceutical and toiletries industries together directly imported £18 million of materials for further processing. Twelve million pounds of this total has already been identified as pharmaceutical chemicals excluded from official statistics of exports and imports, and, of the remaining sum, approximately £4 million can be apportioned to the pharmaceutical industry. Direct imports of raw materials are therefore relatively insignificant. There is of course some further imported element in almost all other purchases by companies, whether the oil from which plastic packages has been made, or the copper in the laboratory central heating, but this is even more insignificant.



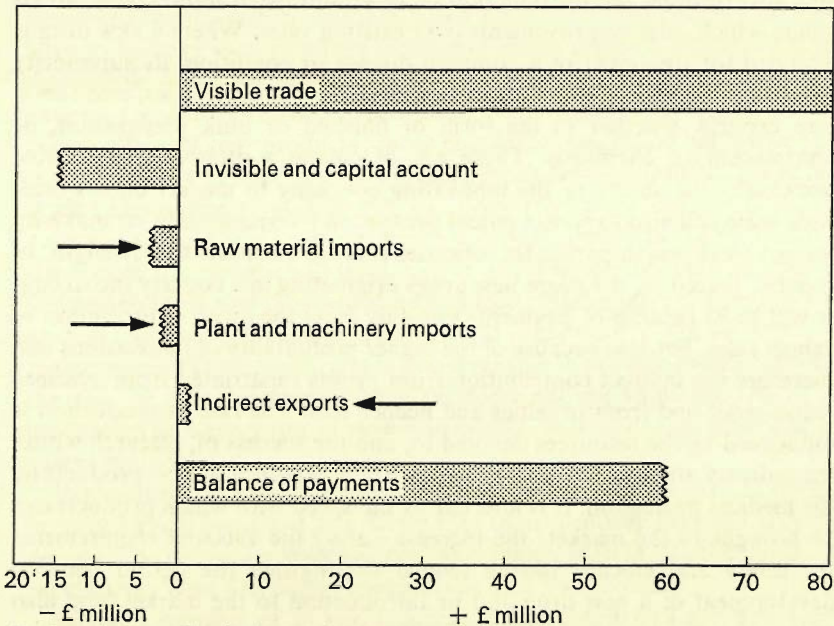
Attempts to place a value on imports of plant and processing machinery by pharmaceutical companies must be fairly speculative. Enquiries in the industry indicate that only in the field of capsule-filling machines are imports running at a high level, the competition mainly coming from Italian firms. In a recent large project by a major British company, imports of plant and machinery amounted to about 10 per cent of total spending. Expenditure by the industry on plant and machinery appears to fluctuate substantially from year to year, having totalled £12 million and £28 million in 1968 and 1970 respectively. At a guess the import component of this item is even less significant than imports of raw materials.

The pharmaceutical industry indirectly generates some additional international receipts through some of its products ending up in other industries' exports; hormones in cosmetics, vitamins in baby food, and, I think, though the industry might claim otherwise, antibiotics in Scotch beef.

And finally there is the saving of imports from the manufacture of patented products in the UK by foreign-owned companies. This element is undoubtedly very substantial and but for the attractiveness of the UK in the past as a base for investment in pharmaceuticals, the level of import substitution would have been much less.

Our brave attempt at assessing the overall balance of payments position of the industry is shown in Figure 1. A high level of confidence cannot be

**Figure 1** *Pharmaceuticals – estimate of UK balance of payments, 1969*



attached to all the figures. Nevertheless, it is clear that the industry improved its already significant contribution to the balance of payments in the late 1960s mainly due to the growth of direct exports. It was of the order of £60 million in 1969, possibly as much as double the 1965 level. On the evidence of the continued buoyancy of exports, it was substantially higher in 1971. If there has been little change in the invisible and capital account and only slight increases in imports of raw material, plant and machinery the contribution will have been around £90 million in 1971 not much less than 50 per cent greater than two years earlier.

In a nutshell the balance of payments contribution of the pharmaceutical industry depends upon the extent and manner in which British resources of men, money, and machines are employed in pharmaceutical activities. A detailed study of such a broad generalisation would involve probing the mass of complex, interacting economic, social and, I suppose, political factors which influence the industry and would require far more time than the allotted span of one hour for this lecture. Instead, let me talk briefly about four of the key factors which are likely to influence the balance of payments contribution of the industry over the next eight to ten years.

Firstly, will there be the flow of new products from British laboratories to maintain our recent export achievements? Product innovation expands the market both by widening the range of diseases susceptible to treatment and also through the introduction of new, and often more costly, treatments which offer improvements over existing ones. Where a new drug is intended for treatment of a common disease or condition, its superiority to existing treatment will sustain substantial world-wide sales, and therefore exports, whether in the form of finished or bulk preparation, or pharmaceutical chemicals. There are of course a number of provisos, principally the ability of the innovating company to market on a world-wide scale and also to secure patent protection internationally, or make-up for any weakness in particular countries through its marketing strength. In general, therefore, the more new drugs originating in a country the stronger will be its balance of payments not only from the direct contribution of export sales, but also because of the higher profitability of innovations and therefore the indirect contribution from profits repatriated from overseas subsidiaries and from royalties and licence fees. The rate of innovation is influenced by the resources devoted to, and the success of, research within the industry and outside, and by the rate of acceptance of new products by the medical profession. It is affected by the speed with which products can be brought to the market: the increase during the 1960s of requirements for safety and efficacy having tended to lengthen the period between development of a new drug and its introduction to the market, and also reduce the number of new drugs reaching the market, because of the in-

crease in costs involved. What can be said then about the future prospects of product innovation in this country?

The UK already is a major centre for research carried out by the world pharmaceutical industry, partly because of the extent of manufacture here, but also because a number of factors have made the UK a relatively attractive base for pharmaceutical research. There is the relatively low cost of R and D in the UK in comparison with the USA; the high reputation of our universities, medical practice and clinical trials; the calibre of British-trained scientists; and the efficient system for the registration of new medicines. R and D in the industry is going through a period of lengthening returns and rising costs. Because successful treatments have been introduced for a wide range of diseases, the industry is increasingly faced with the prospect of having to concentrate its research upon the difficult problems presented by the remaining unconquered diseases. The problem of diminishing returns is illustrated by the fact that, whereas a decade ago only one out of an estimated 3000 compounds synthesised and tested for possible drug activity in the industry's laboratories emerged as marketable products, the corresponding ratio now is about one to 5000 and is still lengthening. The cost of developing a new product has also risen, apart from the general effect of inflation, because the testing for safety and efficacy of drugs has become more exhaustive.

Thus the R and D expenditure necessary today to develop a major new drug typically amounts to well over £3 million. This has important consequences for the size of research-based pharmaceutical companies. They have to be large even to afford a comprehensive research activity in a few therapeutic areas. But they need to be even larger to have coverage of enough therapeutic areas to provide, with a reasonable degree of certainty, a flow of new products; those companies not in the big league thus probably run a greater risk of the occasional product famine. Large size is also imperative to sustain the necessary marketing organisation. The potential size of the market for any new drug is limited to the incidence of the disease it is designed to treat, and in any one country may be small in relation to the R and D expenditure incurred. Marketing on a world-wide basis is therefore increasingly necessary to achieve an adequate return on the investment in research. Size is also desirable to provide protection from the risk of other competing new products cutting short the life of an innovation as a generator of premium profits, well before the expiry of the patent period.

Expenditure on research by the industry in the UK totalled £22 million in 1970 having increased at a faster rate than turnover over the previous decade. The per capita level was probably higher than in all other countries except USA, West Germany, Netherlands and Switzerland.

Whilst a number of British pharmaceutical companies are well estab-

lished internationally, none are in the really big league in terms of either research spending or turnover. It would appear that no British owned company spent more than \$15 million on pharmaceutical R and D in 1970, but nine US, three Swiss and probably two West German exceeded \$20 million. Depending on how the structure of the industry changes, the trends mentioned earlier could affect the flow of new products from the UK industry. With this proviso and assuming that the other advantages UK offers for pharmaceutical research are maintained, the prospects are relatively good for new products coming forward to maintain export achievements.

Secondly, how is the pattern of supply to world markets likely to change? The main forces that have shaped the present pattern of supply are the location of innovation, the existence of economies of scale only in the more capital intensive chemical or biological manufacture of active ingredient, tariff levels and more importantly non-tariff barriers. The last, particularly varying drug registration requirements, together with differing national tastes and fears of political action, have given rise to the widespread carrying out of the later stages of production – formulation, tabling and packaging – within the individual market being supplied. This trend is expected to continue and world exports are unlikely to keep pace with world demand throughout the 1970s. The UK's position as a base for supplying pharmaceuticals to commonwealth countries could continue to decline, and adversely affect UK exports, stimulated somewhat by the tariff situation following UK entering the Common Market.

International harmonisation would boost trade in pharmaceutical preparations, but is unlikely to occur before the 1980s, although some progress might be achieved during the 1970s in the EEC. It would be likely to lead to substantially greater direct trade between UK and EEC countries at the expense of local manufacture.

Trade in pharmaceutical chemicals has been growing faster than in preparations particularly between advanced industrial countries, and this trend also can be expected to continue, affecting both UK exports and imports. It is noteworthy, however, that EEC membership by itself is unlikely to increase imports of pharmaceutical chemicals into the UK because in 1969 the Chemical Industries Association have calculated nearly 90 per cent, by value, were not made in the UK and were thus already duty free.

What are the prospects of the UK remaining an attractive base for investment by the pharmaceutical industry? It is important to recognise that the market for pharmaceuticals is made up of a number of distinct sub-markets with different growth rates. Some companies are expanding much more rapidly than others in the same or in other sub-markets. In the research-based prescription medicines sector several companies are

committed to very substantial new investment in facilities for both research and production in the UK, stimulated by recent successful and profitable product innovations. Other companies, however, whose main products have been superseded and who have not been able to replace them by important innovations, have suffered a decline in market ranking and profitability.

The UK is, and is likely to continue as, a favoured location because of a number of factors. It has an effective and relatively speedy system of registration of new drugs. Its patent system is satisfactory and would be improved with implementation of the recommendations of the Banks Committee. Its language, relative political stability, the standing of the medical profession, the international reputation of its clinical trials and the availability of qualified staff all make it attractive to the multi-national company.

There is however another side to the investment picture. The UK has tended to be one of the lower-priced markets for prescription medicines and a recent study by Michael Cooper, done for the Pharmaceutical Working Party, has shown that this tendency has increased between 1964 and 1970. This is thought to be largely due to the effectiveness of the Voluntary Price Regulation Schemes administered by the Department of Health. The OHE has recently estimated that savings directly due to negotiations under the VPRS totalled £18 million in 1970. Added to this there is the Department of Health scheme to inform doctors of the costs of alternative medicines and it is thought that this leads to more prescribing of generic products than would otherwise occur.

If prices in the UK remained out of line with those in other comparable countries over a substantial period, and in consequence affected profits, both the incentive to invest in the UK and supply of necessary funds would be reduced. This is not only because of lower profitability on home sales but because purchasing agencies in other countries are increasingly relating their purchase prices to those in the company's home market and this would also affect export profitability. Confidence influences investment decisions and *fears* of declining prices and profits could be enough to turn away potential investment by the multi-national companies.

Thus whilst the UK could remain an attractive location much will depend upon the future levels of prices, profits and business confidence compared with competing locations overseas.

Finally, and most speculative, how will the structure of the industry in the UK change? We have noted that no UK company is in the really 'big league' in terms of either R and D or turnover. None, at least as yet, are amongst the world's top ten pharmaceutical companies. Clearly there are pressures on UK companies towards larger size, particularly from the marketing and to a lesser extent the R and D side of the business. I think we

can expect a good deal of merger and acquisition activity over the next ten years. UK entry into EEC will add to the economic forces encouraging this. The industry's future contribution to the balance of payments is likely therefore to be significantly affected by the occurrence and outcome of such restructuring.

We have already noted that the research-based UK companies tend to contribute most to the balance of payments, not only because they tend to have a high level of exports, but also because of their positive contribution on the invisible and capital account. Thus from the point of view of the balance of payments the best outcome would be more and bigger UK-owned groups. But being realistic we can expect little change in the number if size is to increase significantly. Indeed there could well be a reduction in the number should mergers occur between British companies and no newcomers arrive on the scene. Because of the optimum scale of operations and the very long lead time before research activity yields profits the research based sectors have, as the economist would say, high barriers to entry.

About 42 per cent of total UK pharmaceutical output in 1969 originated from foreign-owned firms. Their contribution to the balance of payment varies considerably. It is heavily negative for those having only a marketing operation, or facilities for marketing and the final stages of production and no exports. But it is strongly positive for those with an R and D activity, substantial production operations and exports from the UK.

About one-third of the R and D carried out by the pharmaceutical industry in the UK is accounted for by subsidiaries of foreign-owned firms. Although the net benefit to the UK economy flowing from successful R and D by a foreign-owned firm is likely to be less than that by a British company, it is nevertheless a highly desirable activity: apart from the tangible contribution to the balance of payments from exports and royalties, there is the less quantifiable but probably more important fact that a parent company will tend to back its most successful subsidiaries with further investment.

Successful R and D by foreign-owned companies therefore increases the extent to which the UK becomes a supplier to the world market. But whether, despite R and D successes, further investment will be allocated by a foreign-owned company will largely depend upon the attractiveness of the UK as a location. If the level of prices and profits in the UK are substantially out of line with competing locations, potential new investment will almost certainly find other homes. Getting back to the balance of payments the present structure of the UK industry is such that the industry's future contribution is likely to be as sensitive, if not more so, to what happens in the foreign-owned rather than British-owned sector. If foreign-owned companies expand their research and production activities at all

levels, the overall strongly positive contribution will be maintained or increased: if not, it is likely to decline.

In view of all the uncertainties I would shrink from any quantitative prediction about the industry's future balance of payments position. Futurology is however a little less hazardous when it comes to the balance of trade. Exports are unlikely to continue expanding at the present rate, growth at an average of 8 per cent per annum for the decade to 1980 being more likely. Should this occur, on the best predictions of world output and trade, exports would reach around £300 million in 1980 (at rates of inflation experienced in the 1960s) and the UK share of world trade would have declined slightly, in the main because of an increased proportion of local manufacture in world markets.

The first part of the paper is devoted to a general discussion of the problem of the existence of solutions of the system of equations (1) for arbitrary values of the parameters  $\alpha$  and  $\beta$ . It is shown that the system has solutions for all values of the parameters  $\alpha$  and  $\beta$  if and only if the condition  $\alpha + \beta > 0$  is satisfied. In the case when  $\alpha + \beta > 0$  the solutions of the system are unique and can be expressed in terms of the hypergeometric function  ${}_2F_1$ . In the case when  $\alpha + \beta < 0$  the system has no solutions. The second part of the paper is devoted to a detailed study of the properties of the solutions of the system (1) for arbitrary values of the parameters  $\alpha$  and  $\beta$ . It is shown that the solutions of the system (1) are bounded and continuous functions of the parameters  $\alpha$  and  $\beta$  for all values of the parameters  $\alpha$  and  $\beta$  if and only if the condition  $\alpha + \beta > 0$  is satisfied. In the case when  $\alpha + \beta > 0$  the solutions of the system (1) are bounded and continuous functions of the parameters  $\alpha$  and  $\beta$  for all values of the parameters  $\alpha$  and  $\beta$  if and only if the condition  $\alpha + \beta > 0$  is satisfied. In the case when  $\alpha + \beta < 0$  the system has no solutions.

The third part of the paper is devoted to a study of the asymptotic properties of the solutions of the system (1) for arbitrary values of the parameters  $\alpha$  and  $\beta$ . It is shown that the solutions of the system (1) have the asymptotic expansion  $y_1 \sim \frac{1}{x} + \frac{\alpha}{x^2} + \frac{\beta}{x^3} + \dots$  and  $y_2 \sim \frac{1}{x} + \frac{\alpha}{x^2} + \frac{\beta}{x^3} + \dots$  for all values of the parameters  $\alpha$  and  $\beta$  if and only if the condition  $\alpha + \beta > 0$  is satisfied. In the case when  $\alpha + \beta < 0$  the system has no solutions. The fourth part of the paper is devoted to a study of the stability properties of the solutions of the system (1) for arbitrary values of the parameters  $\alpha$  and  $\beta$ . It is shown that the solutions of the system (1) are stable for all values of the parameters  $\alpha$  and  $\beta$  if and only if the condition  $\alpha + \beta > 0$  is satisfied. In the case when  $\alpha + \beta < 0$  the system has no solutions.

The fifth part of the paper is devoted to a study of the properties of the solutions of the system (1) for arbitrary values of the parameters  $\alpha$  and  $\beta$ . It is shown that the solutions of the system (1) are bounded and continuous functions of the parameters  $\alpha$  and  $\beta$  for all values of the parameters  $\alpha$  and  $\beta$  if and only if the condition  $\alpha + \beta > 0$  is satisfied. In the case when  $\alpha + \beta < 0$  the system has no solutions. The sixth part of the paper is devoted to a study of the asymptotic properties of the solutions of the system (1) for arbitrary values of the parameters  $\alpha$  and  $\beta$ . It is shown that the solutions of the system (1) have the asymptotic expansion  $y_1 \sim \frac{1}{x} + \frac{\alpha}{x^2} + \frac{\beta}{x^3} + \dots$  and  $y_2 \sim \frac{1}{x} + \frac{\alpha}{x^2} + \frac{\beta}{x^3} + \dots$  for all values of the parameters  $\alpha$  and  $\beta$  if and only if the condition  $\alpha + \beta > 0$  is satisfied. In the case when  $\alpha + \beta < 0$  the system has no solutions.



# Profitability, risk and investment in research and development – the UK pharmaceutical industry

Kenneth G D Smith

The last decade has seen both the American and British drug industries face up to the inevitability of increasing governmental concern and intervention in their operations. In this country the establishment of the Committee on Safety of Drugs, the criticisms of the Sainsbury Report, the largely resultant fourth Voluntary Price Regulation Scheme and the 1968 Medicines Act have increased considerably the technical and financial constraints on, in particular, the NHS sector of the ethicals market. The resultant mood of the industry has been one of long-term uncertainty and depression. While the government has been putting pressure on selling margins and profits on NHS sales, costs have been rising sharply in both domestic and the equally important<sup>1</sup> export market. While testing requirements, R and D costs and lead-times have increased, attrition rates in research output appear to be steadily increasing and market penetration rates declining. The result, we are told, declining profitability, increasing risk, with resultant longer-term implications for growth in the industry and for the rate of investment, notably in the research-based sector.

It is this last point which has been the industry's trump card through the years of criticism of its prices, profits and selling methods. Whatever one may think of some aspects of the way in which drugs are put on the market, criticism has stumbled on the problem of research, the need to induce a continued and growing research effort in an area of high social benefit. Unless we are prepared to accept a fundamental change of approach towards the production of prescription medicines,<sup>2</sup> pharmaceutical research remains basically a commercial undertaking induced by profit expectation and financed, by the present results of past research. Is the industry, then, moving into a situation in which levels of investment in research are likely to be adversely affected?

Investment in drug research is dependent on the expectation, on the

1 Taking the sales figures produced in the 1971 ABPI Annual Report, exports constituted almost 44 per cent of the 1970 total, and have been growing significantly faster than domestic sales.

2 The industry would argue, firstly, that virtually every existing product of genuine medical significance emerged from the commercial drug houses and that, failing development of a better understanding of the 'causes' of innovation in this area, it is dangerous to intervene in the system of commercial motivation; secondly that, notwithstanding the apparently high costs involved in the drug marketing process, it has at least resulted in these 'genuinely significant products' achieving market dominance.

part of the suppliers of capital funds, of an economic return at least as high as they could achieve in what are seen as feasible alternative areas at any time – taking account of the relative commercial risk thought to be involved. That is, put formally, the risk-adjusted supply price of capital to research, from companies already in the area and from new entrants, must continue to be met from the returns thought likely to be generated by research output. Should we decide that the latter is decreasing while the former increases over time, we must conclude that there will be a long-run tendency for the investment of capital in the research sector of the industry to decline. Needless to say, such an evaluation founders on our inability, thus far, to say anything definite about the components of capital supply prices and expected returns. These are complex, continually changing and, most important, highly subjective – what motivates company investment behaviour, how does management assess risk and the return from a given investment, what part does ‘rational’ financial assessment play in the allocation of capital funds?

In theory, management will be capable of recognising and assessing a range of investment alternatives at any time, between which it will switch resources in response to relative movements in return and risk as these affect what the company is trying to achieve. The shareholders of a company are seen as ‘communicating’ the supply price of capital to the company, which management can express as a single required yield rate, against which the risk-adjusted expected return from all alternative investment projects can be measured. Achievement of this will just hold the existing level of investment in the area; returns in excess of the existing supply price will attract new investment (and the corollary).<sup>3</sup> Any company constrained from entering a given area by shortage of internal resources will be able to overcome the constraint by hiring resources piecemeal in the market, or by taking over companies already in the area.

In practice this process is more complex, works less flexibly and with considerable time lags. In the first place, investment funds will typically be allocated within a company by product or process areas of activity rather than by project and by reference to much less well defined criteria, with much weaker external influence on management. The level of investment in

3 In these terms, the signal that a company is failing to meet its ‘risk-adjusted capital supply price’ will be a decline in its share price (an increase in the cost of capital); even if the company is not actually being forced to raise new money at this increased cost, investment behaviour will be influenced, if only by management’s fear of the consequences of a significant decline in share price. Apart from the shield against this mechanism afforded by what economists tend to regard as ‘irrational’ behaviour by investors and management, the ‘signal’ is difficult to interpret in the case of a diversified company. This is typically the case of ethical drugs – the price of capital for research is a function of the financial outcome of research in relation to that of the other diversified activities and the overall market expectation of the company as a whole, hence is not immediately observable.

any particular activity will be determined by an interaction of the *opportunity* to invest – recognition and assessment; available *capacity*; the particular *pressures* facing companies, as management sees them.

Both in the case of companies already operating in a particular area and of potential new entrants, continuance or expansion of investment will initially depend on the recognition of *opportunities* thought likely to generate an adequate contribution to the companies' objectives, with a level of risk regarded as acceptable. These objectives are likely to be a complex of growth and profitability, expressible in a variety of more or less formalised investment criteria; what is regarded as an 'adequate' contribution to objectives and an 'acceptable' level of risk will depend, primarily, on past record, financial situation and the relative position of what are seen as alternative investment areas – all of these, in some degree, subjective, all variable with circumstance.

In considering the 'UK pharmaceutical industry' research-based sector, for obvious structural reasons, we are most immediately concerned with the relative position of ethical drugs and the other activities of the diversified companies, based on chemicals, presently carrying out pharmaceutical research, or likely to begin research. From the standpoint of inducement to invest, most obviously relevant in that context is the physical productivity expected in the research area and the profit and growth potential of research successes, in relation to the cost of research failure. A deterioration in expectations will first affect new entry to the 'industry', then, with a considerable lag, investment levels in companies already operating.

By *capacity* I mean the availability of technical and financial resources for the implementation of desired investment programmes – again both by companies already in the industry and by new entrants. The existence of 'surplus capacity' may constitute a strong inducement to continuation of existing or related investment programmes; more commonly capacity will constitute a constraint on ability to pursue an investment policy and the ability to withstand unfavourable outcomes. This will be particularly the case in high technology areas, with relatively large minimum levels of investment required to sustain or to set up operations and with long lead-times involved in the process. The research-based pharmaceutical sector is a case in point; both the research and marketing activities of the industry involve high threshold levels of spending with long time-lags before pay-off, while research and production employ techniques difficult enough to constitute an entry barrier to the industry perhaps for all but the large chemical companies.<sup>4</sup>

4 The experiences of Guinness and Distillers are often quoted to substantiate this point, notably in fermentation technology – also technical constraints limiting competition in the area of sterile preparations.

If opportunity and physical capacity determine and limit the range of feasible investment alternatives available to a company at any time, the likely extent of movement into and out of particular areas of activity will be strongly affected by internal and external pressures on management. On the one hand, there is likely to be strong pressure to maintain at least existing levels of investment in current areas of operation – by virtue of the past commitment of resources and the personal commitment of management specifically involved,<sup>5</sup> by virtue, perhaps, of considerable past success in the area and of the significance of particular activities in the competitive environment of the firm. In pharmaceuticals, the market clearly places a high success premium on product innovation – on-going competitive pressure will, then, tend to act as a stimulus to continued investment in the innovatory processes. In short, we have a powerful inertia in existing areas of activity, which may only be overcome by a relatively considerable and sustained shift in expectations relative to alternatives – particularly if expectations are subject to high degrees of uncertainty. On the other hand, a sustained downturn in growth and profitability will eventually put pressure on the availability of funds for reinvestment and expansion, and will reduce the company's ability to withstand the impact of any given level of risk of adverse outcomes to investment projects. Even then, the extent to which a company can resist the latter type of pressure in any specific area will depend on the degree of diversification of the company – specifically the significance of any one activity in relation to the company as a whole and the extent to which management is prepared to cross-subsidise one activity from another, or raise external finance, in the face of a decline in what are seen as the cash flow sources specifically providing finance for the activity.

Further, the likely reaction of management to adverse pressure of this type, as well as depending on capacity to withstand it financially and on relative expectations, will be influenced by assessment of the reasons for a given decline in, say, profitability and growth. These may be a complex, for example, of technical and commercial failure in the face of a strong competitive situation, of what is seen as an inadequate level of investment under changing circumstances, of an unacceptable degree of pressure on prices and margins, specific to the particular area under consideration, or of a decline in the general commercial potential of an area. The important distinction is between a decline caused by factors believed reversible, which may stimulate an increase in investment (provided financial resources continue to be available) and the converse.

In terms purely of research productivity, the critical point obviously

5 For personality reasons this will tend to be particularly strong in the case of research personnel.

comes when management ceases to believe that an adequate flow of economically viable new drugs can be generated by raising levels of research spending. 'Economically viable' widens the concept of this critical point – can research successes continue to generate sufficient cash flow both to induce continued growth in research spending and to finance it? In so far as government policy significantly reduces the expectation of profit and the cash to generate it, it may accelerate an ultimate decline of investment in prescription medicines caused primarily by failure of expectation that research can generate new 'winners' at an adequate level. Clearly this is both impossible to predict at this point in time and highly subjective – I believe that, in the short run, the most likely change in levels of research spending in this country is a significant jump upwards, with research spending highly resistant to any decline, and that much of the overt pessimism in the industry may be exaggerated. Before looking at the condition of the research-based sector in detail, a useful preliminary is to consider how levels of research spending are determined in the industry and how that expenditure is allocated to individual projects.

#### **Budget formulation and project selection in R and D**

It is extremely difficult to make generalisations on the subject of strategy formulation and project selection in this area. The pharmaceutical chemicals sector of the UK industry is made up of a relatively small number of large, apparently very profitable companies which are either subsidiaries or branches of international firms, or companies which have diversified into the pharmaceutical area from chemicals – of increasing importance as the significance of synthetic compounds has grown – or from food and drink industries. Within these diversified companies pharmaceuticals occupy a position of varying relative significance, all of which combines to produce considerable difficulty in deriving any financial data on 'the UK pharmaceutical industry' or in deciding on the level at which decisions on drug research are likely to be taken. In particular, what degree of cross-subsidisation is permitted (or pursued) both between pharmaceutical and other operating areas and within the pharmaceutical area – that is, between ethical, proprietary and veterinary products?<sup>6</sup> The extent and nature of diversification is extremely significant in determining what management is

6 In conversation with company managers this appeared limited (other than in the case of a company setting up a wholly new operation) though there are, clearly, complex interdependencies in the general field of medical products which must produce cross-subsidisation. All managers were insistent that the only source of research finance was pharmaceutical profit – in every case, however, this was in a situation in which these profits had always proved adequate to finance a 'satisfactory' level or rate of growth of research spending. What would be more interesting is a picture of likely cross-subsidisation of research in the event of a profit shortfall. I know of no evidence on this.

likely to view as immediately alternative investment areas (the fact that many of the companies involved are both large and already diversified may imply a lesser degree of inertia in any particular area – ‘quicker on their feet’ in getting out of a relatively depressed area). The degree of diversification is also significant, in determining the impact of high risk in one activity on the whole company and consequently on the company’s tolerance of and ability to withstand increasing risk in one activity (risk meaning variability of outcome).

As to the research process itself, it is difficult to escape the conclusion that this is a very high risk activity, at least as far as the discovery of genuinely new active drugs is concerned (estimated, at the time of the Sainsbury Report, as involving all but 8 per cent of total R and D spending in the UK industry) – this both as regards the high uncertainty of its outcome and the considerable lead-times involved. These circumstances appear to have led to almost universal rejection of formal financial decision techniques in the research area; there do, of course, exist techniques designed to ‘rationalise’ project selection in areas of high uncertainty, the more elaborate of which would simultaneously determine budget levels and project selection. These range in complexity from simple check lists, to be used in comparing recognised alternatives, to full-scale financial programming models. In the former category, for example, Mottley and Newman(1) suggested grading projects by reference to five factors, scored 1, 2 or 3. These were:

- a) The ‘promise of success’.
- b) Estimated time to completion.
- c) The cost of the project.
- d) Strategic need for the project.
- e) Estimated market gain.

The total value score for each project is then obtained by multiplying each of the scores from (a) to (e).

The weakness of a procedure like this is relatively obvious – equal weight is attached to each factor, there is no formal consideration of the range of possible outcomes nor formal relating of these outcomes to what the company is trying to achieve at the time.

More elaborate financial planning models generally take the form of some variant of DCF analysis. One might, for example, proceed by:

- (a) Defining the objective of the firm and the constraints on pursuit of that objective. The problem here is to express these complex and changing variables in an acceptable shorthand.
- (b) Stating the logic of the R and D process, together with the range of feasible outcomes, isolating the uncertain events in the process and the significant variables affecting these events. The problem, at this stage, is

that of identifying feasible outcomes and the significant variables affecting these.

(c) Assigning probabilities to possible values of these significant variables and from that deriving a probability distribution of the objective being pursued – if the system logic is relatively simple and the number of feasible outcomes and significant variables manageably small, this last stage can be done by analytical methods; if, as is rather more likely, this is not the case, some form of controlled sampling of outcomes and variable values will have to be used to estimate the distribution of the objective in a simulation exercise(2, 3).

With regard to the choice of an objective and relevant constraints, the simplest approach is to assume that the firm is attempting to maximise the present value of expected net income, avoiding, as a constraint, those projects with unacceptably high variances from expected value – unacceptable with regard to their impact on the company's financial position. The most important assumption here is that the company is capable of estimating a single discount rate to represent what I have been calling the supply price of capital over the duration of the project. This, I believe, is not theoretically valid, far less feasible in practice – as Adelson, among others, has argued(4). Nor is the use of variance or deviation from expected value an adequate measure of the impact of a project's outcome on the company, particularly where the project interacts with other aspects of the company's activity.

Assuming project interdependence will be significant (as it is bound to be in new product development) it may be possible to construct a programming model of the company's operations and to test the impact of alternative sets of projects on, for example, cash flow, liquidity, and accounting profitability, taking account of all implications of the foreseeable range of outcomes. Specific constraints, related to these aspects of the company's overall position, may then be built in. In Chambers'(5) approach, for example, capital would be allocated to sets of projects by direct reference to their relative effects on the growth of gross assets, but subject to the constraint that

- a) Published profits have to increase by 5 per cent each year.
- b) Dividends must remain at one third of available earnings.
- c) The ratio of current assets: current liabilities must not fall below three.
- d) The rate of return on gross assets should not fall below 15 per cent.

This type of approach, were it believed to be feasible and worth the time and cost involved, has the obvious merit of forcing management to consider, in detail, the possible implications of any given investment proposal for the company as a whole – even without necessarily being incorporated in a formal model. As far as an investment activity like drug research is

concerned, one is then left with the still more important problem of identifying the alternative outcomes of research decisions and assigning meaningful probabilities to the variables affecting these outcomes.

Say one is trying to operate a decision model at the screening stage of the search for a marketable product. In the normal situation there will be many more compounds coming up for consideration than can be investigated thoroughly. The problem is then to devise a screening test to select compounds for detailed investigation on the basis of expected success from a given total outlay – given that an increased effort on testing each individual compound will give more reliable results, but a lower coverage and a backlog of unconsidered compounds building up. In formal terms the test must estimate error variables and their parameters.

A 'type 1 error' – on the basis of insufficient primary (depth) testing the compound goes forward to secondary stages and is then rejected. The cost is that of the 'unnecessary' tests.

A 'type 2 error' – due to insufficient coverage in the primary screening a marketable drug compound is missed, hence its value lost. The test should then be constructed to maximise expected gain; this would involve estimating:

the cost of screening at all relevant stages – which should be calculable in advance (but you cannot know, in advance, at what stage type 1 errors are likely to be picked up);

the probability of finding an active compound in any given sample of an area;

the probability that an active compound will lead to a marketable drug; the value of a marketable drug.

This list shows up the fundamental problem for a research director attempting to apply formal analytical techniques to the research process in pharmaceuticals, particularly at its relatively early stages in any project area, (particularly when one considers the length of time and the depth of testing elapsing between primary screening and the emergence of a marketable product). The last estimate is the most obviously difficult; only at a relatively late stage in the research sequence will the final product be identifiable and its potential capable of assessment. Assuming that the initial research process was aimed at a specific area of treatment, on the basis of some type of 'lead' or logical analysis, the overall size of the market may be assessable prior to the emergence of any product candidate, and a technical assessment may be made of the adequacy of treatments already available in the area. Less easily judged will be the likely advantage of the new product over these existing treatments, which will substantially determine its initial market price – though presumably estimates can be made of this at on-going stages of the testing process. Other than the possibility that another company may come up with a superior or equally satisfactory



treatment either before or just after marketing, this would leave the question of estimated marketing time and expertise likely to be made available – a factor thought to be crucial in the relative success of a new product. (I believe that the current comparative success of Wellcome's 'Septrin' over Roche's 'Bactrin' provides a good example of the critical importance of intensive marketing effort.)

In addition, the research directors I have spoken to felt unable to assign meaningful probabilities of success at any stage in the testing of new active compounds, given existing levels of knowledge on the nature of drug action. In any project of this nature, therefore, up to the emergence of a recognisable 'product candidate' from the screening and early activity tests, the range of possible outcomes of research is not known, while, beyond that, although this range may be recognisable, even quantifiable, any probabilities attached to each outcome would be entirely subjective – that does not necessarily mean worthless – and, clearly, some degree of quantitative assessment is essential as early as possible in the research and development process.<sup>7</sup> As far as this general analysis is concerned, however, the conclusion is inevitable that the research-based companies are unlikely to determine their level of spending on research on the basis of a fully worked-out financial analysis. Technical and subjective factors are likely to exert strong influence both in determination of overall budgets and of the project components of these.

In so far as any generalisation can be made, from my own conversations with managers in a number of the research-based companies and from the reports of surveys made in this area(6, 7, 8), the following simplified account of the budget decision process emerges. We are, inevitably, involved in a two-way 'haggling' situation. From the research side costs of the on-going operation will be forecast over the budget period. The development and prospects of each project will be reported, in both technical and financial terms and the budget submission decided on basis of consultation between research, sales, production and financial managers; the level of formal quantification will vary, but consideration will clearly be given to estimates of development time, future development costs, implications for production and sales promotion budgets and on-going estimates of sales and profit prospects. No companies appeared to use formalised DCF-type analytical methods for assessing projects – a few research directors had tried this and found the exercise 'frightening',<sup>(7)</sup> largely by virtue of the effects of applying discounting to a heavily lagged development and sales process (I return to this later). Some of the large companies do apply more localised 'decision aids', in, for example,

7 If not, even high technical success in research may, obviously, fail to generate an adequate return, if the products are in an insufficiently large treatment area. (Bayer has, I believe, had this experience recently.)

screening and dosage selection, with debatable success; but full-scale profitability forecasting, at project level, was thought too uncertain to be worth the effort except perhaps at relatively advanced states – by which time, in one way or another, the decision to go ahead or not would be very largely inevitable.

This does not, of course, imply that the decision processes are ‘irrational’, merely that they cannot be fitted usefully into a general model – or at least that such models are thought to add little to the relatively well-defined problems to be faced. Up to a point, if the initial research area has been selected carefully and if the product has any significant merit relative to existing treatments, ultimate profitability is assured, assuming the product can be got to marketable stage – and marketed intensively enough.

None of the managers with whom I spoke had any experience of the imposition of strong financial constraints at this point, but two particular controls on research activity appeared relatively common – a need to overcome ‘research inertia’ in particular long-running projects, where the teams involved were unable or unwilling to make a sufficiently objective assessment of the project’s potential and, secondly, to overcome costly and time consuming parallel development of related active compounds thrown up in the screening (I referred to the trade-off involved here earlier).

To this ‘on-going’ budget, again on the basis of consultation between research and sales sides, will be added indents for the establishment of new projects, either in going areas of interest or in wholly new areas, perhaps following up leads from the technical literature, attempting to develop new active compounds on the basis of known activity, or developing essentially imitative products. It is likely that the managers involved will be extremely conscious of the need to hold a balance in their portfolio of projects on hand:

- (a) between projects at varying *stages of completion* and
- (b) subject to varying *degrees of ‘pay-off-risk’*.

(a) would involve an obvious need to manage the flow of new product candidates through the various stages of testing, development and sales promotion – perhaps especially relating to the last; on the one hand, there are very tight limitations on the number of new products a sales team can handle effectively, and a high pay-off from being able to devote intensive sales effort to a relatively narrow product range, on the other maintenance of a sales promotion effort involves very substantial fixed costs, through which ‘new product hunger’ will quickly be transmitted to research directors.

(b) is normal portfolio selection: Research directors will attempt to hold the content of their budget, and add to it, in some desired distribution of project-type (subject to more short-term requirements of new product

flow): One research director suggested the following range – purely as an illustration – of total budget,

25 per cent on going areas of interest, perhaps best related to ‘defence of market share’.

35–40 per cent on relatively advanced projects, with what are seen as high success probabilities.

25 per cent on speculative, high risk (but high possible pay-off) projects.

5–10 per cent on purely imitative developments (insurance policies?)

5 per cent on ‘feasibility studies’.

Clearly, in so far as such a budget strategy can be maintained the company can trade-off reduced risk against large and increasing levels of investment in research. The number of major projects which can be sustained, however, even at the current top end of the UK spending scale is still relatively small and the uncertainty attached to, in particular, the potential high pay-off projects very great. There is some evidence of a tendency now to concentrate resources on rather fewer projects than before, suggesting that the cost of individual major projects is rising faster than overall R and D spending – conflicting with the expressed desire to generate a quicker flow of new products to compensate for the longer time-lags involved in single major projects. These, then, would constitute the relatively short-term influences on research spending ‘from below’, with a variable element of upward push by virtue of the constantly rising cost of a given operation and the addition of specific new projects felt sufficiently promising.

To this will be added the determinants operating ‘from above’ – the imposition of strategy. The long-term influences on levels of research spending have been expressed in a variety of ways, giving an overall impression of the strong influence of *subjective assessment* – ‘what is felt, in an overall policy sense, to be an appropriate budget size’(7) – and *defensive reaction to competitive pressure* – ‘Companies try to assess the level of R and D spending most likely to generate an adequate flow of new drugs to maintain competitiveness, while holding current profits at an adequate level’(8).

This latter is likely to be particularly important in the face of a run-out of important patents, where the current research effort is not generating an adequate replacement flow. The classic, defensive, ‘neutralising’ strategy seems well in evidence over most of the research-based sector – bidding up levels of research spending in line with sales levels over time and attempting to move from one ‘intensity threshold’ to another, without any strong impression that this is linked to a detailed assessment of profit outcome, purely as internal finance becomes available. In direct monetary terms, three principal thresholds are distinguishable(7).

- 1 'Minimum' (say 3 projects) – £500,000 per annum.
- 2 'UK level' (6–10 projects) – £4 million per annum.
- 3 'USA level' (10+ projects) – £6 million+ per annum.

Nine USA companies alone were at level 3 in 1969 – Merck spending \$60 million; only four UK companies are between levels 2 and 3 at present. Expressing levels of research spending in relation to sales revenue, which is relatively standard practice, is hazardous – depending, as it does, on what sales one refers to and how one defines R and D spending. On the conventional definition, taking R and D as a percentage of all pharmaceutical sales, the large international companies appear to be located in the 7 per cent–12 per cent range(7), with the major UK companies regarding 7 per cent as a floor, below which they will be extremely reluctant to slip. (The Sainsbury Report gave a mean of 10·3 per cent for NHS products only.) One major UK company expressly justified its medium term intention to push towards 12 per cent of pharmaceutical sales, on the basis of a study of the USA industry, which had produced 12 per cent as an 'optimum'.<sup>8</sup> (This range of figures places the pharmaceutical industry well up at the top of the research intensity league, in this country. As far as being an indicator of risk is concerned, this has again to be qualified by the fact that we are for the most part talking about diversified companies whose research effort constitutes a much lower proportion of overall sales revenue.)

Given the uncertainties involved and the extremely long lead-times, companies are likely to be strongly influenced by more or less subjective measures of the likely profitability of research in relation to what they see as alternatives. In particular what management sees as the past success of R and D spending will affect its attitude to current spending – notably, of course, in its own company, but perhaps also, to a lesser degree, in competitors. This may reinforce the already considerable inertia involved in the long-term nature of research investment, which makes it observedly insensitive to short-term fluctuations in sales or profits(6). This comes over particularly strongly in the case of companies like Merck, where the sustained record of research success clearly permeates the entire approach of management.

This very general picture of budget formulation is, to a considerable extent, verified by the econometric investigations of R and D project and budget selection so far carried out in America. One of the earliest was Minasian's(9) study of a panel of large companies, including five predominantly engaged in manufacturing prescription drugs, with regard to the relationship between R and D spending and profitability. He found relatively weak links between changes in profit expectations and R and D spending levels, a much stronger suggestion that the primary influence

<sup>8</sup> Private communication – 'optimum' in terms of physical productivity.

pushing up expenditure was pressure on existing profits, except in so far as existing profit became depressed enough to reduce capital availability (a situation which seems a long way away in pharmaceuticals). To an extent, this is backed by the findings of Mueller(10), again considering a panel of companies in a range of industries, including pharmaceuticals. He concluded that there was a shift towards spending on R and D in periods of declining profitability in existing activities. The relationship, however, appeared highly dependent on:

(a) The extent to which declining current profits were (subjectively) attributed to past R and D failure; in so far as detailed assessments of profit expectations were discouraged, this 'confidence factor', which I mentioned before, acted as a proxy for expectations.

(b) The extent to which pressure on the company directs it towards R and D spending – primarily dependent on the nature of the market and the competitive process (this direction is likely to be strong in the case of the innovatory pharmaceutical firm).

This apart, over long periods, and in virtually every industry, Mueller found the most significant explanatory variable of R and D spending to be the industry index of R and D: sales intensity. Short-run variations in profits and sales had virtually no effect on budget levels, while, lastly, again as might be expected, he showed up the high interdependence of research spending, capital investment and sales promotion in product innovatory industries, where R and D is less an optional strategy than an integral part of the whole process.

Lastly, Grabowski's(11) more recent study found that, given the high unpredictability of the results of research, there appeared strong dependence on past results as a guide to the future. In the specific case of R and D, this meant, at least partially, an assessment of physical productivity (some ratio of R and D input to output). As the CSII Report(7) pointed out, productivity within the firm may be assessed in a variety of ways; Grabowski's index used numbers of scientists employed for input, patent registrations for output – mainly by virtue of the data available. His results suggested that changes over time in this index and in the average R and D intensity of the industry exerted strongest long-run influence on spending levels.

What does this leave us with? Clearly no well-defined model of the R and D decision which could be used to predict the outcome of changes in profitability and risk expectations. The decision process is too subjective and too bound up with the overall situation of the individual company – its structure, degree of involvement in research, the state of its other activities; in all of these respects the companies in the pharmaceutical research sector are too varied to allow generalisation. Given that most of the research-based companies have been highly profitable in the past, should the possibility of relatively spectacular success, though

perhaps reduced, still be present, this is bound to produce a pattern of behaviour which, even over a relatively prolonged period of falling profits, growth and general confidence, will result in a tendency to increase rather than reduce spending on research, (particularly where, as is likely, the deterioration is not uniform across the industry). Even the relatively unsuccessful companies will, in so far as they remain financially able, prevent R and D spending from falling below what they see as the critical level (suggested as being 7 per cent of sales) to ensure survival. Obviously the companies which can cross-subsidise unsuccessful research from sales in other areas, over relatively long periods, will be more strongly placed here than companies more concentrated on the output of genuinely risky long-term research. Again, one returns to the point, crucial in assessment of the impact of research 'risk', that the former circumstance is more common. No company I spoke with seemed to have experienced a situation, as yet, in which it had become so worried about the prospective failure of pharmaceutical activities to meet at least minimal expectations that it was contemplating *major* diversification outwards. The norm still appears to be pursuit of a long-term increase in research intensity, notwithstanding relatively limited attempts by some of the more 'pharmaceutical intensive' companies to diversify (Roche, for example). Whether this is to be seen as a defensive reaction to declining success and impending patent run-outs by well-established companies (Beecham) or offensive strategy by companies building up levels of participation as a result of research success in pharmaceuticals and pressure in other activity areas (ICI), the result is an increase in research spending.

It may be, then, that the supply price of risk capital to research considered in isolation will have to rise very considerably to slow down, far less stop, increases in R and D spending by companies in the research based sector. This says nothing, of course, about the level of new entry to the sector, the second component of any increase over time in research investment. It may be that here we have the area likely to be considerably more susceptible to shifts in relative profitability and risk. The key word here is, of course, *relative*.

Is there still belief, in the industry, that adequately profitable research success can be generated from an increasing research effort? This returns to my set of determining factors – opportunity, capacity and pressure.

### **Opportunity, capacity and pressure in research**

Not surprisingly, in this highly subjective area, one finds considerable diversity of opinion offered by research directors. The case for pessimism is generally made in four parts:

that the *physical productivity* of research has been and is declining;

that *lead-times* in the research and marketing processes have increased substantially;  
that the *cost* of a given level of research effort has been rising rapidly, and that;  
pressure on domestic (NHS) prices has added, dangerously, to the factors already depressing *profitability* and cash flow in the research sector.

#### *Physical productivity*

The argument, here, is two-fold. Firstly that the attrition rate in chemical compounds has increased materially – the standard figure quoted is that it now takes, as a rough average, 5,000 initially screened compounds to derive one final product, considerably higher than in the early 1960s. More significantly, one of the companies quotes figures which appear to indicate that, say, thirty of these compounds will survive to ‘product candidate’ stage (beyond which patenting takes place and 75–80 per cent of total R and D spending is incurred).<sup>9</sup> I was unable to discover whether this 30:1 ratio, which seems more meaningful, represents an increase over earlier periods, though it does, *a priori*, seem a significantly high wastage rate in terms of costs. One research director estimated that a reasonable, if still imprecise, figure for attrition would be that only 8–10 per cent of projects instituted and carried to ‘a significant expenditure level’ resulted in what was thought of as a ‘satisfactory’ market pay-off.<sup>(9)</sup> The director felt that his company had significantly reduced the financial costs involved in wastage rates by imposing a more rigorous technical audit on project teams and reducing the amount of time spent in the investigation of compounds related to an identified product candidate.

Given the relatively narrow technical base of the drug industry on which a strongly product innovatory structure is erected, this pattern of increasing attrition is presumably inevitable in periods between major waves of discoveries – particularly in view of the research methods of the chemicals sector of the industry. Again, except in so far as companies genuinely cannot or will not bear the costs of such attrition, the short-term effect will probably be to increase research spending, while the long-term impact will depend on belief that further major discoveries are possible in commercially exploitable treatment areas. As I have mentioned, this is highly subjective and the very different experience of individual research directors results in an expectedly wide diversity of opinion.

Secondly, and directly relating to that last point, it appears to be generally accepted, again in both UK and USA industries, that the rate of new product introductions has declined steadily over the 1960s. Table 1

<sup>9</sup> Private communication. I could not obtain access to any data which would permit anything very useful to be said on the financial implications of attrition.

relating to the USA, appears to show this clearly, with a drastic fall in all categories of introductions. Column (2) is the most significant in relation to research productivity.

The obvious criticism of these data is that they say nothing about the profit and growth outcome of research successes – in particular the extent to which failures are now picked up, to a greater degree than before, prior to actual introduction. As a corollary of that, we do not know the extent to which the observed decline in introductions is a result of more stringent testing regulation and practice as against deterioration in physical productivity, a distinction which might have some implication for management behaviour should testing methods prove capable of improvement. I have no information on any of these points, excepting the results of an unpublished study, by Carpenter,<sup>10</sup> of the same period, which rated new introductions by degree of chemical novelty; introductions of his top-ranked products also showed a decline over the period, but a very much less significant one, clearly an important factor if there is a close relationship between degree of novelty and commercial success (which is, however, by no means inevitable). To the best of my knowledge, no similar data exist for the UK. Table 2 summarises the Annual Reports of the Committee on Safety of Drugs.

**Table 1** *New pharmaceutical drug products introduced in the USA, 1958–68*

(1) <i>Year</i>	(2) <i>'New single chemical entities'</i>	(3) <i>Firms Introducing</i>	(4) <i>'Duplicate Single Products'</i>	(5) <i>'Combination Products'</i>	<i>Firms Introducing</i>
1958	44	29	73	253	126
1959	63	43	49	203	107
1960	45	32	62	199	109
1961	39	27	32	189	111
1962	27	22	43	180	108
1963	16	12	34	149	89
1964	17	15	29	111	82
1965	23	17	18	71	65
1966	12	11	15	53	52
1967	25	18	25	32	49
1968	11	9	26	50	48

*Source* Paul De Haan, Inc. (14)

10 Communicated to George Teeling-Smith of OHE and quoted in (7).



**Table 2** *New product submissions and rejections*

	1964	1965	1966	1967	1968	1969	1970
New substances remitted of which (+carry forwards) (entirely new formulations)	600 (55)	1,041 (69)	1,004 (66)	888 (56)	875 (56)	935 (66)	836 (69)
reformulations	(545)	(972)	(938)	(802)	(819)	(869)	(767)
Cleared in period	386	807	771	698	669	694	499
Definite rejections or withdrawals	47	138	110	106	119	119	132
Referred back to applicants	99	49	39	43	34	47	68
Still under consideration	68	47	84	41	53	75	137
% rejected (total)	7.8	13.2	10.9	11.9	13.6	12.7	15.8

Source Annual Reports of the Committee on Safety of Drugs, 1964-70.

Given that the significant USA decline took place before 1964, the picture appears broadly similar – ‘wholly new formulations’ show a virtually constant absolute number of introductions, suggesting declining physical productivity of a rising research effort, hence a declining rate of innovation,<sup>11</sup> while there is an upward trend in the rejection rate. It is apparent that there are important problems of definition in the data, but, that apart, their usefulness is, as before, limited by inability to relate apparently declining physical productivity to realised profitability and growth potential. Equally, we have no idea of the actual financial losses imposed on the companies by the quoted rejection rates, hence the extent to which financial risk is increasing.

#### *Product lead-times*

One can identify two significant increases in the time-lags involved in product introduction, again apparently applicable in both Britain and the USA.

(a) *Initial screening to marketing*: It is normally suggested that this period has at least doubled over the last ten or twelve years, with relatively conservative estimates putting the present lag at eight or ten years, by virtue of increasing technical difficulty and increased testing requirements.

(b) *First marketing to peak sales level*: Alan Angilley of ABPI produced some interesting data on product age structure and market share in the CSII Report(7). It would appear that, up to 1962, new introductions achieved their peak market share, on average, within three years, while since then this figure has doubled.<sup>12</sup>

The obvious implication of this is that the overall time-lag between the incurring of research expenditure and the generation of cash flow from research output has lengthened very considerably, increasing capital tied up in the drug production process and, most important, reducing the effectiveness of patent protection as the companies became increasingly unable to generate a rapid enough flow of new products to match patent expiries – if high profitability is largely dependent on the ‘monopoly profits’ of patent-protected major innovations and if that patent protection is already at least potentially weakened by pirating activities and the

11 But see page 85. (The ‘rising effort’ has to be deflated, to take account of cost inflation and increasing testing requirements.)

12 The Report identified the primary causes of this as being the greater conservatism of doctors following the thalidomide tragedy and the more fundamental nature of product innovations, rendering it more difficult to put new products across to doctors – without claiming the slightest technical knowledge of this, I should have thought that, *a priori*, exactly the opposite reason could be cited for greater difficulty in putting new products across, though I gather that this is rejected on grounds that the new products eventually achieve the same rate of acceptance as before.

threat of Section 41 of the Patents Act, this is likely materially to affect expectations in the research area.

Dependence on the patent period for generation of 'research inducing' high profits through high prices would presumably be the counter to an argument that a slow-down in the rate of new product introduction will reduce the impact of one risk characteristic of the industry – rapid change in market share (at the level of the total NHS market, for example, of the ten leading companies in 1962, only three remained in the top ten in 1970).

This rapid change appears to be a genuine enough indicator of market risk – particularly given the narrow product range of most companies' NHS sales, though subject to the qualifications that an overall rapid rate of market growth may reduce the impact of changes in market share, and that the cost impact of rapid product obsolescence is reduced by the versatile capital plant used in batch processing.

### *Research costs*

Lastly, as lead-times have increased, so have the costs of an on-going research effort. On the basis of data I received from four of the research-based companies, an annual average increase of 10 per cent would be a reasonable estimate, at least since 1966/67. The minimum R and D cost per (major) project has been put (7) at £200,000 per annum, but with some companies prepared to spend up to £600,000. (This tallies with the figure, I mentioned earlier, of roughly £600,000 per annum (three or four projects) as the 'entry threshold' to research activity, and implies that, at the very top of the UK spending league, companies are likely to run, at most, six to eight major projects at any time.)

Recognising that the research costs of unsuccessful projects have to be met out of sales revenue from marketed products pushes up the 'full' research costs of successful projects very considerably – it would make, for instance, a figure of £3–5 million, spread over six to ten years appear relatively conservative. Viewing this outlay as the capital cost of an 'average' R and D project and given the lengthy time-lags involved in pay-off, it is hardly surprising that a formal DCF analysis of research spending would produce frightening results, using what are thought of as appropriately high (risk) discount rates to represent the real supply price of capital to research as a separable investment activity.<sup>13</sup>

13 Mund(14) analysed the 'real profitability' of research in the USA industry in terms like this. Using a derived 'average full research cost' of a marketed new chemical entity and a series of assumptions about time lags, profit margins, etc. he reached the conclusion that only a handful of products, currently marketed, in the USA, achieved sales levels sufficient to generate a DCF yield of 13 per cent – thought highly conservative in view of research risk. Apart from reservations about some of the methods and figures used, and about the basic methods of analysis, this approach means very little in an industry for which 'averages' of any kind have almost no significance.

As we saw earlier, visibly, and perhaps fortunately, management does not carry out such an analysis of research projects in isolation from the rest of the firm's operations. As far as the research-based pharmaceutical chemicals sector of the industry is concerned, this seems, to me, defensible, for two reasons.

(a) The research activity cannot, meaningfully, be considered apart from the rest of the operation; they are interdependent, both in the obvious sense that the research process guarantees long-run survival and profitability, underlying the whole competitive structure of the industry, and, less obviously, in so far as research involves spill-off effects. I have in mind, here, the creation of goodwill in the medical market, establishment of a base for negotiating licences, and the scope which an on-going research effort gives for the rapid production of relatively imitative products.<sup>14</sup>

(b) Neither company management nor shareholders are likely to assess the profitability of an entire activity in DCF terms. Where a company is concerned with long-term growth and survival, rather than medium-term profitability, the use of discounting techniques unduly penalises investment projects specifically aimed at long-term growth and survival. R and D investment clearly falls into this category – it has been suggested that, were research to stop immediately and completely across the whole industry, it would remain highly profitable, but its rate of growth would fall materially.<sup>15</sup>

#### *Profits in the research-based sector*

It will be obvious, by this time, that little or no worthwhile data are, as yet, obtainable in the research area of pharmaceuticals, partly by reason of the structure of the 'industry'. This is particularly true of any figures produced to represent profits or profitability, (which should be the centrepiece of this analysis, as they relate most directly to the inducement to invest in research, the capacity to carry it out and the assessment of its commercial success). I should, therefore, make it clear that any figures I do quote are subject to considerable reservations and, further, that I am obliged to refer,

14 Walker(15) suggested that the building up of 'brand name goodwill' by companies in the USA market, at least partly on the basis of research success, had enabled these companies to charge relatively high prices in individual sub-markets and to establish high sales levels for relatively undistinguished products – he went so far as to suggest that the existence of a powerful marketing team could guarantee a market for even what might be classed as the 'failures' of research activity. This type of criticism has, I think, been considerably overplayed, on the basis of a few largely unrepresentative cases; no one has produced any evidence that medically insignificant products achieve undue market success (partly by virtue of the difficulties in defining what is 'medically significant') – even if they did, on occasion, the 'insurance' aspects of this may help induce more socially useful research.

15 Steel H B, Commentary on Mund's paper in *Economics of Drug Innovation*, Ed. Cooper J D(14).

only very generally, to data which are, at the time of writing, wholly confidential.<sup>16</sup>

As I have mentioned, the principal concern of the industry has been that cost inflation and pressure on domestic ethicals prices have significantly reduced sales margins in the NHS market, that the export sector has also been hit by inflationary pressure and is likely to be increasingly affected by transfer effects of UK government intervention. The evidence does seem relatively clear on a significant fall in net profit margins over the 1960s, though it does not enable one to say anything about causation, notably the extent to which margins have been deliberately reduced on some of the (relatively few) major products in the NHS market. Less clear is precisely what this has meant in terms of profits and profitability, though, in the current industrial climate, it seems unlikely to me, that pharmaceuticals have lost any significant relative ground, particularly bearing in mind the condition of virtually every major European chemicals company.

On the 'capacity' side, Table 3 shows the cash flow record of eight

**Table 3**

(1) *Annual percentage changes in (after-tax profit + depreciation) for eight major NHS suppliers (total company profits)*

	1	2	3	4	5	6	7	8
1962-63	0.6	6.4	-0.5	12.0	10.4	-6.0	14.0	3.4
1963-64	13.4	16.3	16.9	17.3	10.9	3.2	2.7	8.4
1964-65	14.5	16.7	35.7	10.4	19.5	28.1	4.0	21.5
1965-66	45.1	37.9	12.3	11.7	15.4	17.0	12.8	33.2
1966-67	14.7	-2.3	17.4	2.7	-5.5	2.1	12.5	12.6
1967-68	19.8	7.7	33.1	8.3	11.2	2.0	29.1	1.7
1968-69	16.8	6.7	11.9	28.4	10.7	36.0	-10.2	29.2
1969-70	16.0	10.2	13.7	3.4	13.3	1.2	5.2	1.5
1970-71	20.7	24.4	8.4	13.9	9.2	—	—	—

Source Published accounts.

(2) *Annual percentage changes in gross profits (industry totals)*

	(1) Total Manufacturing	(2) Chemicals and Allied	(3) Food, Drink and Tobacco	(4) Pharmaceuticals
1965-66	-5.4	5.8	2.3	10.0
1966-67	2.2	8.4	4.0	22.0
1967-68	13.9	12.3	5.6	13.0
1968-69	-5.8	-2.5	-4.0	9.0

Source 1971 Annual Abstract of Statistics, NEDO Report (8).

16 With this in mind, I have omitted reference to my sources for at least part of what follows.

major NHS suppliers, including all the large research-based UK companies and on a more restricted time series, relative changes in the gross profits of total manufacturing and three relevant industries. Part (1) shows, as would be expected, a considerable range of experience in both the size and the variability of annual changes in cash flow, but no clear picture of a downturn over the period and an overall impression of a healthy cash flow situation, with virtually every annual change positive. These are, of course, total figures for the companies' overall activities, which have only been split by principal product area, for net profit and turnover, since 1967. Part (2) of Table 4 shows this division, for three principal UK companies, which does indicate a reduction in annual increases of both profits and turnover in pharmaceuticals – significant as far as investment capacity is concerned, but with the obvious qualifications, with regard to inducement, that, in virtually every case, the downturn is less serious than in the rest of the companies' activities and that the changes remain, for the most part, strongly positive.

Part (2) of Table 3 also shows a healthy picture for pharmaceuticals, markedly more so than for total manufacturing, food and drink, or chemicals, with, again, the reservation that the figures for pharmaceuticals are provisional. Clearly, on the basis of this, admittedly flimsy, evidence, the situation has some considerable way to go before one could regard it as critical.

Relating more directly to the inducement aspect of profits and to the measurement of 'efficiency' in the industry is *profitability*.

The profitability evidence, such as it is, is in the form of historical, accounting ratios of profit to capital employed. Two categories of problems arise in use of this at all, those of (a) *definition* and (b) *interpretation*, (which would merit a separate paper in their particular relevance to the pharmaceutical industry).

(a) The ratio itself may be worked out on the basis of gross or net profit (gross or net or tax/depreciation) and capital employed (gross or net of current liabilities/depreciation). It is highly sensitive to the financial structure of a company or industry, notably the reliance of companies on overdrafts and, in the case of subsidiaries, inter-company current loans (current liabilities).

This is clearly relevant both in comparing rates of return in pharmaceuticals over time and with other industries: in the former case, the financial structure of subsidiary companies (numerically extremely significant in 'the pharmaceutical industry' in UK) is likely to alter as they mature; in the latter, the typical financial structure of the industry may be different.

The ratio, again as far as comparison purposes is concerned, is also sensitive to the relative labour-capital intensity of a company and, more

**Table 4** \*Selected UK company statistics*(1) Overall profit/capital employed (average)*

	1960-64	1965-69	( <i>Extel Definition</i> )
			1960-69
Glaxo	22.7%	24.6%	23.9%
Beecham	35.2%	39.1%	37.8%
ICI	10.8%	10.7%	10.7%
Boots Pure Drug	19.5%	18.8%	19.0%
Smith & Nephew	15.6%	18.9%	17.4%
Reckitt and Coleman	19.1%	17.4%	18.1%
Wellcome Foundation	18.7% (1962-65)	21.9%	20.7% (1962-69)

*(2) Annual increase of turnover in drugs*

	1968-69	1969-70	1970-71
<i>Glaxo*</i>	5.5%	14.5%	9.5%
(Total turnover)	(14.0)	(12.6)	(9.7)
<i>Beecham</i>	33.3%	30%	24.7%
(Total turnover)	(15.9)	(20.4)	(12.9)
<i>ICI</i>	23.5%	14.3%	12.0%
(Total turnover)	(26.3)	(9.5)	(7.9)
(**Pharmaceuticals and Food')			

*(3) Annual increase of profits in drugs*

	1968-69	1969-70	1970-71
<i>Glaxo*</i>	11.6%	11.8%	1.3%
(Total turnover)	(15.1)	(9.9)	(-1.6)
<i>Beecham</i>	21.4%	33.3%	17.6%
(Total turnover)	(21.8)	(17.5)	(16.0)
<i>ICI</i>	60%	25%	0%
(Total turnover)	(43.4)	(8.6)	(-16.5)
(**Pharmaceuticals and Food')			

*(4) Ratio of net profit/turnover*

	1967	1968	1969	1970	1971
<i>Glaxo*</i>	—	20.1%	21.3%	20.8%	19.1%
(Total turnover)	—	(15.9)	(15.1)	(14.7)	(13.1)
<i>Beecham</i>	—	32.9%	30%	30.8%	29.0%
(Total turnover)	—	(18.4)	(18.7)	(18.3)	(18.8)
<i>ICI</i>	29.4%	38.1%	40%	35.8%	33.9%
(Total turnover)	(12.5)	(14.1)	(13.0)	10.8)	(9.2)
(**Pharmaceuticals and Food')					

Source Published Accounts.

obviously, to its policies on the capitalisation of expenditure. The pharmaceutical manufacturing industry is generally taken to be relatively labour intensive, but this is likely to vary between, say, the pharmaceutical chemicals and pharmaceutical preparation areas of activity. More important, despite the obviously 'long-term investment' nature of most research spending, all expenditure except that on conventional 'capital equipment' is written off as incurred – producing highly conservative profit and loss accounts and relatively very narrowly based net asset statements. In a period of accelerating research expenditure this will produce a downward bias in profit to capital employed, which will swing back up again on the pay-off from research accruing to the company. (This may, of itself, account for part of the observed shifts in profitability over the 1960s.) Overall, though, the effect of 'conservative' R and D accountancy will be to inflate profit–capital employed in an R and D intensive group of companies and to render it, at best, a poor comparative ratio. These criticisms will, obviously, apply still more strongly when both profit and capital employed data on pharmaceuticals have to be extracted from financial accounts of subsidiaries or operating divisions of diversified companies.

(b) The interpretation problems follow directly from this – although some of the above problems can be eliminated in the data normally presented for analysis. To these one must add the rather wider question; who precisely is interested in historical profit–capital employed and for what purpose? The usual answer is that both management within an industry and potential new entrants to the industry will assess its overall relative attractiveness at least partly on the basis of historical return on net assets. Clearly, in so far as this implies that managements and shareholders are primarily interested in overall rate of return, it is an oversimplification – even forgetting about the problem of risk and how it is measured, there is growth, cash flow and there is the problem of the diversified company, perhaps with still more involved criteria of judgement. Despite all this, to some of which I return later, it is conventional to measure comparative industry and company performance in terms of historical rates of return.

By any such standard, profitability has consistently been and remains at the top end of the industrial scale. Figures produced for aggregate (net) profit to (net) capital employed in the industry, taking 1968 and 1969 as an example, show:

1. Pharmaceutical industry profitability lying 8–10 per cent above the 'total industrials' average used in the *Financial Times* 'Trend of Industrial Profits' table, and some 12 per cent above the corresponding figure for the Chemicals Industry as a whole (though the latter ratios include overdrafts in capital employed while the former does not).



2. An unusual concentration of high profitability at the upper end of the size scale – including the research-based companies. Median profitability appears to be not far short of 50 per cent of the weighted average, 75 per cent of companies lie below the weighted average and the upper to lower quartile spread is a mighty 22 percentage points – between two and three times the figure for all manufacturing industry.

This is a feature of profitability – its high dispersion around industry mean and median – both in the USA and UK industries which has been used (12, 13) to justify the assertion that the drug industry, say from the viewpoint of a potential entrant, is highly risky and must continue to generate a high level of profitability, if new capital is to continue to flow in. The argument seems weak to me: if variance in profitability is to be considered only on a cross-sectional basis, in an ‘industry’ with as unusual a structure as pharmaceuticals, there are far too many reasons for the higher dispersion of profitability in drugs in contrast to virtually any other comparable industry. More generally, a potential entrant will presumably look only at the record of companies similar in structure and size to its intended structure and size – if the typical new entrant is a large diversified company, it is to these already in the area that it will look. This has been very much the pattern of new entry to the industry, particularly to the research-based sector, and is likely to continue to be, as technical and financial entry barriers increase in both ‘chemicals’ and ‘preparations’ areas of the industry(8).

Without being able, for reasons of space, to defend the opinion, I tend to take the view that technical entry barriers have been rather more significant in the industry than has often been suggested; and further, that these, added to the protection offered existing companies by the patent system (in a rapidly changing product innovatory market), research and marketing thresholds, may have been at least as effective as ‘high risk’ in maintaining above-normal levels of profitability in the industry.

3. What is, presumably, partly the cause of (2), that profitability appears to be very much higher in the export than the domestic side of the ethical business.

On the other hand, entirely on the basis of confidential (and highly debatable) data, covering the period to 1969, overall profitability appears to have been declining over most of the 1960s, but particularly since 1966/67 and particularly in the NHS market – with the industry’s fear growing, as I have mentioned, that the pressure on sales margins, believed to be causing declining profitability, was beginning to spread to export markets. The data are highly contradictory on precisely where the profitability decline is taking place – more or less uniformly across the industry or concentrated on particular areas – and it has not proved possible to look at this in any detail. Apart from cost inflation, the fourth *vPRS*, the impact

of competition or the beginning of a long-term downturn in the industry's prospects the apparent fall in profitability might be caused partly, as I have already suggested, by changes in the financial structure and policy of subsidiary companies in the foreign-owned sector or by the effects of accelerating research spending on the profit to capital employed ratio in particular large companies.

Irrespective of causation, if we accept that profitability has fallen over the 1960s, how significant is this for investment in research? I have two very limited indicators that it might be less important than has been suggested. Firstly, the more limited; Part (1) of Table 4 shows the profitability (on one definition), over the 1960-69 period, of seven major UK research-conducting companies. There is no evidence of any decline in profitability over the latter part of the period. The figures do, of course, relate to the companies, not their pharmaceutical divisions, but I should have thought it, on balance, probable that profitability has held up rather better in pharmaceuticals than in their other principal activities. (Further, without in any way accepting this unreservedly, one of the data sources I have been referring to does suggest that the profitability decline was not taking place, to any marked extent, in the UK research-based sector.)

More important, given that we are concerned with the inducement to invest (and again with reservations about the data), it appears that the 'profitability premium' of pharmaceuticals, over total UK manufacturing and chemicals, has widened rather than narrowed over the 1960s. I have consistently been stressing the need to look at relative figures in this paper - here, again, it seems to me that, relatively, the position of pharmaceuticals, particularly ethical, remains sufficiently strong to obviate concern, at least at present.

### **Conclusions - growth and research spending**

My general conclusion would be that, on the basis of historical information, there seems little immediate cause for concern. Profitability, on the measures used so far, appeared to decline over the 1960s as a whole and 'risk' to increase. The industry, however, remained consistently 'high growth' and highly profitable by all relevant standards. The Chemicals Industry gross output index,<sup>17</sup> 1963-70 shows the pharmaceutical sector with an average annual growth rate of 11 per cent, compared with 6.7 per cent for the general industry index and 3.5 per cent for all manufacturing industry. (The 1969-70 figures are, respectively, 9.9 per cent, 5.9 per cent and 1.2 per cent - again, a slight decline, but not a *relative* decline.)

Table 5 gives the 1960-70 ABPI data on ethical sales and R and D spending, and my estimates of annual growth in each.<sup>18</sup>

<sup>17</sup> *Trade and Industry*, 25th November 1971, pp. 423-5.

<sup>18</sup> Compound rates of growth for each period.

The most significant features of this are:

- (a) Relatively very rapid growth in the export sector (as might be expected from the data on profitability).
- (b) The relatively constant relationship between ethical sales and R and D spending, in direct monetary terms.
- (c) The apparently rapid growth of R and D spending particularly in the second period. This is very heavily qualified by the effects of inflation. Strictly, on the basis of cost inflation mentioned above, it appears possible that the 1967-70 increases in R and D spending did little more than maintain a given 'real' research effort. I believe recognition of this may be partly responsible for the expressed intentions of the major UK companies to increase spending levels markedly in the current period, to produce an overall 'step-up'.
- (d) Visible evidence that there has been no decline in growth rates over the late 1960s.

This is borne out in the profitability evidence I referred to earlier, (bearing in mind the considerable reservations that one has about any such data, as applied to this industry). The growth rates of aggregate

**Table 5** *Sales and R and D spending*

	(1) Sales (£m)			(2) R and D spending (Current) (£m)	(3) R and D as percentage of total sales
	NHS	Export	Total		
	£	£	£	£	%
1960	64	49	113	7.5	6.6
1961	70	54	124	7.8	6.3
1962	76	56	132	8.3	6.3
1963	84	54	138	—	—
1964	89	60	149	10.4	6.9
1965	106	68	174	11.6	6.7
1966	118	75	193	13.0	6.7
1967	129	79	208	14.5	6.9
1968	139	97	236	—	—
1969	154	119	273	—	—
1970	173	134	307	22.0	7.0

*Growth Rates (%)*

1960-69	9.5	9.6	9.5	10.3
1960-65	8.7	5.6	7.4	7.5
1965-69	9.9	12.3	10.1	11.1

Source ABPI Annual Report, 1971.

industry profits and capital employed, over the same periods as used in Table 5 are given in Table 6. (Over the 1960-69 period, trading profits increased by 50 per cent, total sales by 170 per cent, net assets by 90 per cent and R and D spending by 195 per cent.)

The same conclusions apply here - with the same reservations about these being undeflated monetary figures (on the basis of official statistics, the above growth rate of net assets is well over twice that for all manufacturing).

Pharmaceuticals have, then, maintained high growth over this whole period and are apparently sufficiently profitable, in relation to what are seen as alternative investment areas, to continue to attract new capital and increasing levels of R and D spending. Forecasts for the short to medium term(8) point to probable maintenance of these growth rates, and what is more important, probable maintenance of the favourable differential in relation to other branches of the Chemicals Industry. This suggests to me that, even accepting the evidence of an overall decline in the profitability of the industry, investment prospects are still likely to be seen as relatively attractive, with the qualifications that: in so far as profitability of the large research-conducting companies appears to have become more concentrated in the export sector, the spread of price pressure into exports, which the companies believe to be a likely result of government pressure on NHS prices, will ultimately erode this base; and, to the extent that profitability is dependent on existing strong patents, which cannot be replaced fast enough, by even an increasing research effort, the incentive to invest will eventually be eroded.

What does not seem likely is a dramatic surge in new entry to the research sector; as I mentioned earlier the NEDO Report (8) concludes that entry barriers, previously significant primarily in the marketing/brand name area, have increased and will continue to increase in both pharmaceutical chemicals and preparations.

So, in the immediate future, no threat to the level of research investment; in the longer run, one has to finish on an unsatisfactory note.

Until further information is available on precisely how managers assess

**Table 6** *Annual growth rates of aggregate profits and capital employed*

	(a) <i>total capital employed (net)</i> <i>per cent</i>	(b) <i>total profit (net)</i> <i>per cent</i>
1960-69	6.6	5.8
1960-65	4.6	5.5
1965-69	8.9	6.0

research success, and what is regarded as an unacceptable rate of failure, we cannot say very much about the effects of what appears to be a declining success rate. In terms used at the outset, too, the long-term outcome depends on the extent to which management believes that any genuine decline in research productivity is reversible. Should there be no further breakthrough of technical and commercial significance, similar to that in antibiotics and anti-depressants, and should belief in the possibility of one diminish over time, the industry's growth rates and profitability will obviously decline to more 'normal' levels. Whether or not the industry's research effort is in directions likely to produce such breakthroughs, if indeed they remain possible, is for the scientists to say. Should expectations of declining profitability push even a reduced R and D effort towards more fundamental research, it may be in the long-term interests of both the industry and society.

#### References

1. Mottley C M and Newman R D, 'The Selection of Projects for Industrial Research'. *Operations Research*, 1959.
2. Hertz D B, 'Risk Analysis in Capital Investment'. *Harvard Business Review*, 1967.
3. Hillier F S, 'The Evaluation of Risky, Interrelated Investments'. North Holland, 1969.
4. Adelson R M, 'DCF - The Other Point of View'. Spring 1971.
5. Chambers D, 'Programming Allocation of Funds Subject to Restrictions on Reported Results'. *Operations Research Quarterly*, 1967.
6. Reekie W D, 'The Economics of Innovation, with Special Reference to the Pharmaceutical Industry'. University of Strathclyde, unpublished PhD thesis, 1969.
7. Centre for the Study of Industrial Innovation. Report for the National Economic Development Office on the level of Innovative Activity in the Pharmaceutical Industry (1971).
8. NEDO. Report of the R and D Sub-Group and the Structure Sub-Group of the Pharmaceutical Working Party.
9. Minasian J R, 'The Economics of Research and Development'. The Rate and Direction of Inventive Activity, MBEH, 1962.
10. Mueller D C, 'The Firm's Decision Process: An Econometric Investigation'. *Quarterly Journal of Economics*, 1967.
11. Grabowski H O, 'The Determinants of Industrial R and D: A Study of the Chemical Drug and Petroleum Industries. *Journal of Political Economy*, 1968, part 1.
12. 'Profitability in the Pharmaceutical Industry'. Merrett, Cyriax Associates, August 1968.
13. Conrad G R and Plotkin I H, 'Risk and Return in American Industry'. May 1967.
14. Mund V A, 'The Return on Investment of the Innovative Pharmaceutical Firm'. *Economics of Drug Innovation*, Ed. Cooper J D, American University, 1969.
15. Walker H D, 'Market Power and Price Levels in the Ethical Drugs Industry'. Indiana University Press, 1971.

My profound thanks, for considerable assistance in preparation of this paper, are due, first of all, to George Teeling-Smith of OHE, Alan Angilley of ABPI, Professor Alexander of Strathclyde University and Peter Mould of NEDO. Also to Dr L J Edwards of Beecham Research Laboratories, Mr Page of Pfizer, Mr Berry and Mr Beaton of Wellcome, Mr Crane of Merck and Mr George Smith of John Hamilton (Pharmaceuticals).

# Social and economic pressures on the pharmaceutical industry

George Teeling-Smith

The present social and economic pressures on the pharmaceutical industry are neither new nor unique. Viewed historically medicine makers have always been regarded with suspicion. Over the centuries, medicines have been able to influence the minds and bodies of men, and people have perhaps found it hard to believe that their makers could resist taking advantage of the power which this conferred on them. In addition, medicines often act in incomprehensible ways – at least to the layman. The actions of a surgeon are clear to see; by contrast a pharmaceutical preparation acts invisibly. This, of course, leaves the medicine open to the accusation that it may be having unseen harmful effects as well as beneficial ones. To some extent these fears are rational; however, for reasons which I shall go on to discuss they appear now to have resulted in pressures and constraints on the pharmaceutical manufacturers which are unreasonably stringent.

The pharmaceutical industry is not alone in having faced this problem. On the question of safety, I shall give examples of many other products and industries with similar experience. Historically, too, one can compare the present situation of the pharmaceutical industry with that which, in the past, faced the brewers and distillers. In the days of Hogarth, alcohol was frankly and widely abused – just as drug pedlars in those days could sell useless and sometimes harmful nostrums in the market place. As a result of these abuses the sale of medicines was controlled by the Pharmacy and Poison Acts; and the misuse of alcohol was controlled by the licensing laws and by excise duties. Nevertheless, fears in relation to the abuse of alcohol remained unallayed. By the early years of this century, these fears in Britain had led, for example, to nationalisation of licensed premises in Carlisle and to Defence Regulations giving the British government power to nationalise the whole liquor trade, lock, stock and barrel. Similarly, the United States went on to experiment with total prohibition. Gradually, since the 1930s, a more balanced view has prevailed in relation to alcohol. The risk of abuse is no less, but in social policy this risk is now balanced against the benefit derived from the moderate and convivial use of beer, wine and spirits. By contrast, over the past twenty years new and intensified fears have re-emerged in relation to the production, sale and use of medicines. Thus, my theme in this paper is that the control of pharmaceuticals is still, by analogy, heading in the direction of the nationalisation/prohibition phase in respect of alcohol. That is, controls and pressures are

becoming stricter, to some extent over-reacting to fears about the abuse of pharmaceuticals in the way that the American prohibition movement over-reacted to the earlier abuse of alcohol. I shall develop this theme under four broad headings. The first is safety; the second I have called the avoidance of undue persuasion; the third is prices and profits and the last is the social implications of medication.

### **Safety**

A number of tragic episodes have shown over the past thirty years that the products of the therapeutic revolution can cause harm as well as good. Each tragedy has led to a new outcry that medicines must be made safer, that risks must be reduced and that benefits must be demonstrated more clearly to outweigh any possible hazards in new medicines. As I suggested in my introduction, this is a quite general phenomenon, not confined to pharmaceuticals. Society is demanding that the world should be a safer place.

Road traffic accidents are one good example. It is a remarkable fact that the numbers of deaths in road accidents in the 1970s is no higher than that in the mid-1930s, despite the fact that there are about ten times as many vehicles on the roads and average speeds have greatly increased. This achievement has been due to stricter legislation, improved roads, better driver training, and vastly improved vehicle design and medical services. Yet despite this, there is continual pressure for even greater restrictions on drivers and for even more expenditure on road and vehicle safety. With 7,000 deaths a year on the roads, this pressure must, of course, be accepted as desirable – although if it is successful it will bring higher costs and less convenience to the average road user. My point is rather that we now find unacceptable a standard of safety which in terms of mortality per vehicle mile is something like one-tenth of that of the mid-1930s. This is a reflection of society's rising expectation – and demands – that hazards of life should be eliminated. Many other examples can be quoted: food hygiene standards; flammable clothes and other fire risks; electric appliances; risks of poisoning for example from lead and mercury; and even the recent concern about accidents to children on escalators and to infants in carry-cots.

There is another feature of this more critical appraisal and lower threshold of acceptance of risks which is particularly relevant to pharmaceuticals. We seem to be increasingly suspicious of technological advances. In many fields the general application of new technology is tending to fall further behind its initial introduction. That is, there is a widening gap between current technology in use and what can be described as the 'leading edge' of the same technology. Aerospace is an example. In the 1930s, Imperial Airways were using aircraft which were more or less as

technologically sophisticated as any then flying. There was probably little or no more advanced mechanical or navigational technology in use. To a large extent this was still true of the Comets in the 1950s. They were flying at comparable heights and not all that much slower than the contemporary experimental aircraft. In consequence a totally unexpected design fault occurred with the Comets in service, causing a tragic loss of life. By contrast, now in the 1970s, although Concorde is to be the first supersonic passenger transport, it is deliberately designed to rely as far as possible on existing technology. The most advanced aerospace technology is now represented by the Apollo spacecraft. The technological gap between Apollo and Concorde is of a different order of magnitude than that between the Comets or the 1930s airliners and the respective experimental aircraft of their times. Partly in a response to demand for greater safety, new technology is now more slowly applied.

This is a notable characteristic of the pharmaceutical market also as Gordon Hellyer has already pointed out. Certainly under the FDA in the United States the point has now been reached where the delay in the name of safety appears to be wholly out of proportion. No amount of testing before general use can ensure absolute safety in a new medicine. On the other hand, if it has significant benefits, these are denied to patients for each year its introduction is delayed. From Britain, there is also evidence that since the thalidomide tragedy of 1961 doctors have been significantly slower in starting to prescribe new medicines once they are on the market. In the 1950s, new medicines usually reached the peak of their sales within two or three years; now the interval is nearer to seven or eight. Moreover, the delay due to greater margins of safety and greater caution do not occur only in preparation for marketing and thereafter. As Professor Beckett has already described, pharmaceutical development methods as a whole are now very different from the relatively naive approach in the past.

Going back over the centuries, Jenner's smallpox vaccination and Withering's use of digitalis were each based on a personal hunch; it was no more than good luck that in each case the benefits proved to far outweigh the undoubted risks. As an aside, the introduction of leeches and purging, for example, were innovations which did a great deal more harm than good, although they survived for many generations. Although the scientific methods of Jenner and Withering could never be justified in the 20th Century, it was until recently not uncommon for research workers to try compounds on themselves or colleagues if they showed signs of activity in even the most limited of animal tests. As Professor Beckett has explained, it is now no longer regarded as sufficient to know that a new drug or formulation 'works'. All the effects of the compound and its metabolites on the various body systems must be carefully monitored both in several species of animal and in man. The former haphazard approach – and the risks of an



ineffective formulation or unexpected toxicity – is no longer tolerated. In many ways this is highly desirable; but it does mean that our standards of safety in medicines are now set very far above those of the 1950s or earlier and at least in some cases out of proportion to the risks we accept in other fields.

The present imbalance in society's attitude to the safety of medicines can be illustrated by two examples. The first is the concern about mortality due to the oral contraceptives; every death attributed by a coroner to this cause receives widespread publicity. Yet deaths from natural causes during pregnancy and childbirth pass without mention, although a girl becoming pregnant in a given year is about five times as likely to die as one who has avoided pregnancy by the use of an oral contraceptive. Secondly, there is no general concern over mortality due to surgery. At present, for example, elective surgery for the removal of gallstones carries a quite significant risk of mortality, in some series as high as 2 per cent. If the new compound which is at present on clinical trial for the pharmacological treatment of gallstones proved to have anything like the same risk of mortality – or even a tenth or hundredth of it – it seems unlikely that the Committee on Safety of Medicines would accept it. Yet the surgery continues unquestioned. Indeed the principle of the controlled clinical trial, which for the past decade or so has been generally applied to pharmaceuticals, is still comparatively unusual in other fields of medicine and surgery. This is because these have never been subjected to the same public outcry demanding safety in relation to efficacy as there has been in the case of pharmaceuticals.

Before leaving the subject of safety, I would like to end with a more general statement. Any human activity can be made absolutely safe – even if in the extreme case this means banning it altogether. However, in practice, absolute safety in life as a whole is unattainable. It is therefore irrational, if the cost is excessive, to demand absolute safety in any single one of our inherently risky activities. Either society or the individuals concerned have to decide what is the acceptable degree of risk in each individual case. Even on this score alone there are indications that national regulatory bodies controlling the introduction of new medicines may now be unreasonably cautious. However, with medicines there is a second much more important consideration. There is also the balance between possibly lifesaving benefits and the known or unknown toxic risks. It is on this balance that the FDA, at least, is at present failing to reach the correct equilibrium. Manufacturers throughout the world have accepted the need for independent surveillance on their own safety measures: but they are concerned that in response to irrational public demands safety regulations are now in some cases being applied in a way which is to the detriment of the public interest.

### **Avoidance of undue persuasion**

I have argued on many previous occasions, and I think it is now widely accepted, that sales promotion is essential for prescription medicines. New medicines which are not advertised will be very little used, and will thus fail to benefit patients and incidentally will fail to provide commercial returns for the R and D costs incurred in producing them. Nevertheless, there continues to be an undercurrent of opinion that the pharmaceutical manufacturers' sales promotion activities are in some sense excessive. Critics argue that too much is spent on promotion and that the claims made for products are over-enthusiastic. As in the case of safety, I want to put this point of view into a broader perspective – this time against the problem of excessive enthusiasm for therapy as a whole. Thus I would argue that Osler took too narrow a view when he said that the desire to take medicines was a distinguishing characteristic separating man from other animals. Instead, it could be said that man is alone in being prepared to go to almost any length to avoid unpleasantness which is beyond his control – which in the health context means avoiding physical, mental or social discomfort. Hence mankind is in a continuous search for the illusive panacea which will bring the state of complete wellbeing which the World Health Organisation defines as health. In consequence the public has to be protected by law from exploitation by quacks or other misguided healers of one sort or another.

In the case of prescription medicines, of course, there is no question of the public being misled or unreasonably persuaded by advertising. The prescribing decision is taken by the doctor, and the accusation in this case is that the doctor is beguiled into too lavish prescribing by the correspondingly lavish blandishments of the pharmaceutical manufacturers. But again, if one takes a broader view, pharmaceutical promotion can be seen as only one factor affecting doctors' decisions on therapy as a whole. It is also the one factor which is singled out for exceptional restraint.

Fundamentally – just as the public yearn for a panacea – the doctor is subject to various motivations to provide patients with treatment of some sort. These motivations are only now beginning to be fully understood. At its simplest, when faced with a patient who describes some discomfort, the doctor is understandably reluctant to turn the patient away with nothing more than advice 'to grin and bear it'. Even, in the extreme case, if the doctor knows in his innermost heart that the patient's disease is incurable he may be reluctant to admit this to himself or to the patient. His vocation is to heal. Although the evidence points to no effective treatment being available, he may still advise some form of therapy merely because it seems preferable to doing nothing. As far as the general practitioner is concerned in cases of serious illness, this normally means referring the patient to hospital. There, the consultant is faced with the same dilemma. For very

understandable human reasons he may advise surgery or other similarly drastic treatment because he too is reluctant to admit that nothing can be done to improve the prognosis of the case.

All this is particularly likely to happen – if in perhaps less clearcut terms than I have described – because of the fact that so little surgical or medical treatment (except for pharmacology) has been subjected to the discipline of the controlled clinical trial. Many treatments in hospital are still performed on the basis of clinical opinions rather than scientific evidence. Hence a surgeon or physician, whatever he suspects, at least often avoids the embarrassment of facing up to hard evidence that his treatment is unlikely to benefit a particular patient. However, more recently when such treatments have been performed under the conditions of a controlled clinical trial they have in several cases been shown to be ineffective and sometimes even to reduce expectation of survival rather than to lengthen it.

Returning to the dilemma of the general practitioner, he faces another type of problem in the case of patients who persistently present with some minor symptom. He may strongly suspect social or psychological factors as the true underlying cause, and he may painstakingly try to explain this to the patients. However, if the latter continue to persist in reporting troublesome dyspepsia or backache, for example, the general practitioner dare not refuse the patients' requests for a second opinion. Even if the doctor is right in his psychosomatic diagnosis in ninety-nine cases out of a hundred, one single error in which an ulcer or a spinal abnormality has been missed because a second opinion was refused could result in serious legal consequences. Thus, again in these cases, the general practitioner must refer the patient to hospital. Finally, the general practitioner may simply express his frustration and impatience with his local practice problems by almost automatically referring any difficult or troublesome patient to hospital.

These various motives to invoke further costly diagnostic procedures or to initiate therapy probably have a much more profound influence on the usage of health service resources than any conceivable blandishments of the pharmaceutical manufacturers. Yet there is no procedure for surveillance of doctors' behaviour in these respects under the National Health Service – even though hospital costs represent almost two-thirds of health service expenditure. By contrast, doctors' prescribing habits – which are responsible for 10 per cent of costs – are regularly monitored and doctors whose prescribing is significantly more expensive than the average face individual discussions on their pattern of prescribing. Thus any undesirable effects of pharmaceutical sales promotion can be quickly identified in a way that the effects of more subtle motivations on other treatment would not. Indeed, when undesirable prescribing patterns have occasionally

been revealed by this monitoring process, corrective action has immediately been taken, for example, by 'counter promotion' by the government both by direct mail and by visits by Department of Health Regional Medical Officers.

In addition to this, since 1958, the pharmaceutical manufacturers themselves have exercised formal self-restraint through their Code of Practice, under which any complaints of misleading advertising are investigated. More recently, the Medicines Commission and its Committee on the Safety of Medicines have become interested in the content of pharmaceutical sales promotion material, and the Commission will in future examine and approve the statutory 'data sheets' which must be sent to every doctor before any new medicine is advertised to them. This is a further new measure of restraint on pharmaceutical promotion. It has been pointed out within the medical profession that there is no corresponding Commission or Committee on the Safety of Surgery.

Thus, in this second area also, it appears that excessive concern has been directed to the possibility of adverse effects from undue persuasion to use new medicines. There are already widespread measures to ensure restraint. Taking the wider view, it appears that public concern might more appropriately now be directed to other factors which may result in uneconomic or even harmful forms of medical treatment.

### **Prices and profits**

The third area of conspicuous pressure on the pharmaceutical industry is over its prices and profits. Again, there is a partly emotional background, with misgivings about 'making profits out of sickness'. Clearly that is quite irrational; anyone working in medical care is profiting personally from doing so. Moreover, it would be just as logical to accuse food manufacturers of profiting from hunger. However, this sort of irrational concern about the industry making any profits at all was compounded, a decade or so ago, by wild allegations that it was earning 'several thousand per cent' profit on its sales. These allegations were based on taking the chemical ingredient cost of a medicine and dividing it into the selling price. This sort of calculation ignored all the general costs of running a business, and in particular the cost of R and D. Fortunately, in general the debate has now moved onto a more rational plane; but the discussion still focuses on the question of whether the manufacturers are making 'too much' profit from their sales of prescription medicines or not. This, of course, immediately poses the question of how one should define 'too much'.

As has already been stated, there would be general agreement that downward pressure on prices which restricted the growth of investment into socially useful pharmaceutical R and D would be against the public

interest. The problem, as Kenneth Smith has pointed out, is that it is extremely difficult to demonstrate at any particular point that this degree of pressure has been reached. Furthermore, with a timelag of seven or eight years between initial investment in a research programme and the possible marketing of the first successful medicines derived from it, there is a real danger of what the physicists call a 'hunting mechanism' being set up. This occurs when the timescale between an action and its reaction are out of balance, and is typified by the wild swings of an instrument needle as it over-corrects backwards and forwards across the true reading. In the case of pharmaceuticals; one can quickly depress prices which seem excessive when a company is in a successful phase; but if there is a consequent reduction in  $R$  and  $D$  the reduced yield of new medicines from it will not become apparent until perhaps a decade later. At that stage, with prices already depressed and with fewer new products appearing to replace those which have become obsolescent, the firm would have no option but to cut further into its  $R$  and  $D$  budget. At this point the government could readily see the disastrous effect of its pressure on prices, and would no doubt allow substantial increases. However, even if all the additional income were ploughed into  $R$  and  $D$ , the downward plunge might continue for perhaps another ten years, before the increased  $R$  and  $D$  were reflected in new products and increased sales. If the firm survived and its renewed  $R$  and  $D$  were successful it might re-emerge with an equally wild upward swing into another spectacular boom situation. Unless government had by then learnt its lesson the 'excessive' boom profits might again be pruned, and another wild downward swing in the 'hunting' cycle would begin. This may seem an exaggerated picture of the risks, and it certainly overstates the case in order to make the point. However, the fact remains that the timescales in question must be measured in decades not years, and for an industry which is less than 30 years old it would be foolish to be dogmatic about the healthy long-term prospects for the industry if it is now faced with substantial price reductions.

Thus government is faced with a dilemma. On the one hand, it is tempted to yield to political pressures to force pharmaceutical prices down. On the other hand, it is aware that in Britain, at any rate at present, it dare not risk government interference stifling another industry in the way that some others have already suffered. Within the health field, for example, one can point to the demise of the British-owned hearing aid industry because the Health Service chose a Committee-designed aid – produced under contract by the Post Office – rather than those which were already commercially available. Similarly, the British medical instrument industry is presently in dire straits because the health service purchasing policy has failed to take account of the necessary conditions for the survival of a research-based industry of this sort.

The local British aspect of this is particularly important. The pressures on prices and profits are now a world-wide phenomenon, and to the extent that all firms suffer equally, the only effect would be to delay the overall rate of pharmaceutical progress. However, if the British government is in the forefront of those forcing pharmaceutical prices down, it is selectively the British-owned firms which will suffer most. With prices in their home market depressed, and with many overseas countries linking their local pharmaceutical prices to those in the country of origin, the British companies' international price levels will tend to be forced below those of their competitors. This must inevitably reduce export earnings, which for many firms are substantially in excess of sales to the National Health Service.

The British pharmaceutical industry, as has been made clear in these lectures in earlier years, is well aware of the political problem represented by its above average profitability. It is also aware that, as Kenneth Smith has confirmed, present economic theory cannot confirm or deny whether the 'hunting mechanism' will be brought into play if the industry's prices are forced below their present level. It no longer unquestioningly accepts, however, that the political difficulties and lack of satisfactory economic theory necessarily justify special regulation of pharmaceutical prices. It now questions the repeated claim that a price regulation scheme is justified because the prescription medicine market is sheltered from normal competitive forces.

It is true that classical price competition is absent in the prescription medicine market. Doctors do not necessarily prescribe the cheapest medicine available for their patients. However, classical price competition no longer occurs in the great majority of other markets either. Whereas in classical economic theory price was the main determinant of sales volume, this is no longer the case for manufactured goods as a whole. Competition does not now occur between almost identical commodities as it did in the 19th Century. Products are now differentiated from each other by innovation, design, brand names and sales promotion. For the whole range of consumer goods and industrial supplies, price is now only one of many factors taken into account in the purchasing decision. The design, performance and reliability of the goods will often be just as important as their price. A more expensive product may be preferred to a cheaper one, if it is likely to prove more satisfactory in service. The same is true for pharmaceuticals. Unless one assumes that doctors are wholly unaware of prices there is no reason to suppose that they would disregard them in their prescribing decisions. And the Sainsbury Report, for example, showed that doctors were generally aware of the approximate cost of the medicines they prescribed.

If a highly-priced medicine is markedly superior to its competitors, it

will be prescribed; otherwise it will probably be ignored. It is only in the very rare exceptional case that a particular product or group of products are so outstandingly better than their competitors that they will be widely prescribed more or less regardless of their price. This happened, for example, with the tetracyclines. Unfortunately, it is these few exceptional cases which gain the publicity and allow it to be said that prescription medicines are not exposed to normal competitive forces. To use an analogy, these exceptional cases are like Rolls Royce motor cars, whose sales are restricted by rationing rather than price and which would still often be purchased even if their price were doubled. The more normal situation in pharmaceuticals is equivalent to the competition between Hillmans, Vauxhalls or Morris', where unless each manufacturer looks over his shoulder at his competitors' prices he risks losing the market.

Thus in this third case also, although the present pressure on pharmaceutical prices and profits has an identifiable historical background, it now seems less justifiable than in the past, and indeed within Britain may possibly now be harmful because of its international repercussions on Britain's balance of trade.

### **Social implications of medication**

The last main area of pressure on the pharmaceutical industry is the most far-reaching of all, and – unlike the previous three – it is one where the main pressure is only now beginning to build up. It could represent perhaps the greatest threat of all to the future development of new medicines if it is not intelligently anticipated and sensitively tackled. This is the long-term fear that medication may have profoundly harmful social implications for mankind. At its extreme, it is represented by phrases such as 'therapeutic pollution' or 'promiscuous prescribing' which have both already entered the literature.<sup>1</sup> Whereas it was unquestioningly accepted that medicines such as insulin, vitamin B<sub>12</sub> and penicillin were desirable, this is by no means now the case with medicines such as the sex hormones, the hypnotics, the tranquillisers and the antidepressants. In the eyes of the critics, modern medication has empowered the human body to perform in an unnatural way and it has allowed individuals to be sheltered from the normal forces of nature to which, it is argued, they should desirably still be subjected. Modern medicines have also been said to have exposed the body to potentially harmful effects. Superficially, these are attractive arguments and the 'unseen effect' of medicines to which I referred earlier give them added force. Adverse reactions certainly still occur and it is possible to claim that the long-term effects of widespread therapy are completely unpredictable.

1 These phrases have been used by Dr E V Kuennsberg of Edinburgh and Dr P A Parish of Swansea, respectively.

The distinction between 'desirable' and 'suspect' medication is not, of course, clear cut. There is a continuum ranging from the clearly invaluable medicines, such as my example of insulin, to those which are now obviously suspect, such as the amphetamines. It is important to remember, however, that even with what now seems a clearcut case as the amphetamines, it is only within the past decade that they have been widely criticised. When first introduced their usefulness was unquestioned. The danger, which is illustrated by the example of the amphetamines, is that at present the borderline between what are regarded as socially desirable medicines and those which are regarded as undesirable seems to be shifting very rapidly along the continuum between the two. As a result an ever-widening range of medicines are being classed as 'suspect' or 'undesirable'. As another example, in the 1930s and 1940s, few would have thought to question whether the use of hypnotics was desirable, or to doubt that they greatly improved the quality of life for those previously condemned to insomnia. Now there is a widespread demand for restraint in their prescribing and for more rigid controls on their availability. This is despite the fact that modern hypnotics are generally very much safer and less harmful than those of thirty years ago. Nor can the present concern be explained by a continuing increase in prescribing. In England, the numbers of prescriptions for hypnotics fell slightly between 1967 and 1970, the most recent years for which a comparable series of figures are available – from 19.5 million to 18.8 million. The change in attitude simply seems to reflect a more critical approach to the use of medicines generally, and particularly to those affecting the central nervous system. Caution by the medical profession in all aspects of medical care is, of course, desirable. However, as a result of public pressures, scepticism about prescribing may be in danger of getting out of perspective compared with the less critical attitudes to other forms of medical care which I have already mentioned.

This increased hostility towards pharmacology seems particularly likely to develop for two interrelated reasons. First, the potential scope for pharmacological interference with the functioning of the body and the mind is continually increasing. Secondly, the more recent medicines – and especially those which are likely to emerge from future research – are tending to have an increasingly intricate effect on the control systems of the body. For example, the intention with antibiotic therapy was to attack only the invading bacteria without affecting the human host at all. This is no longer possible in the same way with antiviral agents, because the viruses themselves operate within the human cells. Similarly, changes in body chemistry brought about by medicines such as the hormones may alter a whole biochemical system.

The implicit hazards inherent in this situation are, however, already fully taken into account in the increasingly complex and cautious safety



testing procedures which have already been discussed. Thus it can be said that legitimate public concern is already reflected in procedures for the introduction and monitoring in use of these more sophisticated new medicines. The danger is that beyond this rational caution over new medicines there may be a stronger and a largely emotional backlash against medication as a whole. This could be heightened by the present public concern over the social misuse of drugs generally. In an effort to establish as rational a view as possible, it may be useful briefly to mention some aspects of the present attitudes and fears.

The first are concerned with medicines whose inherent value is not in question, such as the vitamins and antibiotics. In their case the present concern is that they are excessively and unnecessarily prescribed. Even vitamin B<sub>12</sub>, for example, is said to be used to an extent which could not rationally be justified by the reported prevalence of pernicious anaemia. The fact that it is quite harmless and very inexpensive – in other words an ideal placebo – does not prevent medical scientists from criticising the amount prescribed. Similarly with antibiotics, there is apparently a growing feeling that minor infections should again be left to cure themselves – as they had to be in the 1930s – because the risk of development of resistance does not justify the convenience of a quicker cure, for example, for a sore throat. This, however, again seems to be a case in which the risks are seen out of perspective. Cross-infection with resistant organisms is very rarely a problem outside hospital.

More fundamental difficulties arise in connection with the treatment of presymptomatic abnormalities. Typical of such cases is moderately raised blood pressure. This may cause no symptoms, but it can be shown statistically to reduce significantly a person's expectation of life. At present it is doubtful whether the public or the medical profession as a whole would consider antihypertensive therapy justified in such cases. It can be seriously questioned whether this is rational at a time when most doctors would actively persuade their patients to give up smoking. The harmful effects on health of smoking may be very much less than those of asymptomatic blood pressure, and giving up smoking can produce just as severe side effects as starting antihypertensive therapy. The potentially lifesaving scope for correcting abnormalities such as high blood pressure will greatly extend in the future; however, the potential will only be realised if such treatment becomes regarded as generally acceptable. At present as one aspect of general current scepticism about pharmacology, the treatment of asymptomatic conditions does not appear to have gained favour.

Next, there is the question of the treatment of minor diseases. I have already pointed out that it seems to be in the nature of men to seek to avoid all discomforts – including aches and pains, dyspepsia and insomnia, for example. It is difficult to say where the threshold should be below which it

is unreasonable to seek such relief, because the symptoms themselves must be subjectively assessed. However, again the generally more critical attitude to medication, particularly in respect of hypnotics and to some extent analgesics, almost implies a return to the Victorian ethic of 'suffering being good for the soul'.

Perhaps those medicines acting on the central nervous system represent one of the most troublesome areas of all. Even here, there are many indisputably desirable applications. For example, outside the field of medical care, the great majority of people regard the social use of alcohol as desirable, despite its dangers. Similarly, in the field of medicine, if a suicidal depressive can be relieved by anti-depressant tablets, no one would question their value. Problems arise, on the other hand, in trying to define the legitimate use of the milder tranquillisers. If an individual soothed away every anxiety with whisky or gin he would be regarded as an intemperate and inadequate member of society. Presumably it would be equally wrong for his doctor to allow him to do the same with a tranquilliser instead, although severe and incapacitating anxieties must certainly justify relief. A more profound though perhaps more esoteric problem can be illustrated in the case of schizophrenia. If one takes the R D Laing view that this is a subconsciously rational response to an essentially evil and irrational social structure, attempts at the biochemical control of schizophrenia must be regarded as merely compounding society's evils – and this indeed seems to be the view which Laing expresses. Perhaps not many would agree with him, but in purely scientific terms this view cannot be convincingly refuted. One has to admit that this is an area in which the disease process, and hence the eventual role of pharmacology, is still inadequately understood.

Finally, there is the whole field of what can be described as social medication, which will inevitably extend in the future. Here one must include the oral contraceptives, medicines which affect body performance such as the anabolic steroids, and the widening range of mood-modifying preparations – which may in the future challenge the traditional place of alcohol, caffeine and nicotine as 'socially acceptable' medicines. Here, not only the Medicines Commission, but the social sciences as a whole must have a legitimate concern in defining the acceptable frontiers for the new pharmacology.

All of this merely confirms that there is no easily definable area within which medication is generally desirable and socially acceptable. In many cases its great value is undisputed. In others present reluctance to accept treatment appears irrational. In others again, the justification or lack of it for particular therapeutic applications remain essentially a matter of subjective judgment. Hence my original plea, that this subject be sensitively handled. It is obviously wrong to argue that all medicines at all times

and in all circumstances must be desirable. On the other hand the industry must safeguard its own interests and those of the public against the present encroachment on what has in the past been regarded as the field of legitimate therapy. It must also anticipate the natural anxieties generated by the industry's own excursions into new therapeutic or quasitherapeutic areas. The industry must strike a delicate balance. On the one hand, manufacturers must not be brow-beaten into withdrawing or withholding medicines which they know to be of value; on the other, they cannot disregard the long-term social implications of preparations such as the oral contraceptives and medicines which enhance or modify natural mental states. There is need for a frank and intelligent discussion of the long-term social effects, to replace the present sometimes hysterical response to the extending scope of modern pharmacology.

### **Conclusion**

Because of the special nature of its products, the pharmaceutical industry must necessarily exercise a very special degree of responsibility in its behaviour. This paper has not discussed the many national and international measures which have been introduced to ensure that it does so, for example in relation to safety, pricing and sales promotion. The paper has instead concentrated on the external pressures brought to bear on the industry. In the past, these pressures have been one factor stimulating the industry to ensure that its behaviour is thoroughly responsible, and to that extent the pressures have acted in the public interest. Concern expressed about possible or real abuses is always legitimate in any field and makes an important contribution towards achieving socially responsible behaviour.

However, this paper has argued that the continued application of these pressures on the pharmaceutical industry often with increasing intensity, may now no longer be acting in the public interest. It is, as it were, as if the self-appointed guardians of the public conscience were continuing to cry 'wolf', even beyond the point when all the wolves have already been killed. The result must be that those who are continuing to snipe at the industry must now be in danger of killing other less offensive animals – even perhaps including the geese which have in the past laid so many golden therapeutic eggs.

To a large extent, the continued wave of pressure for further restraint on the pharmaceutical industry and its activities is being swept forward by the general demands for social responsibility, protection of the environment and safeguards for the consumer. In other fields, which have in the past been less exposed to criticism than pharmaceuticals, there may still be legitimate grounds for concern. However, there are dangers from an over-protected social environment as well as one in which hazards are too freely accepted.

Certainly in relation to pharmaceutical safety, prices and sales promotion there now seems to be a real danger for society from continued more stringent controls. On the broader issue of the social implications of medication in the future, it is more difficult to see where the right balance should lie for the greatest benefit to mankind. As the scope and complexity of medication extends, there are bound to be new far-reaching social issues to be considered. It is to be hoped that the pharmaceutical industry, doctors, social scientists and politicians can all work together in a rational atmosphere to determine a socially responsible policy. However, the current sometimes almost hysterically irrational anxiety about the more straightforward matters in relation to the control of pharmaceuticals does not, unfortunately, augur well for a rational policy in respect of the more difficult ones.

The first part of the book is devoted to a general survey of the history of the subject, and to a discussion of the various theories which have been advanced to explain its origin. The author then proceeds to a detailed examination of the evidence in support of each of these theories, and finally reaches a conclusion which is based on a careful analysis of all the facts which have been brought to light by the researches of other writers on the subject.

CHAPTER I

The first part of the book is devoted to a general survey of the history of the subject, and to a discussion of the various theories which have been advanced to explain its origin. The author then proceeds to a detailed examination of the evidence in support of each of these theories, and finally reaches a conclusion which is based on a careful analysis of all the facts which have been brought to light by the researches of other writers on the subject.

# Index

- ABERDARE, LORD 32  
Academy of Pharmaceutical Sciences 26  
Accidents, road 90  
ADELSON, R M 65  
Adverse reactions 98  
Aerospace 90  
Agent, export 3  
Alcohol 89, 101  
American investment 50  
Amphetamines 99  
Anabolic steroids 101  
Analgesics 101  
ANGILLEY, A 76  
Animal and human studies 22  
Antibiotics 25, 35, 51, 100  
Antibiotics, resistance and cross-infection 100  
Anticoagulants 25  
Antidepressants 98  
Antifungal agents 25  
Anti-inflammatory agents 25  
Antiviral agents 99  
Apollo spacecraft 91  
Approved names 48  
Aspirin xiv, 25  
Association of the British Pharmaceutical Industry (ABPI) 32, 34, 76  
Australia 35  
Austria 33
- Backlash xvi  
Bactrim 67  
Balance of Payments x, 45 *et seq*  
Banks Committee 55  
Barriers to entry 56, 61  
Beecham (Group) 12 *et seq*, 32, 34, 40, 72, 80, 84  
Belgium 33  
Bencard, C L 12  
Biological availability 26 *et seq*  
Blood pressure 100  
Boots Pure Drug Co 80  
Brazil, trade 47  
BROOKE, M 11, 18  
Budget for research xii
- Caffeine 101
- Canada 35  
Capitalisation of research 82  
CARPENTER, J 74  
Cash flow for research 76  
Cash flow, annual 80  
Central nervous system 101  
Committee for the Study of Industrial Innovation 1, 71, 76  
Cephalosporins 45  
CHAMBERS, D 65  
Chemicals EDC's Pharmaceutical Working Party 46, 55  
Chloramphenicol 25  
Chlorthiazide-potassium 26  
Classical price competition 97  
Clinical trials  
certificates for 36  
local 34  
Japan 34  
too few 94  
UK, USA 35  
Code of Practice 95  
Colombia, trade 47  
Combination drugs 37  
Comets 91  
Committee for Agricultural Products (Veterinary Products Safety Precautions Scheme) 32  
Committee on the Classification of Proprietary Pharmaceutical Products 31  
Committee on Safety of Drugs/Medicines 31, 36, 59, 92, 95  
Common Market 54  
Companies  
international specialisation 2  
multinational operations 2 *et seq*  
Concorde 91  
Consumption (drugs) per capita 46  
Consumption (drugs) correlated with income per head x  
Contraception, oral 41, 92  
Controls on safety and marketing 9  
Controls, need for flexibility 32  
COOPER, M H 55  
Corporate behaviour 1  
Corporate objectives 1, 7

- Costs  
 effect on location 7  
 escalation 41  
 of medicines 19, 29, 31  
 of new drug introduction 19 *et seq*  
 'Counter-promotion' by government 95  
 Cross-licensing 42  
 Cross-subsidisation 63, 72
- Dangerous Drugs Act 31  
 'Data sheets' 95  
 Defence regulations 89  
 De HAEN's New Product Parade 42  
 Denmark, trade 47  
 Department of Health and Social  
 Security xv, 32, 36, 55  
 Department of Health Regional  
 Medical Officers 95  
 Digitalis 91  
 Diosgenin 45  
 Diphenylhydantoin 26  
 Quality, causes of lack of 23  
 Distillers 61  
 Diversification 62-63, 72  
 DJERASE, C 41  
 Documentation for drug approval 35  
 Drug Efficacy Review 37  
 Drugs  
 consumption per head 46  
 'equivalency' 26-27  
 delivery system development 22  
 good practices 24 *et seq*  
 formulation 25  
 increased demand 46  
 metabolism 21  
 misuse of 29  
 pattern of supply 54  
 quality control 24  
 DUNLOP, SIR DERRICK 31  
 Duplicate drugs 42  
 Dyspepsia 100
- Ecological balance xv  
 Economics of scale 54  
 Egypt, trade 47  
 'Equivalent' drugs 26-27  
 European Economic Community (EEC)  
 EEC and German drug law 39  
 need for harmonisation 39  
 European investment 50  
 Exporters - top 3, top 20 48  
 Exports  
 future of 57  
 pattern of 2 *et seq*  
 problems of 34
- Finance Act (1967) 48  
 Fisons Group 14 *et seq*  
 Fixed-dose combination drugs 37  
 Food and Drug Administration  
 (FDA) 9, 33, 37, 41  
 Foreign companies xi, 56  
 France, trade 47
- Generic prescribing 55  
 Germany 33  
 Glaxo 80  
 Government pressure on profits,  
 impact on research 60  
 GRABOWSKI, H O 71  
 Greece 33  
 Griseofulvin 25  
 Growth of Market in 70s/80s xiii  
 Guinness 61
- Health, Ministry of 31  
 Hearing-aid industry, UK demise 96  
 'High growth' rating of drug  
 industry 85  
 Holland 33  
 Hormones 98-99  
 Hospital, reference to 94  
 Hostility to pharmacology 99  
 'Hunting cycle' due to prices  
 pressure 96-97  
 Hypnotics 98-99, 101  
 Hypoglycemic agents 25
- ICI 80, 86  
 Imperial Airways 90  
 Incentive to invest 87  
 India 35  
 'IND' investigational exemption  
 for new drug 37  
 Inflation problem 45  
 Innovation  
 mainly from companies ix  
 product 61-62  
 prospect in UK 53  
 Insulin 96  
 Insomnia 100  
 Integration, pressures for 56  
 Investment  
 company motivation xii, 60  
 criteria 61  
 'Invisibles' and capital a/c 49  
 Ireland 35  
 Italy 33, 47
- Japan 33, 35, 46  
 JENNER, E 91  
 Joint ventures 5

- KALDOR, PROF NICHOLAS xiv  
 Key question xiv  
 KUENNSBERG, E V 98
- Labour-intensive 82  
 LAING, R D 101  
 Latin America 33  
 Lead-times 61, 64, 76-77  
 Legal consequences of faulty  
   diagnosis 94  
 Licences, drug, reqd, in UK 36  
 Licensing 4 *et seq*
- Macrobiotic diets xvi  
 Managerial capitalism theory xiii  
 Manpower availability 8  
 Market growth in 70s/80s xiii  
 Marketing  
   agreements 5  
   employees 8  
 Maverick individuals xii  
 Medical instrument industry 96  
 Medicines Act, 1968 32, 34, 36, 59  
 Medicines Commission 95, 101  
 Merck (Sharp & Dohme) 70  
 Metabolism, factors 21  
 Metabolites 91  
 MILLS, PROF D H 27  
 MINASIAN, J R 70  
 Minor diseases, treatment 100  
 Mood-modifying preparations 101  
 Models for decision-making 68  
 Motivations 93  
 MOTTLEY and NEWMAN 64  
 MUELLER, D C 71  
 Multinational firms 1, 6, 47, 55  
 Multinational operations 11
- National Academy of Sciences 37  
 National drug authorities/  
   registration agencies 9  
 National Health Service (NHS)  
   cost of medication 19  
   reference to hospital 94  
   sales of medicines to 49, 97  
 National Research Council 37  
 Nationalisation 89  
 NEDO I, 46  
 Netherlands 47, 53  
 New drug development costs 53  
 New single chemicals introduced  
   in USA 42  
 Nicotine 101  
 Non-tariff barriers 54
- Office of Health Economics (OHE) 55
- Oral contraceptives  
   and mortality 92  
   social medication 101  
 Organisational case studies 11 *et seq*  
 OSLER 93  
 Oxytetracyclines 25
- PARISH, P A 98  
 Patents Act, sec. 41, 77  
 Patents  
   and product life 1  
   protection 76  
 Patient protection 29  
 Penicillin 25, 98  
 'Pirate' competitor 76  
 Pharmaceutical chemicals, trade in 54  
 Pharmaceutical company standards 43  
 Pharmaceutical industry, UK as  
   investment base 54  
 Pharmaceutical Manufacturers'  
   Association (PMA) 38  
 Pharmaceuticals  
   export forms 7  
   manufacture 7  
   product range 9  
   production control 24  
 Pharmacist, role of 29  
 Pharmacy and Poison Acts 89  
 Pharmacology  
   acceptable frontiers of 101  
   hostility to 99  
   role of 101  
 Phenindione 25  
 Phenylbutazone 25, 28  
 Plant, imports 51  
 Plant, outlay on 51  
 Policy Advisory Committee,  
   Drug Efficiency Study 26  
 Political action, fears of 54  
 Post Office 96  
 Prednisone 25  
 Premium on product innovation 61  
 Prescriber information and  
   protection 28  
 Prescribing habits monitored 94  
 Prescribing patterns 93, 95  
 presymptomatic abnormalities 100  
 Price control, Japan 35  
 Prices and profits xii, xvi, 55, 97  
 Prices and research xiii  
 Product lead-times 76  
 Product (new) introduction  
   decline 73  
*Profitability in the Pharmaceutical  
 Industry*  
   Merrett, Cyriax *Asstes.* 1968 76



- Profits**  
 data 78  
 falling 59, 84  
 maximisation 1  
**Prohibition (US)** 89  
 'Promiscuous prescribing' 98  
**Psychological factors** 94
- Quality control**  
 defects 23  
 good practices 24 *et seq*  
 Queen's award 34
- Registration of product**  
 agencies 9  
 compliance 40  
 countries enforcing 33  
 harmonisation 38, 54  
 impact on innovation and  
   product improvement 39  
 impact on integration 40  
 longer development time 39  
 national differences 39
- Research and development** 9, 19 *et seq*  
 budget for 69  
 capitalisation of outlay 82  
 common controls on 68  
 critical level of spending 72  
 diminishing returns on 53  
 'economically viable' 63  
 expenditure and size of company 53  
 failure rate 42, 87  
 foreign firms 56  
 per cent of sales spent 70  
 price squeeze and level of xiii  
 productivity of 72  
 profitability of 72 *et seq*  
 project grading factors 64  
 project selection 64 *et seq*  
 risk-adjusted supply price of  
   capital for 60  
 UK outlay on 53, 63, 77
- Residue studies** 36  
**Rickett & Coleman** 80  
**Risk assessment** 60  
**Risks**  
 assessment of 90  
 balance with benefits 92  
 degrees of 92
- Roche** 67, 72
- rising expectation of 90  
 suspicions of 89-90, 99  
 testing procedures 100  
**Sainsbury Report** 29, 46, 49, 59,  
 64, 70, 97  
**Sales promotion** 93  
**Scandinavia** 33  
**Schizophrenia** 101  
**Scowen Committee** 9  
**Second opinion** 94  
**Seprin** 67  
**Sex hormones** 98  
**Smallpox vaccination** 91  
**Smith & Nephew** 80  
**Smoking** 100  
**Social factors** 94, 98 *et seq*  
**Social medication** 101  
**Social misuse of drugs** 100  
**Social pressures** 98 *et seq*  
**South Africa, trade** 47  
**Spain** 33, 47  
**Stability studies** 34  
**Statistics, selected** 80-81  
**Steroids** 25  
**Stifling effect of govt. interference** 96  
**Subsidiaries, overseas** 6  
**Subsidiary company structure** 82  
**Sulphanamides** 25  
**Sulfisoxazole** 25  
**Surgery, cf. mortality** 92  
**Surgery, no committee on safety of** 95  
**Sweden** 33
- Tariffs** 10  
**Technological gap** 90-91  
**Technology, slower application** 90  
**Teratogenicity studies** 34-35  
**Thalidomide tragedy** 91  
**'Therapeutic pollution'** 98  
**Therapeutic revolution** viii  
**Therapeutic Substances Act** 31  
**Threshold levels of spending** 61,  
 69-70, 77  
**Tolbutamide** 25  
**Top ten companies and exporters** 48  
**Toxicity tests** 21 *et seq*, 34-35  
**Trade controls** 10  
**Trade, visible** 46  
**Trade, world** 47  
**Trade, dominance by 5 countries** 47  
**Tranquillisers** 98, 101
- Unemployment problem** 45  
**United Kingdom trade** 47  
**UK favoured location for  
   manufacture** 52 *et seq*  
**United Nations** 39

- United States, trade 47  
United States, research 53  
'Unseen effects' of medicines 98
- Venezuela 33  
Veterinary products registration 36-37  
Veterinary products cost of 38  
Veterinary Products Safety Precautions Scheme 32  
Visible trade 46  
Visible trade, interpreting UK figs. 47  
Vitamin B<sub>12</sub> 98, 100  
Vitamins 100
- Voluntary Price Regulations Schemes (VPRS) 55, 59, 84
- WALKER, H D 79, 88  
Wellcome Foundation 17 *et seq*, 67, 80, 84  
Western Europe, drug demand 46  
West German trade 47  
West German research 53  
WHO Expert Committee Report (No. 418) 23  
WILKINS, G J 32  
WITHERING, 91  
Working Party, EDC 55  
World trade in pharmaceuticals 47