RISK AND RETURN IN THE PHARMACEUTICAL INDUSTRY

OHE

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Based on papers delivered at the OHE Conference, London, 5 December 1996

Edited by Jon Sussex and Nick Marchant

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Office of Health Economics

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FOREWORD

This book has been built up from the papers delivered at the Office of Health Economics conference which took place at the Langham Hilton Hotel, London, on 5 December 1996.

The speakers assembled for this symposium represent important contributors to the economic analysis of the risks inherent in pharmaceutical research and development (R&D) and the returns achieved by it. Together these authors bring to this analysis a unique combination of academic rigour and detailed knowledge of industry practice. The result is a series of telling insights into the peculiar characteristics of the risk/return trade-offs intrinsic to R&D in the pharmaceutical industry.

Chapter 1
Technology, Marketing and Risk in the Evolution of the Pharmaceutical Industry

JOHN SUTTON

The pharmaceutical industry, in contrast to many other high technology industries, remains fairly fragmented at the global level, with the largest handful of firms each holding a global market share in the three to six per cent range. In recent years some useful models of market structure have been developed which help explain the processes by which a highly concentrated global market emerges in some research and development (R&D) intensive industries but not in others. In what follows, I would like to look at the case of the pharmaceutical industry against this theoretical background.[1]

Our point of departure lies in a very simple-looking economic question, which has actually proved to be rather a difficult to answer. The question is this: if you look across different industries, what is the relationship between R&D intensity, measured by the ratio of R&D spending to sales, and the level of concentration in the industry, measured for example by the market share of the largest firm or the largest four firms in the global market? There has long been an idea that these two variables are fundamentally related. It turns out, however, that this relationship is rather complicated. We know that there are many industries which are very R&D-intensive and which are highly concentrated globally; the market for large commercial jets is a familiar example. Equally, we know that there are many areas, such as scientific instruments, where there are very high levels of R&D spending but the market is very fragmented, in the sense that the market supports a large number of firms, none of which has a large market share.

Traditionally, this issue has been approached at the empirical level by simply running a cross-industry regression between concentration and R&D-intensity in order to try to uncover some relationship. The results

1 In so doing, I draw heavily on my recent book 'Technology and market structure' (MIT Press, 1998). Readers who wish to pursue the argument in detail will find a fuller discussion in chapters 1, 2, 3 and 8 of that volume.

of such regression analyses, however, are disappointing. The most authoritative recent survey of the literature is that of Cohen and Levin (1991). Most researchers who have investigated the relationship, they note, have found that the two variables are positively related: industries in which the ratio of R&D spending to sales revenue is high tend to be dominated by a fairly small number of firms. On the other hand, some researchers disagree with this finding, arguing that the relationship is not even a monotonic one: if we plot concentration against R&D intensity, these authors argue, we find that concentration first rises then falls. A third group of authors take a rather different view: they point out that if we incorporate in the usual regression analyses a few 'dummy variables' that control for broad industrial sectors (distinguishing, for example the 'Food and Drink' sector, the 'Mechanical Engineering' sector, the 'Chemicals' sector, and so on), then the apparent correlation between R&D intensity and concentration vanishes. In other words, a scatter diagram of concentration versus R&D intensity shows a huge, diffuse cloud of points. Within this cloud, some broad industrial sectors exhibit both low R&D intensity and low concentration. These weak sectoral effects can, if they are not controlled for, induce a weak positive correlation between the two variables across the sample of all industries. Once, however, we exclude such effects, there appears to be no simple relationship between R&D-intensity and concentration within each broad industrial sector.[2]

In what follows, I will suggest that there is indeed a sharp and clear relationship linking these variables, but it is not of a kind that can be captured by regressing R&D intensity against concentration.

Given the confused and unhelpful picture that emerges from attacking the question empirically by way of conventional regression studies, it is natural to ask: what should we expect to find on the basis of theoretical considerations?

2 A further line of argument holds that R&D intensity and industry concentration are positively related somehow, and that the apparent exceptions we see are merely problems of aggregation. That is to say, if you define each industry narrowly enough a simple positive relationship between R&D intensity and industry concentration will emerge. This, unfortunately, is just not so. For a full discussion of this 'aggregation' argument, see Sutton (1998), chapters 1 and 3.

General perspectives

Recent progress in understanding the evolution of market structure has rested in large part on the use of game-theoretic models. The central lesson of these models is that the form of market structure will be influenced by many factors, some of which are difficult to measure, proxy, or control for in econometric studies. Such 'problematic' factors include, for example, the details of the entry process, or the form of price competition in the industry. Very often, we are forced to treat factors of this kind as 'unobservables', while accepting that they may have an influence on outcomes that is both large and systematic. In spite of these difficulties, however, some clear lessons emerge: there are some economic mechanisms at work which are robust enough in their operation to override the complications posed by these unobservables. It turns out, moreover, that these robust mechanisms impose a lower bound to the level of concentration that will be attained in the industry. While the theory will not predict the actual level of concentration, it will place a constraint on the minimal level that must be attained.

There is one fundamental economic mechanism which is common to all R&D-intensive industries. The mechanism works in the following way. If an industry consists of a large number of small firms, so that the level of concentration is low, it may become profitable for a firm to break ranks by outspending its rivals on R&D, with a view to capturing a large share of the market. Under these circumstances, an overly fragmented industry will be unstable. Escalating R&D outlays may squeeze out all but a small number of high-spending firms.

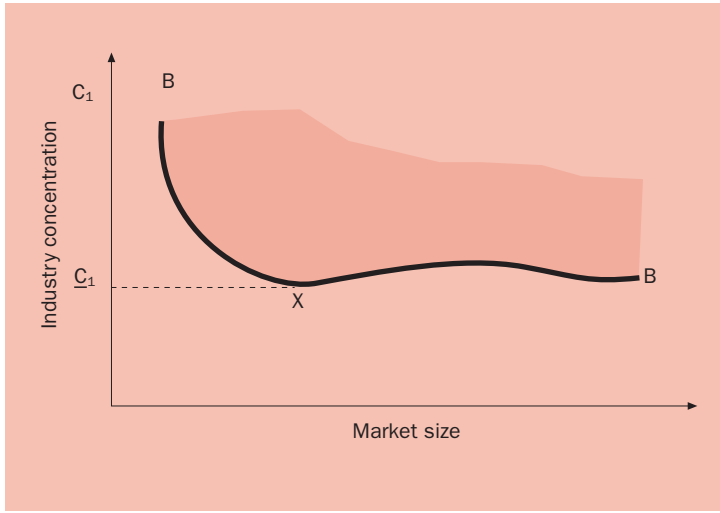
The question is: what are the industry characteristics that determine the strength of this 'escalation mechanism'? In what follows, I describe a way of classifying industries which places large commercial jets at one end of the spectrum – where the escalation mechanism is very strong – while the pharmaceutical industry will turn out, in terms of its underlying technology, to be pretty near the opposite end of this spectrum.

How would we expect to find a market becoming fragmented, i.e. divided between a very large number of small players? Clearly, this will depend, among other things, on the size of the market. Growth in market size, as measured by the size of the population of buyers,

induces the entry of new players, and this may lead to the fragmentation of market shares. This can be seen in many commodity-type industries, which end up with a large number of small firms, so that the level of concentration – as measured by the market share of the largest firm, say – falls towards zero. This also happens in some, but not all, high technology industries. It is the characteristics of those industries in which such fragmentation fails to occur that we aim to uncover.

The relationship of interest is illustrated in Figure 1.1. We want to ask whether, as we increase the size of the market, the level of concentration falls towards zero or not. The fundamental mechanism I wish to discuss is one that prevents fragmentation proceeding beyond a certain point and thereby ensures that a small number of large firms will dominate the global market, no matter how large that market becomes. That is to say, as the market grows, so that we move to the right in Figure 1.1, there exists a lower bound to the level of industry concentration, (labelled $\underline{C}_1$).

Figure 1.1 **A non-convergence property**



Within the shaded area in Figure 1.1, there may be no strong economic mechanisms that force concentration to remain at any particular level. Mergers and acquisitions could increase the level of concentration for any given market size and there will be circumstances under which this more concentrated market structure can be maintained. What is impossible is permanently to reduce concentration below $\underline{C}_1$: there is a fundamental escalation mechanism that will come into play if C_1 is below this level, thereby restoring a higher level of concentration.

Can a fragmented industry be stable?

Imagine an industry that is fragmented, in the sense that there are many roughly equal-sized firms. The limited sales revenue achieved by firms in this market places a corresponding limit on the R&D spending of any single firm. Now suppose one firm deviates from its strategy by simply outspending everybody else on R&D and so offering a better product than its rivals. The profitability of such a high-spending strategy will depend on the extent to which a high R&D-spender can guarantee itself a large market share, irrespective of how many low-spending rivals it competes with.

We can pose the question more precisely, as follows. Suppose the deviant firm outspends all its rivals on R&D by some factor K. Suppose that, given the size of the market S, this yields the firm a certain 'gross' profit[3] $S\pi$. How is π related to K? In what follows, we aim to associate with each industry some relationship between K and π. With that in mind, we proceed as follows: suppose we could find, for some value of K, an associated constant a, such that the deviant firm who outspent all rivals by a factor K earned a gross profit $\pi S \geq aS$. (Its actual profit πS will of course depend on the number of rivals it faces and on the level of spending of each of these firms. The constant a, however, is independent of this.) The central theorem now states that the one-firm concentration ratio, which corresponds to the market share of the largest firm, cannot fall below a/K, no matter how large the market. Thus it is

3 I.e. profit prior to the deduction of R&D outlays. We adopt the convention of expressing the profit earned by a firm in the form $S\pi$, so that π is the profit 'per head of population'.

the ratio a/K which matters. Let us now pick the highest attainable value of a/K and call it α. The parameter α tells us how well a firm can do by simply outspending everyone else in the market on R&D. The essential thing we are asking is 'how well can the high-spender guarantee that it will do, independently of how many low-spending rivals come into the industry?'. The punch line of all this is that there are some kinds of industries in which a high-spending firm could have its market share gradually eroded by the proliferation of large numbers of relatively low-spending firms; but that there are other types of industry in which this cannot happen. In the latter setting, if the high spender offers a 'better quality' product it will be able to command a price premium over its rivals while continuing to retain some minimal fraction of customers, i.e. those who are more 'sensitive to product quality', say.

The key question then is: to what extent can the entry of many low-spending rivals erode the high spender's market share? This question cuts through much of what has been written on the economics of industry structure, and of the structure of the pharmaceutical industry in particular. It is quite different, for example, from the usual question asked in the literature on the pharmaceutical industry, which is couched in terms of whether there are 'increasing returns to R&D'.[4]

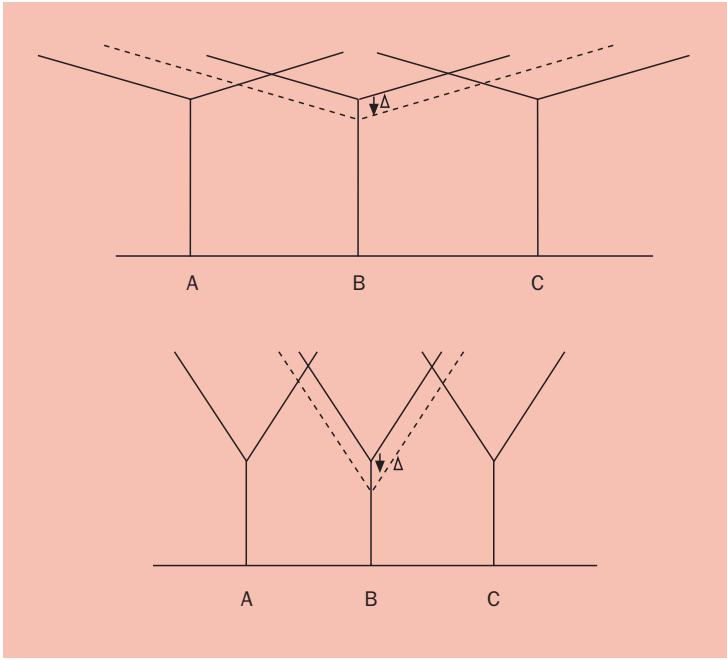
Determinants of the escalation parameter α

What determines the value of the escalation parameter α? A simple picture will serve to provide some intuition for the questions that must be asked in order to decide whether or not the technology of the pharmaceutical industry is one that drives it inevitably to some high level of global concentration. The picture derives from the classic model of competition between differentiated products, which was introduced by Harold Hotelling in 1929.

Imagine a beach on which rival ice cream sellers are located at points A, B and C, as in Figure 1.2. The heights of the vertical solid bars at A, B and C indicate the different ice cream sellers' respective prices. Consumers are spread along the beach and each one chooses between

4 On the relationship to this latter idea, see Sutton (1998), chapter 8.

Figure 1.2 **Interpreting the escalation parameter α**



the ice cream seller to his left and that to his right. Consumers do not like walking along the beach; so we add to the ice cream seller's price an imputed cost to represent the disutility suffered by having to walk to a distant vendor. Adding these imputed costs, which rise with the distance travelled, to the vendor's price we obtain the total cost of getting an ice cream. Where the 'umbrellas' constructed in this way intersect (see Figure 1.2), we have a customer who is indifferent between patronising the seller to his left or the seller to his right. Any price difference between the two sellers is offset, at this consumer's location, by the difference in the imputed travel cost. If the umbrellas are flat, as shown in the top panel of Figure 1.2, this indicates that consumers do not much mind walking along the beach. If an ice cream seller cuts his price in this situation, he can greatly increase his sales volume, since many consumers consider that the lower price is enough to compensate for a

longer walk along the beach. The lower panel of Figure 1.2 shows a case where consumers impute a high cost to walking along the beach. To them, the products of the different ice cream sellers are poor substitutes, and if a seller cuts his price he will attract few extra customers.

Now imagine, for the sake of argument, that one seller introduces a quality 'improvement' in the ice cream he offers. The value of this improvement is equivalent in the eyes of consumers to a price reduction of Δ, say. This is represented in Figure 1.2 by a vertical downward shift of the umbrella by the amount Δ. The impact of this improvement on the volume of sales of the deviant firm will depend on how flat the 'umbrellas' are, and so on the degree of substitution between rival products.[5] The impact is greater in the top panel of Figure 1.2, where the products are closer substitutes.

The value of the escalation index α, then, depends on two factors. The first relates to the effectiveness of R&D in a technical sense: by how much do R&D efforts improve the therapeutic effectiveness of the product I offer (and hence move my umbrella in Figure 1.2 downward)? The second factor relates to the breadth of the market segment within which I can draw customers away from rival products. The most favourable outcome would correspond to the case where a new and improved product displaces all existing products within a single therapeutic category. In the top panel of Figure 1.2 that scope is great but in the bottom panel it is weak.

We could be working in a world in which all the products are very close substitutes, so that one large commercial jet is very much the same as another, for example. All that the buyers care about is the cost per passenger mile which it offers to cross the Atlantic. If I reduce the cost or improve the performance of my commercial jet, therefore, I can pull a lot of customers away from Boeing. On the other hand, in the pharmaceutical industry, it may be no good at all having an excellent ulcer drug if the customers really want to buy some aspirin. The pharmaceutical industry, unlike the large commercial jet industry, comprises a

5 I have deliberately avoided a discussion of the way in which changing the slope of the umbrellas affects equilibrium prices, and how this in turn impinges on the value of alpha. For a full discussion of this, see Sutton (1998).

large number of categories of products that are very poor substitutes for one another. Thus pharmaceuticals are in the lower panel of Figure 1.2, so that a firm increasing its R&D spending has a very limited power to pull in additional customers from the other firms in the industry. In other words: pharmaceuticals may be considered a low α industry.

R&D trajectories reconsidered

The discussion so far has been couched in terms of the notion of a single 'R&D trajectory'. More generally, the market can be thought of as comprising a number of R&D trajectories, each with its associated sub-market consisting of products produced along that trajectory. This picture fits most R&D-intensive industries well. It allows us to distinguish markets comprising one R&D trajectory (e.g. colour film) from those comprising many trajectories (e.g. flowmeters, of which there are several kinds: electromagnetic, ultrasonic, and so on). A simple extension of the story allows us to deal with industries that contain several sub-markets whose R&D trajectories are linked via economies of scope (as in the case of large commercial jet aircraft, where aircraft of different size categories may share strong commonalities in areas like wing design).

But does this kind of story fit the case of pharmaceuticals? Can we identify a set of sub-markets and their associated R&D trajectories in this sense?

The obvious candidate for a 'sub-market' might seem to be the therapeutic category, and it is indeed at this level that most of the earlier literature on the pharmaceutical industry has focused. But a therapeutic category usually comprises several product groups, which differ fundamentally in their chemistry. In looking for an R&D trajectory, it is at the lower level of a 'chemically related group' that we need to work.[6]

6 A therapeutic category is then thought of as a market containing several sub-markets, each corresponding to a different chemically related group of products. The R&D trajectories associated with each chemically related group are independent, in the sense that a knowledge of the common chemistry of one group is of no benefit to researchers working on a different group. On the demand side, however, the associated groups may be more or less closely linked. In some cases, drugs in different groups within a therapeutic category may be close substitutes in treating certain conditions; in other cases, they may not.

In the preceding section, we raised the question: can a firm that outspends its rivals on R&D by a factor K attain a profit exceeding aS (where a is a constant associated with K)? Applied within a sub-market associated with some particular chemically related group, what this asks is whether the expected profit (or, more loosely, market share) of a high spending firm can be eroded indefinitely by the presence of a large number of low spending rivals. One way of addressing this question is to ask whether a firm that has established an early lead in some category can maintain its position. Can later arrivals, who have not incurred any earlier R&D outlays in this area, enjoy an equal chance of discovering the next important product in this family?

Two extreme cases arise. In the first, success is a function of total spending to date in this category. Here, the picture corresponds closely to that of the 'R&D trajectory' outlined earlier. At the other extreme, we may imagine progress to occur in a sequence of rounds, each marked by the discovery of some new major drug within the family. At each round, we may imagine that all firms competing in this round enjoy an equal chance of success as a function of the R&D spending they incur in the present round, independently of any earlier spending they have incurred in earlier rounds. In this latter case, the notion of an R&D trajectory becomes redundant: we can model pharmaceuticals R&D as a simple search process. If such an interpretation is valid, our earlier conclusion that the escalation parameter α is small can be strengthened further: in this setting, the value of α is zero.

To see this point, it is helpful to think of the R&D process in the following way: suppose a firm can buy a ticket at some fixed price which entitles it to undertake a search for a new pharmaceutical in a given category. Imagine that the firm's probability of being the (first) one to find the new entity is proportional to the number of tickets it has bought. Suppose I buy several tickets in this contest, but each of my rivals buys just one ticket. In that case, my chance of winning depends on the number of rival firms I face. Given that I buy K tickets, while N rivals each buy one, my chances of winning are K/(K+N), and this probability declines to zero as N increases. In terms of our earlier discussion, there is no pair of numbers K and a, with a strictly greater than zero, that satisfy our condition that the

firm which outspends its rivals by a factor K shall earn a gross profit exceeding aS. By letting N be large enough, we can drive the profits of this high-spending firm as close to zero as we wish. Hence the value of the escalation parameter α is zero in this setting.

If this is a fair representation of the process of R&D competition in pharmaceuticals, then there is no reason – from the technological side – why a fragmented global market should not prove to be stable over time. But is this a fair representation of the nature of R&D competition in pharmaceuticals?

There is one thing which might modify this simple 'search' story: this relates to the possibility that 'research traditions' matter. Let us suppose that there is a sequence of drugs within some therapeutic category that are chemically related, and suppose that by establishing an early lead in this area I may enjoy a continuing advantage over my rivals in discovering later drugs in the same family. Under these circumstances, the R&D process might be less akin to the simple search story described above, and more akin to one in which rival firms were advancing along the same R&D trajectory over time, their differing capabilities in respect of new drug discovery being in part determined by their earlier efforts and/or successes within this family of products.

Chemically related groups

In order to analyse research traditions at the level of chemically related groups, I begin by dividing drugs into the basic therapeutic categories of the *British National Formulary* (BNF). Then I sub-divide each of these therapeutic categories into a number of chemically related families. (For example, within the BNF category of cardiovascular drugs, 'potassium-sparing diuretics' appears as one of the chemically related groups.)[7]

I next focus attention on 'major' drugs. The reason for this focus is straightforward: in the typical portfolio of a major pharmaceutical company, the large majority of the drugs it offers contribute little to its total profit, most of which is earned from a handful of top-selling

7 The process of identifying chemically related groups is described more fully in chapter 8 of Sutton (1998).

drugs. What is economically interesting, therefore, is whether there is any serial correlation in the discovery of the top-selling 'breakthrough' drugs. To assess this, I looked at three dates at intervals of 13 years, namely 1960, 1973 and 1986. For each of these three reference years, I identify the 50 top-selling drugs in that year. For each chemically related group, I ask whether any new top-50 drug appeared within that group in 1973 that had not been on the top-50 list in 1960. Similarly, I ask whether any new top-50 drug appeared in 1986 that had not been in the list for 1973. Operating in this way, I identify 26 instances where there was a 'follow-on' top-50 drug. I then ask whether the company that discovered and introduced each new top-50 drug had discovered and introduced a top-50 drug which appeared in the same chemically related group 13 years earlier. In other words, what I am asking is whether there is any serial correlation in firms' discovery and introduction of top-50 selling drugs within chemically related groups. I find that any such serial correlation is very weak.

The 26 major discoveries are listed in Figure 1.3. Of these, I found that only seven were genuine examples of follow-on discoveries by a

Figure 1.3 **Frequency of major follow-on discoveries**

Chemically related groups	*Number of new entries*	*Number introduced by a firm selling a top 50 drug in this category 13 years earlier*
Potassium sparing diuretics	1	0
Beta blockers	2	0
Nitrates	1	0
Antihistamines	1	0
Benzodiazapines	3	0
Phenothiazines	2	1
Penicillins	2	0
Cephalosporins	5	1
Tetracyclines	3	3
Sulphonylureas	2	1
Salicylates	4	1
Total	26	7

Figure 1.4 **The instances of major follow-on discoveries**

Chemically related group	*New top 50 drug*	*Firm*
Phenothiazines	Trifluoperazine	SmithKline
Cephalosporins	Cefaclor	Lilly
Tetracyclines	Minocycline Doxycycline Demeclocycline	Lederle Pfizer Lederle
Sulphonylureas	Tolazamide	Upjohn
Salicylates	Sulindac	Merck

firm that had a top-selling drug in this category 13 years earlier. Moreover, of those seven instances, three occurred in the (very special) area of tetracyclines[8] (see Figure 1.4). In the large majority of instances (19 out of 26) it was an outsider company, defined as one that did not have a top-50 drug in this chemically related group 13 years earlier, that came in with the next big breakthrough drug in the group. What this suggests is that the R&D process in pharmaceuticals may be approximately represented by the simple 'search model' outlined earlier, in which all firms stand on an equal footing in terms of their capability of discovering major drugs in each successive generation of products, independently of their previous track records within the same chemically related family. If this is so, there is no reason on the technological side for the pharmaceutical industry necessarily to evolve towards high levels of concentration. To understand the factors that underlie the evolution of market structure in the pharmaceutical industry, we need to look beyond the nature of the R&D process.

Beyond technology: marketing pharmaceuticals[9]

A series of regulatory changes that defined a category of drugs available only 'on prescription' set the stage for a change in the character

8 For the details, see Sutton (1998), chapter 8. The complex history of tetracyclines makes this a very special case and one which is difficult to compare with the others.
9 This discussion is taken directly from Sutton (1998), chapter 8.

of marketing both in the USA and elsewhere from the 1950s onwards. The new trend ran in favour of devoting the bulk of promotional expenditure to visits by company representatives to individual physicians, a practice known as 'detailing'. In 1972, promotional spending accounted for 12.4 per cent of industry sales in the USA, while R&D accounted for about seven per cent. Over half of promotional spending was associated with detailing activities, while only one-seventh was associated with journal advertising.[10]

Detailing efforts by all major companies had become intensive by the early 1970s, when the average US physician received 1.7 visits per week. The level of a company's detailing activity was closely related to its size: of the 17.4 million detailing visits made in the USA in 1972, 5.2 million were made by the eight largest drug companies. A representative of each of these eight companies would call on each physician about four times a year. There is an obvious economy involved in the provision of such detailing visits by larger companies: a typical visit may last ten minutes and the incremental cost associated with extending the visit time to discuss several products is modest, given the fixed cost of travelling to each physician.

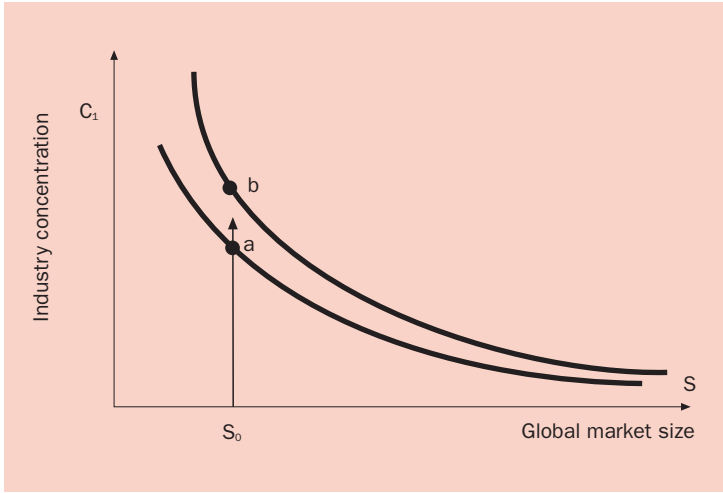
How effective is such activity? A valuable point of reference is provided by the evidence of the Sainsbury Commission in the UK, which reported on the practice in 1966. The Commission investigated the information that individual doctors had on four drugs, prior to first prescribing them for their patients. While doctors were influenced by that they read in medical journals, and considered such information to be reliable and unbiased, this was not their most frequent source of information. Rather, for three of the four drugs investigated, company sources were the most frequently cited source of doctors' information. One of the drugs had been available for only four months and 24 per cent of doctors had still not heard of it, but of those who had heard of it 43 per cent had already prescribed it for patients.

10 Schwarzman (1976) cites a figure of $721.8 million for all promotional spending in 1972. Of this, $396.3 million was spent on detailing time and $31.6 million on detailing literature. Journal advertising accounted for $110.3 million, while the rest included both direct mailing and sample distribution and spending associated with conventions, exhibitions and presentations.

Doctors received company information both through mailings and through visits by representatives. Sixty per cent of doctors saw all representatives who called, and almost half of all doctors were willing to prescribe a product solely on the basis of information provided by the company representatives. On the other hand, doctors did discount some of the claims made by representatives as exaggerated, and some expressed concern at the limits of the representatives' knowledge of their products.

If marketing activity can expand demand, what does this imply about the value of α? Given a number of firms whose portfolios of drugs are equal in terms of therapeutic effectiveness, could a firm that outspent its rivals on marketing efforts achieve some minimal market share, however numerous its rivals? No definitive answer to the question will be attempted here, but we tentatively conclude that the value of α is probably small. This conclusion rests on a claim that we develop in the next section: marketing efforts can be extremely effective in raising sales to some ceiling level determined by the drug's therapeutic effectiveness, but such efforts are much less effective beyond that

Figure 1.5 **The effect of an increase in exogenous marketing outlays**



point. Heavy detailing efforts in practice reach a saturation level at which all prescribing physicians have been contacted several times, and further promotion beyond this level may be quite ineffective.

If this is so, then from an analytical viewpoint, marketing efforts play a role analogous to a 'set-up cost' or a 'unit size' effect. They raise the fixed outlays incurred in bringing a drug to market and this increases the minimum level of concentration that can be attained in a market of any given size. In Figure 1.5, a rise in the (exogenously fixed) outlays required for marketing shifts the lower bound to concentration upwards, so that the minimum value of C_1 rises from a to b in a market of size S_0.

The effectiveness of marketing

How does the effectiveness of marketing vary with the therapeutic effectiveness of a drug? Schwarzman (1976) cites some examples of drugs identified by the US Food and Drug Administration as having 'little or no gain' in therapeutic properties over earlier drugs. He cites Merck's Vivactil, an antidepressant which Merck spent $3 million to promote but sales of which did not exceed $2.5 million. The A.H. Robins company spent more in promoting the tranquilliser Tybatran than it earned in sales. Further examples of ineffective promotion also exist.

A 1977 report of the US Federal Trade Commission came to similar conclusions. They investigated the fate of follow-on products in two major areas, anti-anginals and diuretics, and found that the first firm to introduce an innovative product spent a lower proportion of sales on promotion, but continued to enjoy a dominant position in terms of market share. It concluded that 'neither heavy promotion nor low price appears to have been sufficient to persuade prescribing physicians to select in great volume the substitute brands of late entrants'.

In contrast to this, drugs that have offered substantial therapeutic benefit have sometimes done so with little promotional support. Schwarzman (1976) cites Hoechst's diuretic, Lasix, as an example. This drug filled a gap in the market for a rapid-acting strong diuretic, and achieved very high sales with very modest marketing support. In cases like this, where no close substitute exists, a little promotion may go a long way.

All the above examples relate to extreme cases. The case of greatest interest in assessing the importance of promotional efforts is one involving drugs that are roughly equal in clinical terms. The ideal 'natural experiment' would be one in which one drug appears first and rivals follow later. The later entrant normally fares less well, even if it is of similar therapeutic effectiveness, since physicians and patients are accustomed to the established product and will only switch if some potential therapeutic advantages can be offered. This kind of setting offers an opportunity to examine the notion that heavy marketing efforts may be both necessary and sufficient to establish a pattern of market shares that reflects the relative therapeutic effectiveness of the products. It also offers an opportunity to examine the limits of what can be achieved by marketing.

Zantac versus Tagamet

In the early 1970s, several drug companies, including SmithKline, Pfizer and Lilly in the USA and Glaxo in the UK, were searching for a cure for ulcers. It was already known that a naturally occurring substance, histamine, stimulated acid secretion and this suggested a hypothesis that blocking the action of histamine might control acid secretion and so cure peptic ulcers. The breakthrough came with the launch by SmithKline of cimetidine (marketed as Tagamet), based on pioneering work by Sir James Black. Within five years of its launch, Tagamet became the world's top-selling drug.

Research at Glaxo over the same period led to their altering the molecular structure of one of the compounds they were investigating, ranitidine. Ranitidine also worked by inhibiting the action of histamine and so blocking acid secretion. This led Glaxo to its discovery, which it marketed under the brand name Zantac. The R&D process leading to Zantac was very rapid. By undertaking in parallel a number of stages that would normally run sequentially, Glaxo accepted a very costly and risky investment, but it thereby brought the drug to market in five years rather than ten. Early clinical trials indicated that Zantac performed in a broadly similar way to Tagamet. The advantages of either drug, relative to the other, might vary from patient to patient, and the profile of side effects might be expected to show dif-

ferences. The success of Zantac would depend, in the first instance, on persuading physicians that it might offer a better alternative for at least some of their patients, and secondly it would depend on the degree to which those patients stayed with the new drug. The first step was crucial: once Zantac was prescribed, its prospects might be good. But persuading physicians to prescribe it, in the absence of any clear and systematic advantage over Tagamet, would require an intensive detailing exercise.

The US Food and Drug Administration rated Zantac as making 'little or no contribution to existing drug therapies'. Glaxo researchers, however, believed that they had found a product whose action was more selective that Tagamet's and which would have fewer side effects. Tagamet was perceived, however, as a very safe drug, and Glaxo's marketing department had initially planned to market Zantac as a 'me-too' product. As happens with many second movers, Glaxo set out to optimise all possible secondary features of its product. The standard Tagamet dosage was four times a day, a double quantity being taken on the fourth occasion. Zantac was supplied in a 'one tablet a day' form.

Early clinical comparisons indicated a slightly (six per cent) higher ulcer healing rate for patients taking a standard (twice daily) dosage of Zantac, as compared to a standard (four times daily) dosage of Tagamet. Comparisons based on twice daily dosages of each drug indicated a wider, 12 per cent, gap. More importantly, perhaps, two studies published in leading US and UK medical journals in 1984 and 1985 indicated that the patients taking Zantac showed a lower rate of recurrence of ulcer problems during the year following an initial successful treatment. The gap was wide in this case (12-15 per cent for Zantac as against 30 per cent for Tagamet) and this was cited heavily in Glaxo's detailing presentations.

The approach which Glaxo took in marketing Zantac was heavily influenced by the firm's earlier experience with its asthma drug salbutanol (marketed as Ventolin). The company felt, with hindsight, that this could have become a top-selling product, but it failed to do so because it was launched at a relatively low price and was given inadequate marketing support (Anglemar and Pinson, 1992). In market-

ing Zantac, it was decided to price it at a level higher than Tagamet and to spend heavily on marketing efforts. Within its domestic UK market, Glaxo had a sales force of similar size to SmithKline's. Elsewhere, however, Glaxo's sales force was inadequate to allow the company to equal the detailing efforts that SmithKline was devoting to Tagamet. Glaxo doubled the size of its French sales force by hiring freelance representatives, and elsewhere entered into a series of joint marketing agreements aimed at supporting Zantac. Its partners included Menarini in Italy, E. Merck in Germany and Sankyo in Japan. Glaxo's ranitidine was sold by Glaxo representatives under its Zantac brand name, while Glaxo's partners sold the same product under alternative names. This device permitted a major increase in the number of representatives supporting Glaxo's product. In Italy, SmithKline's 95 representatives compared with Glaxo's 250 and Menarini's 220. In Germany, SmithKline's 100 representatives were matched by a combined sales force of 160 (Anglemar and Pinson, 1992).

The launch of Zantac in European markets met with substantial success. Within a year of its launch, it achieved a market share in the ulcer drug market of 23 per cent in the UK, around 40 per cent in France and Germany, and 80 per cent in Italy. Prior to Zantac's US launch, SmithKline responded to Zantac's European success by increasing its sales force from 725 to 850.

The marketing of Zantac was carried out at a level of intensity that may have been close to the point of saturation, beyond which further efforts became counterproductive. In some countries, each general practitioner was visited annually be three different Glaxo representatives, each emphasising a different aspect of Zantac: it use against acute peptic ulcers; its role in 'maintenance' (prevention of recurrence); etc.. This division of effort, in combination with the multi-branding by Glaxo's marketing partners, appears to have led to some resistance by physicians who were visited repeatedly in connection with the same product (Anglemar and Pinson, 1992).

Glaxo entered into an arrangement with Roche Inc., the leading Swiss pharmaceutical company, which had a large US sales force which, at that juncture, was seriously underemployed. Thus Zantac would be

supported in the USA not only by 450 Glaxo representatives but also by Roche's 700. This arrangement allowed Glaxo to embark on an unusually ambitious marketing campaign. A useful measure of detailing effort is the total number of minutes spent by representatives in talking about a drug to physicians. For Tagamet, this averaged around 100,000 per month in the three years prior to the launch of Zantac. From its launch in late 1983, Zantac was supported by 150,000 detailing minutes per month and this level was maintained for the next decade, showing no sign of the decline that usually follows the first few years of active promotion. SmithKline responded by raising Tagamet's support to around the same level, and it too maintained its support up to the end of the decade. Over the same period, Zantac was supported by an advertising spend that averaged around $600,000 per month, while Tagamet's advertising stood at about two-thirds of this level.

In 1987, Zantac's US sales overtook those of Tagamet, and by the end of the decade its US market share stood at 53 per cent, while its global share had reached 42 per cent (Anglemar and Pinson, 1992).

Zantac's success stands in sharp contrast to the fate of the third and fourth entrants within the H2-blocker anti-ulcer drugs. Famotidine, developed by the Japanese company Yamanouchi, was marketed in the USA by Merck under the brand name Pepcid. Priced 10 per cent below Zantac, it achieved a global market share of 12 per cent by 1989. The fourth candidate, Eli Lilly's nizatidine (marketed as Axid), achieved a market share of two per cent. Both these drugs were, like Zantac, rated as making little or no contribution to existing therapies.[11]

Benefits of size

By using an unusually intensive level of marketing support, Glaxo succeeded in more than offsetting the usual disadvantage faced by

11 A new type of anti-ulcer drug was introduced in 1988 by the Swedish company Astra. This new class, known as proton (acid) pump inhibitors aimed to heal ulcers by inhibiting gastric activity. By 1989, Astra's Losec had achieved a five per cent share of global sales of anti-ulcer drugs.

second entrants who offer products with broadly similar therapeutic properties. The contrast between Zantac's performance and Glaxo's earlier experience with its under-marketed Ventolin is striking, as is the contrast between Zantac and later H2-blockers. A small company, with an inadequate sales force, might succeed in marketing a drug which offered dramatic therapeutic advantages, but its success with a drug that offered only a slight therapeutic advantage would probably be greatly inhibited by inadequate marketing support. But while Glaxo's experience underlines the value of large scale marketing support, it also suggests that the lack of adequate scale can be at least partly offset by way of joint marketing agreements. There is, however, a further disadvantage suffered by small and medium size firms in the pharmaceutical industry, which is not so easily remedied.

A high proportion of pharmaceutical companies' sales tends to derive from a handful of products. Even for the largest companies, the reliance on a single product can become very great. For the top 25 pharmaceutical companies in 1988, the revenue from the company's top-selling drug amounted on average to 20.9 per cent of its total pharmaceutical sales. In four cases it accounted for around half of total revenue. Temorin accounted for 52 per cent of ICI's revenue from pharmaceutical sales, Tagamet for 51 per cent of SmithKline's, Zantac for 49 per cent of Glaxo's and Capoten for 48 per cent of Squibb's. When patent protection lapses, a company that relies heavily on one or two major products can become very vulnerable. Its overhead costs may be out of proportion to its diminished revenues, and adjusting the size of its sales force and its R&D staff to fluctuations in its activity level may be costly. In such a position, there is a strong incentive to try and get together with another firm. One recurring theme in press accounts of several recent mergers in the industry relates to the two intertwined themes of over-reliance on a single drug and the notion that mergers will be followed by amalgamation of sales and research staffs and a subsequent reduction in total staffing. In 1989, Bristol Myers merged with Squibb. In the same year, Beecham and SmithKline merged. In 1995, Glaxo merged with Wellcome, and, in 1996, Sandoz merged with Ciba. Three of these four recent mergers involved one of the four companies most reliant on a single drug for their 1989 sales.

Concluding comments

The crudest representation of the technology of pharmaceuticals R&D in the simple 'lottery' model. This model captures the key role played by the occasional major successes which contribute heavily to companies' profits. It is, however, an oversimplification. Once any new product of major therapeutic value is introduced, a race begins to introduce similar or related drugs. In this chapter, we have focused attention only on the peaks represented by top-50 drugs, and looked at sequences of highly profitable new introductions within a category. Below this level, however, there is a plethora of less successful drugs that follow each major advance. Patent restrictions eliminate direct imitation, but 'redesign' of the molecular structure can often produce a patentable variant of the original drug that offers advantages for some patients, or for some conditions. In other cases, the follow-on drug may have little to offer in comparison with the original. The success or failure of these follow-on products may depend very heavily on the marketing efforts of the companies involved.

This suggests a more complex model than the simple lottery. Instead of lotteries leading to isolated successes, we can think of the winner of the lottery as acquiring a 'first mover' position within some new category of chemically related entities. There then follows a game in which rival firms vie to introduce products within the category, while facing a double disadvantage. The first firm enjoys patent protection which inhibits rivals' abilities to introduce identical products. This first mover status might in principle make it easier to develop major follow-on drugs, though we have argued above that this advantage is slight. More importantly, the first mover enjoys a marketing advantage in having informed physicians of its product first, and in having created an awareness of its properties, and this appears to place rivals with similar but imitative products at a disadvantage. The fate of such late arrivals whose products offer small but significant advantages, will depend to an important degree on their marketing efforts.

While the R&D technology of the pharmaceuticals industry is that of a 'low α' kind, there are two key features of the industry that disadvantage smaller firms. The first relates to the marketing side, where

the scale of effort needed to exploit discoveries may be achievable only by way of joint ventures. The second relates to the 'portfolio effect' which makes small and medium size research companies vulnerable to takeover. It is to these latter factors, rather than to the nature of the R&D process, that we need to look in understanding the limits to fragmentation in the pharmaceutical industry.

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Chapter 2
The Chances of Market Success in Pharmaceutical Research and Development

TREVOR JONES

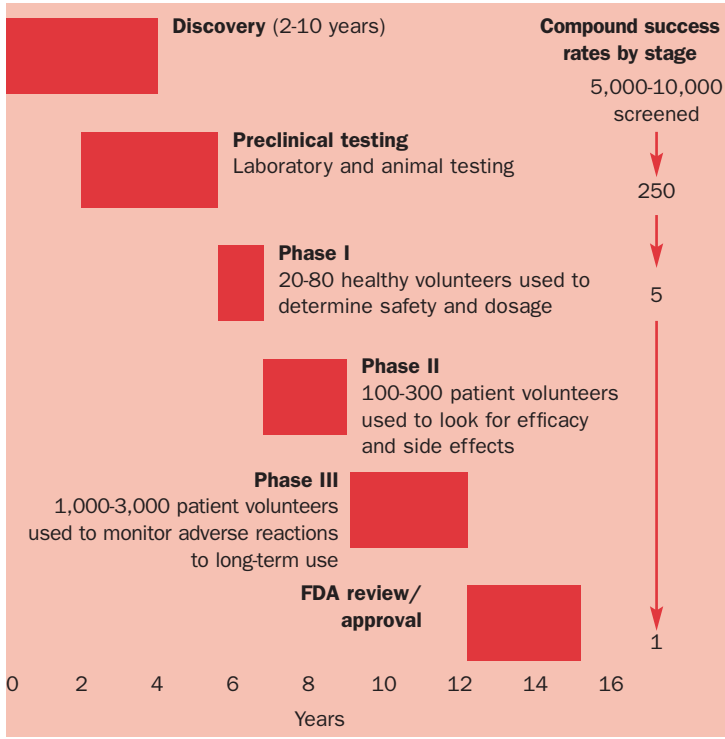
This paper discusses the chances of market success and reducing risk. In my experience, those within the pharmaceutical industry engaged in R&D are only too conscious of this particular need. It is not just the pride of the 'my lab' syndrome that we share with academia but more particularly it is the 'my product' kind of accolade that drives many researchers and developers and generates success, both economically and therapeutically.

I wish to stress the point that researchers in the discovery of medicines, at least in the laboratories of the pharmaceutical industry, are drug hunters rather than just pharmaceutical scientists. That is not to say that during the very painstaking time of trying to find new, therapeutically active molecules they do not often discover underlying mechanisms and fundamental principles governing the function of our bodies and of disease in general. But that is not their purpose nor the purpose of the industry. Rather, it is to produce invention from discovery and to turn that into clinically effective and, very importantly, cost-effective practice.

Although serendipity plays a very large role in that particular search, it is not a game of chance, especially nowadays. Once the target has been established – whether it is an ion channel, receptor, part of a gene, or whatever – the focus of research that then takes place, to reduce the chance of failure, is geared towards a very much sharper identification of a lead compound, i.e. a compound robust enough to withstand the huge expense and uncertainty of the long process of development.

In recent years, it has been customary to preach a litany that for every 5,000 to 10,000 compounds synthesised, only one will reach the market place (Figure 2.1). However, it is likely that this ratio will alter radically in the future. The genomic revolution, and the advent of combinatorial chemistry, high throughput and high intensity screens over the last two to three years, have rapidly increased the number of compounds available to probe the ever more specific targets. I would

Figure 2.1 **Success rates**



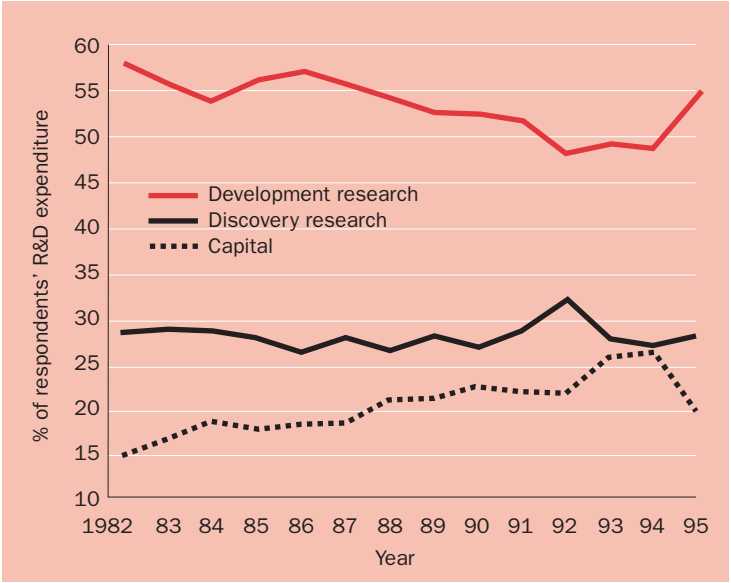
suggest that from 1996 onwards the ratio of compounds chemically prepared to evaluate against particular targets versus those that will successfully enter the market will be more in the order of one million to one.

It could be argued that the greater degree of blind screening is increasing the gamble. I do not think this is the reality, however. Ten to 20 years ago, blind screening meant taking almost all the compounds you could find, throwing them at a disease model and hoping you might find a hit. Nowadays we have, or we at least think we have, the targets much more closely in our sights. What we are looking for, therefore, are more ways to explore how these targets could be interacted with

and how we might affect them. We will improve at this, especially with our increasing knowledge of the human genome and the genomes of pathogens we shall be finding over the next few years.

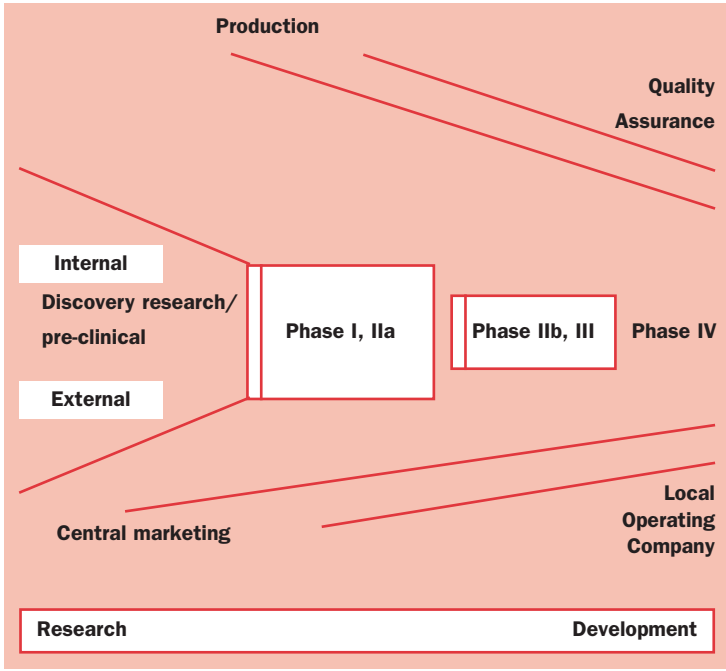
Research over many years has shown that work relating to discovery is the smaller component of the overall spend on R&D. Figure 2.2, using data for 1982 to 1995, shows that discovery research comprises about 30 per cent of total R&D expenditure. The majority of money in R&D is spent in development. This means that, unless we get it right in terms of discovery, the very high spend in development will not be optimised. Remember, we need to move from discovery to proof of principle, to full-scale development (Figure 2.1). It is vital then to determine at what point, by whom and how, decisions are taken during these processes.

Figure 2.2 **Proportion of UK pharmaceutical R&D expenditure on discovery research, development research and capital**



Source: CMR

Figure 2.3 **The R&D funnel**



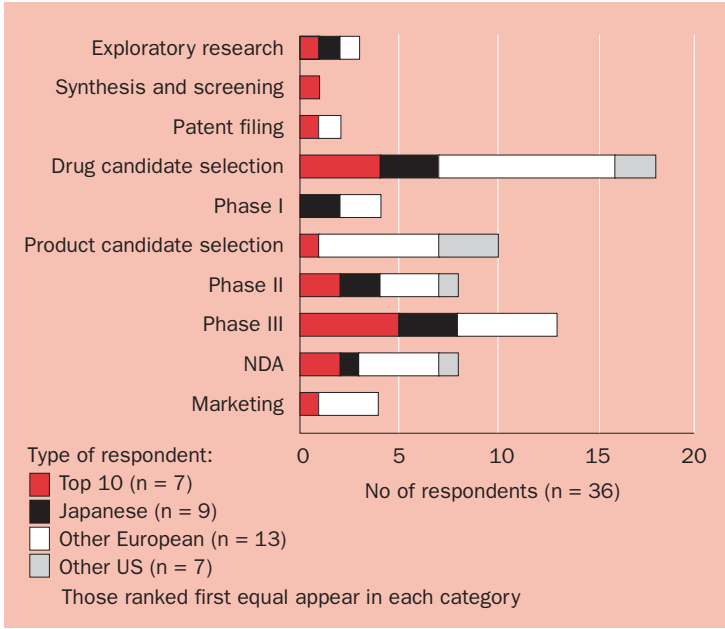
The difficulties are aptly represented by the funnel analogy shown in Figure 2.3. In the research discovery phase, whether using in-house or external research, the important task is to find a way of narrowing the number of compounds down to those few which reasonably and ethically should go into phase one or phase two and, from there, the very critical decision of what proceeds into phase three. The products that a company selects for phase three testing determine the shape and nature of the company, and its future profitability. In my experience, decisions to proceed to phase two testing are best taken in research and decisions to proceed to phase three are best taken corporately.

The possibility of using a 'virtual' discovery approach has been raised in recent times. I do not believe this to be feasible. Undoubtedly, the use of more and more contract research and contract development

organisations will be an inevitable, desirable and very useful part of avoiding some of the peaks and troughs of success and failure that can happen. However, unless you have sufficient people working with you who really understand and are competent in these technologies, you will not know who to go to for external research and, when they tell you, you will not understand whether it is true or whether it is hype. So you need a dynamic group, working closely with you both in research and in development. This is the balance between internal and external research required to optimise the process.

Given that, I think there are two very clear processes, i.e. discovery and R&D. The research done by the Centre for Medicines Research (CMR) has quantified this in a positive way. Figure 2.4 shows the various points in the overall R&D process – from exploratory research

Figure 2.4 **The most important decision point**



Source: CMR

through to the actual licensing – which pharmaceutical companies believe are the most important decision points. Selecting the drug candidate is the prime point, where the decision to spend high levels of money is taken. But phase three is perhaps the most critical. At this stage a company is committing not only large resources but also its reputation, because stock analysts and the world are looking very closely at this point in time and determining the future of the strategy. Minimising risk and chance, therefore, is about making sure that at least these two decisions are well taken.

In my experience, there is no absolute, predetermined point when a decision can be planned. The decision does not occur at a particular deadline; rather it is a gradual emergence of the understanding of whether the product is worth developing beyond that point. Frequently, and properly, the people involved in this process change. I referred earlier to the 'funnel' (Figure 2.3) which shows the need to involve a central marketing group in this decision process, the need to involve local operating companies as well as production colleagues, and so on. CMR have quantified this in recent years, by looking at the involvement of people outside R&D departments in decision-making. Their research demonstrates that most companies involve many more people in these critical stages of allocating resources to the future of their portfolio.

The need to quantify risk has meant that R&D executives are continually being told of the merits of probability theory that predicts how many compounds will go from A to B and in what time etc.. However, this has never seemed to me to be as good as human intuition, as good as sitting down with people who really understand the therapeutics, the market, the research and its potential, and working out together the chances of this compound withstanding the process. Even if the sophistication of discounted cash flows and the usual parameters which produce some evaluation of whether a compound is worth £100 million per annum, £200 million per annum, or whatever, are used, this still depends heavily on the ideal profile that you have created and how you expect the profile of your compound to turn out. The difficulty in managing risk is that you do not know how a compound will truly perform until it is well through the development process; and really not until it is on the market. To my mind,

therefore, sophisticated calculations of cash flow have a legitimate place but they should not override human judgement.

I have already discussed the overall ratio of success. Various researchers have looked at the failure rate from the time a compound enters the pre-clinical evaluation stage to the point where it enters the market place. Figures estimated by four research teams are presented in Figure 2.5. The 10:1 ratio reported in three of the studies between numbers of compounds entering the preclinical phase and numbers eventually launched, represents, I hope you would agree, an unacceptably high level of failure. I believe that as genomics and molecular biology techniques improve, better compounds will be chosen and more will make it through the pipeline, i.e. I predict that these 'attrition' rates will fall dramatically. Certainly it is something the industry will be monitoring. To minimise the peaks and troughs of resource allocation, contract development at this stage will be an increasing and ever-present part of expenditure.

The difficulty in terms of the process of minimising risk, is that success should not be measured in terms of getting a product licence, but in having a successful product, both commercially and therapeutically. I have not yet seen a drug with a poor therapeutic profile succeed with good marketing, but there are many examples of the reverse. The target for development, therefore, should not just be to get a product licence, but to ensure that the product is robust enough so that it can compete adequately.

Figure 2.5 **Number of compounds surviving**

	Centre for Medicines Research	*Cox & Styles*	*Gordon & Wirenga (P.M.A.)*	*Wellcome History*
Preclinical	10	10	10	7
Phase I	3.3	5	7	5
Phase II	–	3.3	3.3	3.4
Phase III	1.4	2	2.7	1.4
Launch	1	1	1	1

The costs of carrying out R&D today are well documented. Global expenditure on pharmaceutical R&D is currently running at about US$45 billion per year. This has increased dramatically over the past 10 to 20 years, partly because of extra regulation and partly because the globalization of the industry has meant that R&D is being done better, on a broader base, which raises costs because of the increased trials required. Figure 2.6 gives a breakdown of how the R&D money is spent and shows how many projects come through from phase one, phase two and phase three. The cost of getting an NCE to market is estimated, by Lehman Brothers, at $611 million (in 1995 prices). $441 million of this is spent on failure and $170 million is spent on success.

Figure 2.6 **$600m to get an NCE to market (1995 $m, including failures)**

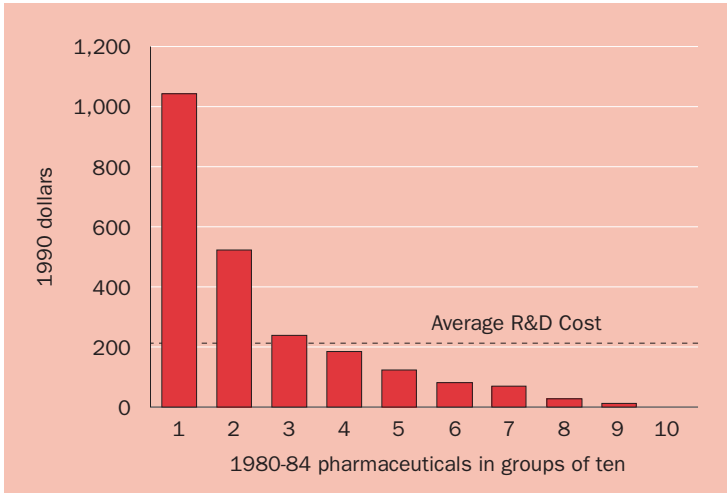
	Drug discovery	*Preclinical*	*P1*	*P2*	*P3*	*Approval*	*Total*
Number of compounds entering stage	many → projects	11.8 →	4.7 →	3.3 →	1.7 →	1.1 →	1
Number of compounds failing		7.1	1.4	1.6	0.6	0.1	11
Cost ($m) per compound completing stage		6	12	12	100	40	170
Cost ($m) of all failures	230	65	44	28	70	4	441
Total cost ($m)	230 (discovery and infrastructure costs)	71	56	40	170	44	611

Source: Lehman Brothers Pharmaceutical Research. (Data from Zeneca. Decision Support Group)

The bulk of the spend occurs in phase three. It is critical, therefore, that before commitment to the expense of phase three is made, the *corporation* must decide that the risk is acceptable: not just the research director, not just the clinical director, or even the marketing director, but the corporation. Even a major corporation can only handle a small number of phase three trials. Unless the corporation commits to that kind of understanding of risk and failure, therefore, it should not be surprised if its fortunes turn - because failures will occur.

Surprisingly, although the industry has re-engineered the development process, with the goals of increasing efficiency and reducing failures, data collected over the past 15 years indicate that it is not getting much better at it in terms of time. Mean development times are still running at 10 to 12 years. The speed of development of biotechnology products has, on the whole, been faster. Different therapeutic categories of cardiovascular, immune, endocrine and anti-cancer drugs take 10 to 12 years to develop; whereas biotechnology products have on the

Figure 2.7 **Earnings performance for 1980-1984 pharmaceuticals**



Source: Grabowski H and Vernon J (1994) 'Returns to R&D 1/16/96 on new drug introductions in the 1980s', *Journal of Health Economics*, (13)

whole taken a much shorter time, around six years, to develop. The application of genomics in the evaluation of safety and the targeting of new drugs could considerably speed up this process.

One final issue of great concern is illustrated in Grabowski's work on the US market. It looks at the earnings performance of a series of pharmaceutical products introduced to the market in the 1980-84 period (see Figure 2.7). It shows that very few of these products achieved commercial success, based on the total amount they earned, after-tax, relative to the average cost of developing a molecule. This is of concern because we must surely be seeking commercial as well as therapeutic success.

Chapter 3
Managing Risk – the Pfizer Approach

GILLIAN SAMUELS

Before discussing Pfizer's risk management strategy in R&D, I will give a brief outline of the company's current R&D position. Pfizer is a large transnational pharmaceutical company with almost 41,000 employees world-wide. Sales in 1995 were approximately $10 billion, over 80 per cent of which was from human pharmaceuticals and the majority of that from prescription medicines. Most of Pfizer's major compounds will not come off patent until well after the turn of the century. Pfizer has four research sites: Groton in Connecticut, USA, which is about twice the size of the Sandwich site in the UK; Amboise in the Loire Valley, which performs toxicology studies mainly on UK-produced compounds; and Nagoya in Japan. About 1,500 people are employed in R&D at Sandwich, where compounds are taken from early stage discovery to clinical evaluation and registration. The R&D staff at the site are complemented by around 1,500 marketing and production employees. Sandwich is uniquely large for a non-UK company's R&D investment in the UK.

Pfizer attempts to deliver a continual cycle of innovative products to the market place, thus avoiding significant variation in income over time. The aim is for enduring market leadership, not cyclical peaking and troughing in revenue. All pharmaceutical companies are aiming for less clinically precedented targets now, although they do generally concentrate their efforts in the disease areas in which they know and understand the medical need. This requires an unwavering commitment of resource.

The pharmaceutical industry is an intrinsically risk-intensive business. I believe that only those companies prepared to take reasonably high-level risks will be among the industry's leading players. However, to succeed in implementing high risk projects requires the ability to manage those risks. In this paper, I am taking risk to mean not only exposure to mischance – by for example taking a compound that is not sufficiently robust into further clinical evaluation – but also exposure to the consequence of missed opportunity, of inadequately swift and timely progression of projects.

How is Pfizer positioned with respect to its current portfolio and the kind of risks it will be exposed to in the future? In terms of anticipated new chemical entity (NCE) roll-out, Pfizer is in a relatively healthy position through to the year 2000. To maintain this competitive position Pfizer needs to deliver two or three NCEs to the market each year and these NCEs should be the best in class and/or the first in class, which meet the medical needs of the 21st century. Such NCEs do not have to be home-produced. There is no feeling within Pfizer that a licensed-in compound is deficient in any respect in terms of quality simply because it was not invented at Pfizer. Indeed, strong partnerships between scientists and their commercial colleagues have helped in identifying and securing licensing deals.

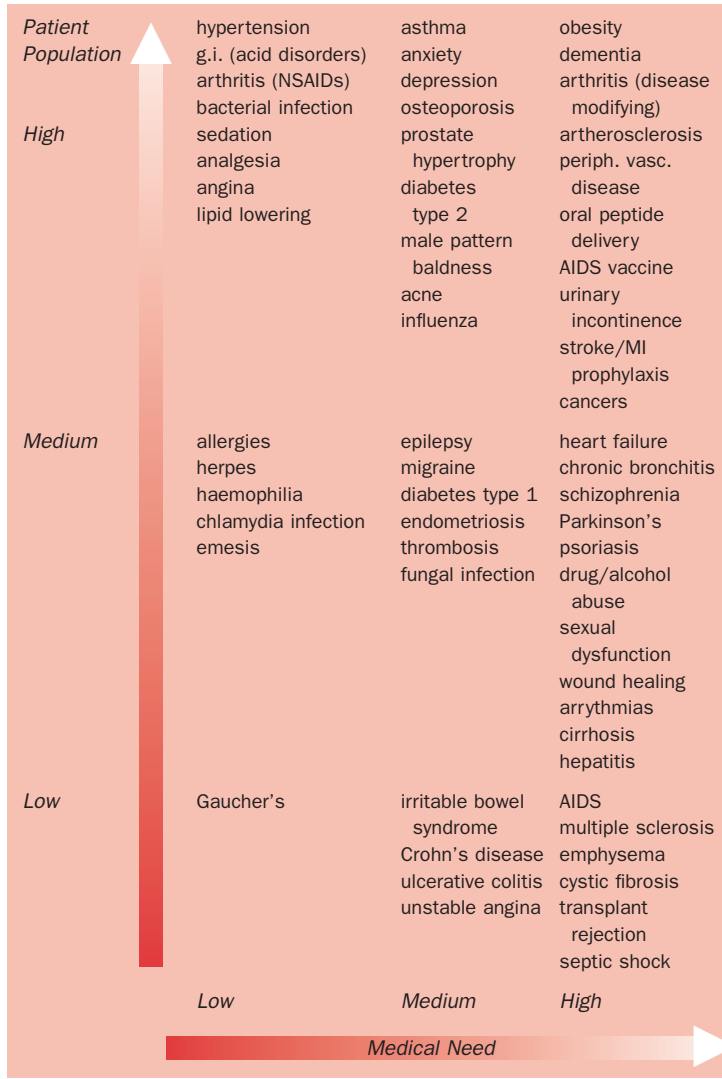
Pfizer's overarching objective is to discover novel, cost-effective therapeutants which clearly meet the medical needs of the 21st century and which are differentiated from competitor products. In attempting to achieve this objective, Pfizer spent $1.7 billion on R&D in 1996, $1 billion of which went on human medicinals.

Pfizer has a very broadly spread R&D portfolio. The high degree of competition and the number of opportunities available necessitate that this breadth is maintained. Pfizer must generate as many high quality compounds as possible to enter into clinical development. It is an opportunistic company, driven by the new science and maintaining a strong focus on both commercial and medical opportunity.

The R&D portfolio is divided between three major sites. The relationship between these sites is one of co-operation rather than competition; the same therapeutic area is not covered on two sites. Even where two sites appear to be active in the same broad therapeutic area, they are actually concentrating on quite separate elements of it. For example, neuro degeneration is studied both at the Sandwich site and in the US, but the R&D in the UK is targeted at strokes whereas in the US it is targeted at senile dementia. This split capitalises on cultural differences between the local science bases. There is strong co-operation between the groups, enabling portfolios to be discussed and ideas to be shared.

How does Pfizer decide which projects to invest in? Pfizer's decision-making process is based on epidemiology, on medical need and on

Figure 3.1 **Driven by medical need**



Source: Lehman Brothers

scientific 'do-ability'. The therapeutic areas targeted are those with high populations and high medical need, based on the burden to the patient and/or to the health service due to there being no adequate treatment currently available. Figure 3.1 illustrates how certain disorders appear under these criteria. Those of highest 'need' are shown in the top right-hand corner and include disorders such as obesity, dementia, atherosclerosis and cancers. These rate higher than disorders in the middle of the chart, such as epilepsy, migraine, thrombosis and fungal infections, through a mix of higher patient populations, greater burden of disease and less adequate treatment availability.

It is important to note that, as a company, Pfizer relies greatly on the science base and on the principal contributors to it, amongst whom I would number the pharmaceutical industry. We depend on government-funded basic research undertaken by, for example, the National Institutes of Health in the USA and the Medical Research Council in the UK; and privately funded basic research undertaken by, for example, the Wellcome Foundation in the UK and the Howard Hughes Medical Institute in the USA. Any legislation or action which puts this knowledge base at risk puts the pharmaceutical industry at risk, because we add value to this fundamental knowledge base, creating products which are clinically effective agents and which can cut the cost of health care.

In achieving this additional value to the science base, Pfizer has, over a number of years, built up substantial internal capabilities: ranging from classical pharmacology and chemical synthesis, through to molecular biology, high throughput screening and the development of combinatorial libraries of compounds. This extensive capacity does have limits, however, and so it is supplemented through networks with academia and with small and medium-sized enterprises (SMEs), forming mutually advantageous partnerships which allow Pfizer to leverage internal capacity substantially. Collaborators include academic institutions such as Washington University in the USA and Manchester University in the UK, as well as SMEs such as Oxidase Symmetry in the UK and Insight and Inusol in the USA. The objective in forming these alliances is to provide our discovery scientists

with whatever technology and new science they need to progress therapeutic programmes at an appropriate pace.

In selecting partners, Pfizer carefully assesses numerous aspects of the relationship: the potential impact on discovery goals; the importance of the selected disease target; the strategic relevance to other initiatives (some of these partnerships may impact on more than one initiative); the therapeutic scope of the science and technology with which we are getting involved; the strength of the partner company; and the impact and opportunity cost of the resources being committed, both now and in the future. One question which must be asked in all cases is: 'If we do not form this alliance, will it have a serious effect on our ability to prosecute the programmes?' Pfizer spends a substantial amount on these partnerships, $80 million in 1996. One initiative, PfizerGen, which comprises mainly biotechnology alliances, accounts for a large percentage of this expenditure. DrugPfinder, a separate initiative, is designed to enhance the company's ability to internalise novel targets arising in academia. Both DrugPfinder and PfizerGen are designed to leverage internal discovery capabilities; to accelerate programmes and to enhance productivity; to build key technology, and to provide business development opportunities for risk management by increasing awareness of new areas.

There is obviously a strong tension in resource allocation between investing in external technologies and product roll-out. Those of us in the industry know that this is an active point of discussion in every budget year!

How does Pfizer select projects and targets? There is competition between ideas and opportunities to construct a research portfolio in Pfizer. Multidisciplinary groups get together from clinical development, discovery and market intelligence. These groups produce project operating plans (POPs), which define research opportunities and compete with one another for resource allocation. A decision to commit to a specific project area is extremely tightly focused and resourced according to its relative progress within the portfolio. POPs are reviewed frequently with senior line management to ensure that, where teams have problems, the full experience of the organisation is

utilised to solve and to remove these difficulties.

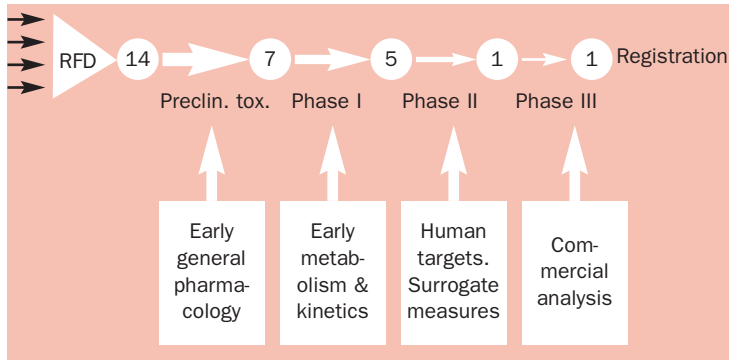
Project progress is charted using a matrix, making it highly visible to all concerned. The matrix facilitates resource allocation. Several stages are used to describe projects. Firstly, there is the exploratory phase, just after the POP is written, where appropriate screens are developed, both internally and with external collaborators. Screening and design synthesis follows, at which point our chemical colleagues become involved. Next comes the lead development phase, where a compound is identified which has affinity for the receptor or the enzyme being targeted. After successfully identifying leads, we proceed to the candidate-seeking phase. If successful there, the candidate is nominated and we go to back-up seeking and, further, to candidate support.

Selection of high quality scientists, providing them with the right equipment and making sure that the team is well seeded with an experienced cadre of drug hunters who are skilled at converting scientific knowledge into drug molecules, are all essential to achieving the goals in new medicine development. Pfizer is heavily reliant on experienced scientists and does everything to facilitate diffusion of learning both by careful team structure and by internal training. Industry insiders all know individuals who are particularly skilled in this and who often have a very strong urge to innovate, i.e. to translate scientific discovery into true innovation.

Historical calculations of attrition rates for Pfizer are shown in Figure 3.2. 'RFD' refers to recommendation for development of a compound when it comes out of the basic discovery laboratories. Our calculations suggest that we needed some 14 compounds going into development – prototypes and back-ups – in order to get one compound to registration. Compounds fail for different reasons at different stages in the portfolio. This may change in the future, with more unprecedented mechanisms being utilised in the early stages of the portfolio. It means that it may not be until phase two that you have a reasonable assessment of potential clinical utility, which alters the pattern of resource allocation.

Just as we have multidisciplinary project teams that plan and execute the pre-clinical programmes, we also set up multidisciplinary candi-

Figure 3.2 **Candidate survival**



Source: Pfizer Central Research

date management teams (ECMTs) to plan and co-ordinate development activities. These teams contain many of the individuals who worked with the project from the earliest stages, from writing the POP. This, we believe, is key to providing a seamless transfer across departments, to progress issues and to develop innovative solutions to problems. There is nothing like the project champion who is determined to solve any problem, wherever it originates. There is a continuous focus on process improvement in these groups, for example, the shortening of times from RFD to first-in-man trials. Many of these improvements have been highly successful, despite the fact that, on occasion, project teams feel that process improvement is a bit like trying to service a moving racing car.

Designing the groups in this way facilitates skills transfer within the organisation and produces ambassadors who reach out into the organisation to set the scene for project progress in the future. Again, there are regular formal reviews with senior management and the ECMTs, who oversee the phase one and phase two studies, and facilitate the research review and development decision process – the so-called R2D2/1 – which culminates in a decision on whether or not to plan phase three trials. Transparency and visibility of decision-making in staged investment programmes are central to their success,

and their acceptance. Playing still on the importance of teams and the process involved, the ECMT prepares a full report which goes to senior line management. This includes not only the drug candidate profile but also the description of clinical studies, the projected market profile and, importantly, any critical issues we see arising in terms of development. Candour is key here. When this is endorsed by central research management, an advanced candidate team is formed, comprising individuals both from central research and from Pfizer Pharmaceuticals Group. This core advanced candidate management team creates the development strategy and operating plan which governs the progress through phase three trials. It is this plan which is used to facilitate relative resource allocation in the phase three portfolio and can result, if successful, in the establishment of a global candidate team which implements all the phase three studies – global because we choose to develop in all countries.

When contemplating entering phase three studies, a second decision matrix is established, similar to that used in early project assessment. This looks at: the kind of resource allocation required; the probability of success; the timing of filing registration documentation and launch, both on the US market and internationally; and the cost of goods and the potential sales. The likely indications applicable and the various development options available are also listed. For all relevant categories we generate a best guess, an optimistic assessment and a pessimistic assessment. All candidates are subjected to this process. As with the early project decision making system, this methodology allows competitive resourcing of projects and staged investment. One may find oneself in a position where, for example, a commitment to indication A is made now but an option to buy into indication B may be possible at a later stage in the year, depending on the relative progress of other projects.

Subsequently, the successful prosecution of pre-clinical and clinical testing will form the basis of our international registration dossiers. Pfizer has teams on both sides of the Atlantic which produce investigational new drugs (INDs) and new drug applications (NDAs). We appreciate that individual countries may require locally sponsored clinical studies to meet specialised regulatory requirements. At this

stage there is a high degree of transnational co-ordination, which is key to timely completion.

Summing up, we believe the ingredients important for successfully navigating a competitive pharmaceutical R&D organisation in today's marketplace include: planning and anticipation of issues; speed of execution; leverage of internal and external resources; analysing programme cost and relative resource allocation; effective technology transfer, internally and externally; plus effective regulatory strategy. All of these are vital for satisfying the market's demand for high quality, cost-effective, new medicines. Each stage of discovery development has its own investment dilemmas and I hope that I have illustrated some of those which we identify and work on. To resolve these dilemmas the project teams must be able to adapt to changing environments, learn from them and pass that learning into the organisation. Building internal alliances is key to seamless and timely innovation; not just innovation in science and technology, but also in processes. These high-speed efficiency and quality goals can only be met with investments in automation, by technology focus and strategic sourcing. Regulatory demands will continue to increase, whilst resources available for the candidate are likely to decrease, partly because of the number of candidates we wish to progress.

Finally, technology investment must be balanced against the product roll-out resource, in order to maintain and improve performance. In essence, we believe that the key to success in risk management is competition between ideas, whether in project or process improvement. It is key to select the right idea and then to gain effective co-operation between people within the global organisation. When decisions and commitments to actions are made they must be resourced at an adequate level to ensure that projects are brought to fruition.

Chapter 4
Managing Risk – Glaxo Wellcome Approaches

RITA SULLY

I have been trying to stand back from a portfolio management view and understand why the pharmaceutical industry is suddenly getting very interested in embracing new approaches. Yes, it is to do with the increasing costs of development, and it is to do with the fact that there is risk in product development. But it is also to do with the market place and the fact that customers are becoming more sophisticated in what they are looking for.

A brief outline of Glaxo Wellcome may help you understand better the company's strategy on risk management. Glaxo Wellcome is the world's leading pharmaceutical company measured in terms of both sales and market share, although it has a global market share of only five per cent. The company is second or third in terms of market value in the UK stock market, and about fourth or fifth globally. It has subsidiaries in over 50 countries and manufacturing plants across several continents. Over the last five years, return on capital employed has averaged around 40 per cent.

It is in the area of maximising future performance that Glaxo Wellcome seeks to add long-term shareholder value. This it does by trying to invest above the cost of capital in all projects undertaken, both capital projects and R&D projects. Investment in R&D is key to this long-term value creation. It is particularly important as it is the largest on-going single investment. In 1996 it totalled £1.2 billion, equivalent to 14 per cent of sales. To date, this investment has been quite focused in the pharmaceutical area, making it easier to compare and contrast the performance of projects.

We are all aware that getting a product to the market is a risky process. Figures from the Glaxo company, taken before the acquisition of Wellcome, indicate that getting a product from pre-clinical through to phase one has a 63 per cent probability of success. Taking a product from the pre-clinical phase through to the market has only a seven per cent probability, however. It should be noted that these figures are

averages, based on the performance of many products. The averages are useful as a base marker, but when trying to differentiate between projects it is important to break the figures down on an individual basis.

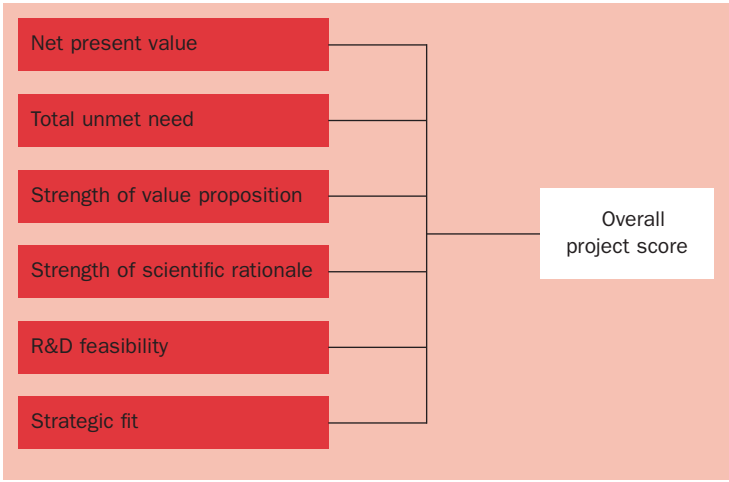
Before discussing the portfolio review process, it is vital first to have an understanding of how the strategic direction of Glaxo Wellcome is determined. This takes us to three main areas. One is the scientific and technological innovation opportunities that are presented. The second is the commercial opportunities: the unmet needs which should be focused upon for the future. Lastly, how does this fit together to give a corporate strategy all groups can buy into?

Glaxo Wellcome uses Strategic Therapeutic Area Reviews. These involve cross-functional teams looking at the three different perspectives discussed above and presenting the findings in open forum. This enables three key questions to be answered. What will the key unmet needs be? Which therapeutic areas or diseases should Glaxo Wellcome focus on? What are the technological drivers that may open up new areas of research?

It is against this background that the portfolio can be reviewed. All projects, which do not equate to products in the marketing sense, are evaluated on an ongoing basis. Around 170 projects, including those licensed-in, are under evaluation at any one time. This 'portfolio review process (PRP)' enables projects to be evaluated from the pre-clinical phase through to registration and post-launch. In addition to regular management by R&D personnel, the whole portfolio can be reviewed by cross-functional teams and by senior management, allowing the more strategic questions of balance and fit to be addressed. To achieve this, the PRP must be understood and accepted across the organisation; with the scientists, the marketing team and the management buying in.

The portfolio analysis model has six key components (Figure 4.1), the first three of which address the commercial opportunities of the product. Net present value (NPV) is an estimate of future cash flows, but net of all costs covering the life cycle of the project. The unmet need is a theoretical figure, computed from unmet medical need

Figure 4.1 **Portfolio analysis model**



Source: GlaxoWellcome

scores collected by sophisticated market research with opinion leaders. Disease prevalence estimates are combined in this. This gives an overall assessment of the economic potential from a disease area. Strength of value proposition is a preliminary assessment of the cost versus the income profile of the target product. It serves as an early indicator of profitability.

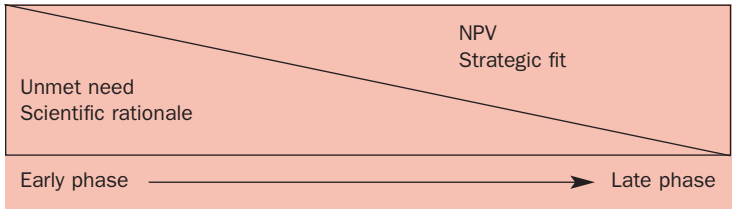
Strength of scientific rationale and development probability are both measures of risk. The first of these is a measure of the confidence that the product profile defined will be achieved, based on the scientific hypothesis that has been put forward. This often generates dichotomous views, which can be handled in the model. R&D feasibility measures the product's chance of success as it moves through various hurdles of development. Strategic fit measures how the product fits in with future franchises that the company hopes to have. It is closely aligned to the strategic direction, referred to earlier.

All of these project ratings are brought together within a 'black box', a computer spreadsheet, to create an overall score. This allows all projects to be ranked, which is generally done within product phases rather than across the whole portfolio. The method of collection also enables, importantly, component scores to be evaluated individually. For example, a potentially high commercial opportunity can be identified in the model even if the overall score looks unfavourable. Projects with high commercial opportunities are highlighted and ways of improving the unfavourable scores are sought. This process drives an informed discussion within the organisation on all the projects and ensures that decision making takes account of a wide number of factors.

Similar information is collected for each project, but its value to the company differs depending on the phase and the stage of risk it is collected at. A weighting system is therefore applied to the different phases as shown in Figure 4.2. For example, early stage projects are driven most heavily by scientific rationale. This remains the case until proof of concept and proof in man are obtained. NPV becomes increasingly important at the later stages of development. This is the key driver by the time phase three is reached, where the largest costs are incurred. The parameter weightings are adjusted over time to take account of such matters.

Glaxo Wellcome uses a standard method throughout the company for valuing capital projects – estimating future cash flows and deducting all relevant project costs, with the exception of capital. Estimating the

Figure 4.2 **Criteria weighted according to phase of development**



Source: GlaxoWellcome

cost of the remaining phases of development is based upon how many full-time equivalent staff are required to do the work. The net cash flows are then adjusted for the development feasibility. This can and does vary from project to project and year to year. The adjusted net cash flows are then discounted by the company's weighted average cost of capital (WACC), estimated at 12.5 per cent. The model and decision-making process are, however, not particularly sensitive to WACC.

To create the sales forecasts, models have been developed for each project that try to define the market place, both in terms of the size of that market as it will be in the future and the potential share a project may have. Although NPV is not weighted heavily in the early stages, it is still an issue, as it indicates whether there are any areas of potential concern for the future (such as an insufficient population, or whether it is an area of very low price where achieving a viable price would be difficult). Incremental sales also need to be considered.

Glaxo Wellcome measures eight stages during the development process. Feasibility for the project is desired at each stage. The stages are: small-scale development; short-term safety; scale-up for manufacture; long-term safety; initial human safety and tolerability; initial human efficacy; large-scale human safety and efficacy; and regulatory approval. Estimates for each of these phases of development are collected and then multiplied together to give an overall assessment of value for each project. As you would expect, the projects at early stages have a higher risk than those at the later stages.

The area of commercial risk is also looked at. As I noted earlier, customers' requirements are critical to the success of a product in the market place and will become even more critical in the future. The company therefore needs to have a much better understanding of the way the market views products, and the balance between benefit and cost that customers are prepared to pay. Data suggest that only 30 per cent of marketed products recover their R&D costs post-marketing. Glaxo Wellcome uses a limited version of a Monte Carlo model to try to identify the factors that may impact on a product's performance in the market place. These include: innovative competition, reimburse-

ment, prescribing restrictions, position to market, generic competition and price. An attempt is then made at gauging the likely impact of each factor on the project. The expected value of the project can then be estimated, and this figure can then be used in the NPV calculation.

Numerous challenges arise from the PRP. The main challenge is getting credible data. This relies on talking to the people who have the best knowledge. It also relies on judgements. There is no certainty about the future. All the PRP model is doing is taking a number of different judgements and putting them together. A further challenge is the long time scale involved. A project may be assessed for seven years before launch, with the life cycle of its possible commercial opportunity modelled for another 12 years plus. Glaxo Wellcome has been able to build some quite good models in this area, thanks to the considerable amount of historical data available about our own products and other companies' products. Another key factor with PRP is the need for transparency and gaining 'buy-in'. It is important to have the approach understood by a wide number of people in different functions. The financial language used should be understood by scientists as well as economists. That way the judgements are explicit and they are on the table. This enables a group or project team to have a shared understanding of the assumptions underlying the judgements. They can, therefore: (a) challenge them, and (b) better understand and be able to represent them in another forum.

The PRP can and does apply to a wide range of R&D projects. It is not limited to traditional pharmaceutical molecules, although that is most of Glaxo Wellcome's business. It can just as easily be applied to a NCE, a vaccine or a diagnostic. Licensed-in compounds are treated in the same way as 'home-produced' projects. The information gathered, particularly with respect to the commercial opportunity, also feeds into the type of deal the company makes for a licensed-in compound and how much it is prepared to pay for it.

PRP is now embedded into the culture of the organisation, such that a project cannot now enter the development process or move onto the next phase of development without being assessed for portfolio rea-

sons. At key milestone points in a project's development, new information from clinical trials can alter the expected profile of the drug and therefore impact the sales forecast; alternatively the project could have a changed risk profile. Previously when this happened, all projects were reviewed at key milestone points for go or no-go decisions. What the portfolio process adds, however, is the opportunity to realign resources and to re-prioritise the project each time it is assessed. In this way we are able to make better use of the resources available and to allocate them appropriately to some high priority projects. It also makes a no-go decision easier, not because the information is any different but because already on the table, in a transparent and open form, is the decision that would support the no-go. Thus, if anything, it allows for faster no-go decisions.

As well as an aid to decision-making at project level, the PRP also enables us to view the total portfolio of the company and to consider other aspects, such as shape, disease area profile, value, and strategic issues such as balance. Its first major application arose during the acquisition of Wellcome, as we were faced with looking at two companies' portfolios and in a six-month time span had to combine the two and make clear decisions about priorities, projects to drop and projects to license out. Since then, the PRP has been used on a regular basis for planning. Twice a year it is considered by the senior management in each discipline in a cross-functional forum. At the very minimum it adds insight and knowledge within the company. At best it provides a framework for debating and deciding upon some of the strategic issues present which, until we had portfolio review, we did not even know we faced. It allows us to look at the future value of the company, and to plan the quantity and type of resources needed – pharmacy versus clinical versus regulatory. Balance and shape can be assessed, and the way we use that to try to come up with decisions. The PRP can also be used to set targets and goals for the company, and to evaluate progress.

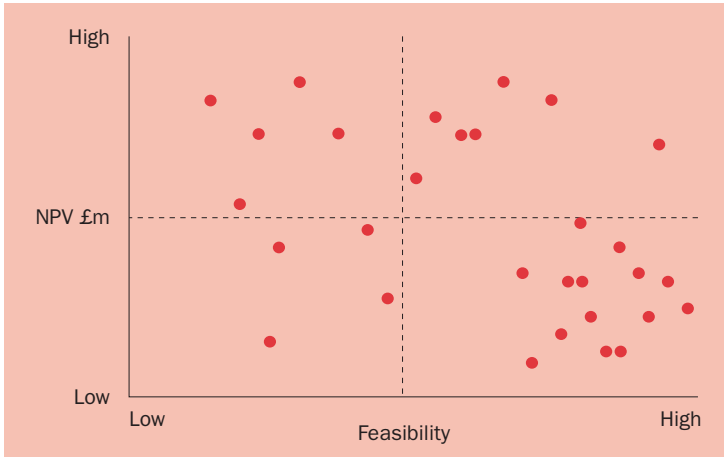
With target setting, for example, knowing the attrition rates per phase of development allows us to have some idea of the number of projects we ideally want in the pipeline at each stage of development, so that a target number of new product launches per year can be obtained.

The same analysis can be driven the other way round. Knowing the target amount of money that the company wishes to realise from the new product portfolio, enables an idea to be obtained of the number of products required to secure it for the future. A third way that PRP can be used is to map on the number of projects in each phase either over-capacity or under-capacity, possibly indicating the need for external facilities.

The PRP model also enables the business of the future to be valued, within all the constraints referred to earlier. The long-term outlook for the company can be gauged by taking existing business, which is forecast anyway by the company, and adding on the probability-adjusted forecasts for future business. This is useful in identifying peaks or troughs in sales and earnings for the future, allowing time to look for other strategies to help us through those periods. The same analysis can be used to look at the company's disease profile and how it will look in the future.

The PRP allows the issue of balance to be addressed: the contention between risk and return. Figure 4.3 shows this diagrammatically, with feasibility rather than risk being used along the x-axis. A low feasibility represents a high risk. The high risk/high return projects therefore appear in the top left quadrant and the low risk/low return ones are in the bottom right quadrant. Only about 30 per cent of projects that get to the market succeed in a commercial sense and, therefore, it is vital that as many projects as possible are kept in the high risk/high return category. In addition, it is desirable to have some projects in the bottom right-hand blocks, as not only are these more predictable sources of earnings but often, because they are new formulations or line extensions, they are protecting or enhancing the existing business. Although it is not easy to quantify this 'halo' effect on our existing franchises, we do want to support it where possible. A balance, therefore, is required between the top left and bottom right quadrants. The projects demanding particular scrutiny are those which appear to be high risk for relatively low reward – bottom left on the chart. Often these are NCEs at a very early stage of development, hence the high risk. The low risk/high reward category incorporates those projects that will be done anyway – the 'no brainers'.

Figure 4.3 **PRP applied to planning: balance**



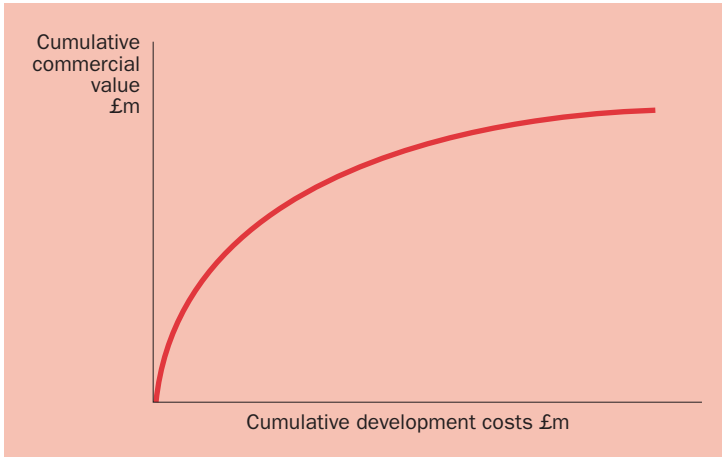
Source: GlaxoWellcome

Sometimes projects feature in this category because they are in a late stage of development, with the cash flows just round the corner. They will come through very positively in any portfolio analysis.

Balance may be judged on parameters other than risk and return, such as NCEs versus line extensions. In early-stage compounds it may be more appropriate to look at economic potential rather than NPV and compare this with the overall project score. A further consideration is strategic fit: how well does the portfolio fit with the agreed strategic direction for the corporation, which again may be considered against overall score. Once the data have been obtained they may be cut in a variety of ways, enabling a number of different perspectives to be taken.

With respect to planning, it is beneficial to model a 'diminishing returns' graph (Figure 4.4). This plots the cumulative commercial value versus cumulative development costs. By adding projects in order of their productivity, it is possible to gain some perspective on the sort of flatness, or 'tail', present in the portfolio. Clearly, if the tail

Figure 4.4 **PRP applied to planning: diminishing returns**



Source: GlaxoWellcome

flattens or starts dipping there are problems. The graph will give an indication of where the R&D should be cut back. The PRP can be utilised for project selection when resource constraints exist, as was the case when Glaxo and Wellcome combined. Projects most worthy of continued R&D expenditure were identified by plotting all projects in terms of expected risk and return against the line of R&D expenditure thought to be available in the new combined company. This methodology will be used in the future at Glaxo Wellcome at a time when the number of projects exceeds the amount of R&D expenditure available.

This paper has highlighted the range of perspectives that a PRP (portfolio review process) can offer to aid both strategic planning and the allocation of resources. PRP is not, however, a substitute for decision-making. It should not detract from the inherent intuition and gut feel that is required in science, particularly in the early stage of compounds. Rather, it tries to bring this to the surface and make it transparent. As such, it is as much an art as it is a science.

Mathematical approaches themselves are much more advanced than the quality and sophistication of the estimates that we are able to put into the models. We at Glaxo Wellcome could spend, and have spent, hours debating whether to use Method A or Method B, option theory or Monte Carlo modelling. However, once you get a model that works, it is better to stop the debate and address the real issues: how do you get credible information and how do you extract the best judgements on projects?

Applying a PRP at Glaxo Wellcome has resulted in better internal systems being set up that measure project costs on an on-going basis. It has forced the company to think long-term about diseases, how and when a product might interfere with that disease, whether to just give symptomatic relief and whether it is altering the course of the disease or slowing the progression. The PRP encourages us to try to stand back from the disease and look at the different approaches that we may not be taking but others perhaps are; to try to get some perspective on the sort of unmet need that will exist by the time the product hits the market; and how the product will stack up against that new market situation.

The PRP has given the company an agreed product profile for every single project. All departments are now clear on the potential of each project and what is trying to be achieved with it. This increased transparency has improved the quality of discussion within the company and, as a result of that, has also opened up a lot more debate.

Investment in R&D is key to long-term value creation in the company and therefore to shareholder value. The PRP provides us with a method, a process and a systematic approach to evaluating all the projects in R&D, from the pre-clinical phase through to registration. This enables us to prioritise projects and make sure that there is an appropriate allocation of resources. The PRP is an aid to strategic planning across the whole organisation, not just in research or development but also for the business in its total form.

Chapter 5
Measuring Pharmaceutical Risk and the Cost of Capital

STEWART MYERS

I am writing as a student of financial markets and corporate finance. I am not an expert in pharmaceuticals *per se*, although I have been working in this industry as an opportunity to develop new financial tools. I shall, therefore, talk about risk from the financial market's point of view. That turns out to mean something different from risk in the everyday sense, so I will define terms as I go along.

The heart of this paper is the risk-return 'staircase'. The 'staircase' means that the cost of capital goes down as you go from basic research towards product introduction. That will not seem surprising. The reason the cost of capital declines as R&D goes along, however, is not what you think. It has nothing to do with the risk of failure; it has nothing to do with the fact that you have to try a thousand compounds to get one to come out the other end.

The key is to explain why risk goes down as you proceed from basic research towards the introduced product. If you understand that, you will see that I can test the staircase by looking at the relative risks, defined from the point of view of investors, in biotechnology stocks as against mature pharmaceuticals. Biotechnology stocks are pure plays in R&D, so if I can show that the risk of the biotechnology stocks is higher than mature pharmaceuticals – for my reason – then my point will be made.

This way of analysing risk and return also leads to a simple way of valuing R&D investment in pharmaceuticals. I hope I do not mean 'simple-minded'; I certainly do not mean easy. I do not mean to downplay the difficulties of getting data here; but my method is simple relative to a theoretically complete approach.

I will start with some background. The bulk of the paper will then focus on the staircase of the cost of capital. Finally I will comment on how a rational financial investor would go about valuing R&D.

Why did I get into this business? First, I was frustrated by the lack of attention given to the biases in accounting profitability measures for

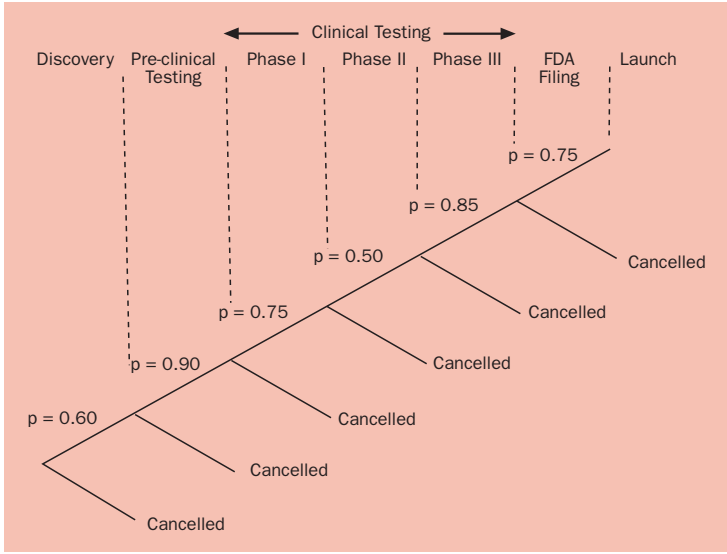
the pharmaceutical industry. It was mentioned earlier that Glaxo Wellcome was earning 41 per cent on capital. That is not true. They are not really earning 41 per cent on capital. It is just that the standard accounting measures are grossly upward biased because they treat R&D as an expense rather than as an investment. Hence the asset base is underestimated and the rate of return overestimated.

In addition to that frustration, I was also drawn into a study of the pharmaceutical industry by the Office of Technology Assessment of the US Congress. As a result, I and a colleague have published a paper on the cost of capital (Myers and Shyam-Sunder, 1996).

That led to the idea of the staircase for the cost of capital and led me to think that perhaps the pharmaceutical industry was a place where you could understand the financial economics of R&D. Why is that? It is not just that R&D is so expensive and important to this industry. R&D in this industry is also regularised. We know exactly the phases that a new drug has to go through. There are data on how long it takes, how much it costs, the success rates, and so on. Thus, although there is still massive uncertainty, we do at least know the structure of the problem to a much greater extent than in other industries. Furthermore, the existence of biotechnology companies in the pharmaceutical industry which focus solely on R&D, provides a way of testing hypotheses and calibrating our modelling.

I and my colleagues at MIT therefore built a simulation model of investment in pharmaceutical R&D. I do not want to dwell on this model, except to say that it traces the life cycle of a drug from when it is invented all the way to the point when it goes off-patent. The model is a Monte Carlo simulation which discovers drug candidates and tracks them through the various stages of clinical testing, where the drug candidates may or may not survive. Figure 5.1 summarises the probabilities assumed in the model (which are based as far as possible on actual experience). If and when a drug gets FDA approval and reaches the market, it is modelled randomly to have a commercial outcome at one of five levels ranging from 'breakthrough', through 'above average', 'average' and 'below average' to 'dog'. We model randomly whether the newly introduced drug gets additional

Figure 5.1 **Summary of the development path – probability of success at each phase**



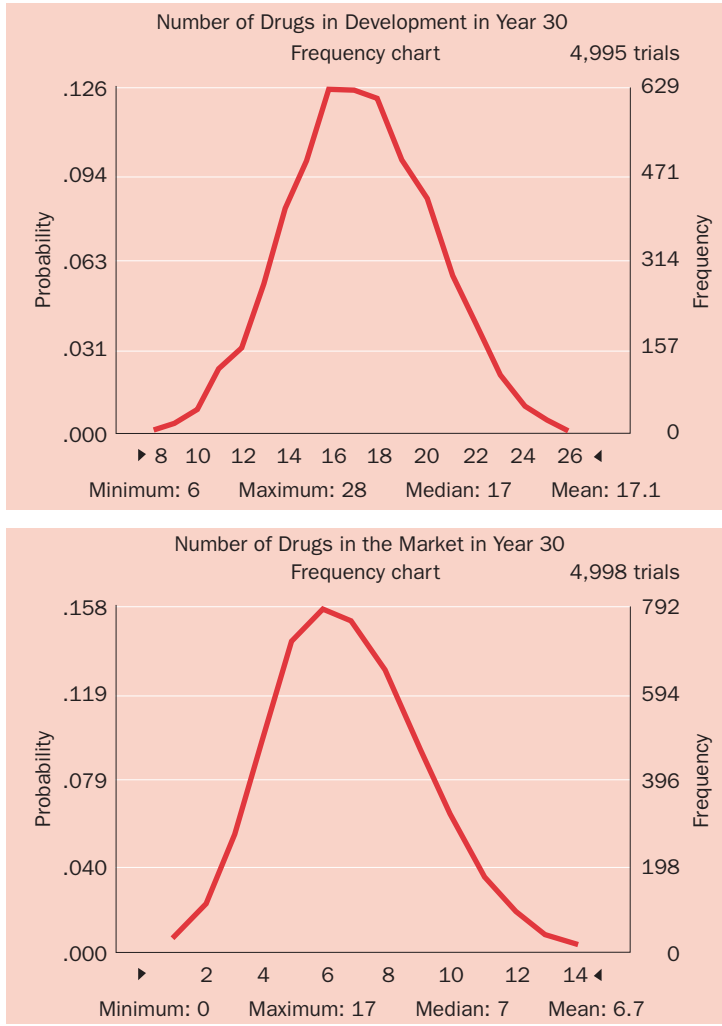
Note: FDA=US Food and Drug Administration

indications. There is also some random level of competition for the drug. Finally, a drug's sales are assumed to drop precipitously when its patent expires.[12]

Each iteration of the model tracks the life histories of a portfolio of drugs over 40 years. Thus, we are not modelling an individual drug but rather a portfolio of drugs invented over a period of time. So think of this as a pharmaceutical research programme or, probably better, a small pharmaceutical company modelled over its life cycle. Iterating the model a few thousand times generates distributions of outcomes that look like Figure 5.2. This is the distribution of the number of drug candidates in development, i.e. in the pipeline, at

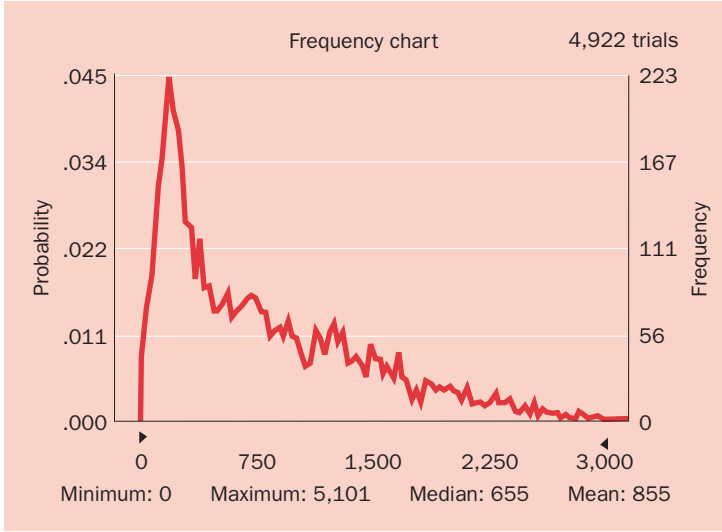
12 For a fuller explanation of the model see Myers and Howe (1997) 'A life cycle financial model of pharmaceutical R&D', Massachusetts Institute of Technology Program on the Pharmaceutical Industry.

Figure 5.2 **Results of Monte Carlo simulation**



year 30. On average our model has about 17 drugs in the pipeline; the 'good luck' scenarios produce outcomes in the high twenties, but some scenarios produce only six drugs. At the bottom of Figure 5.2

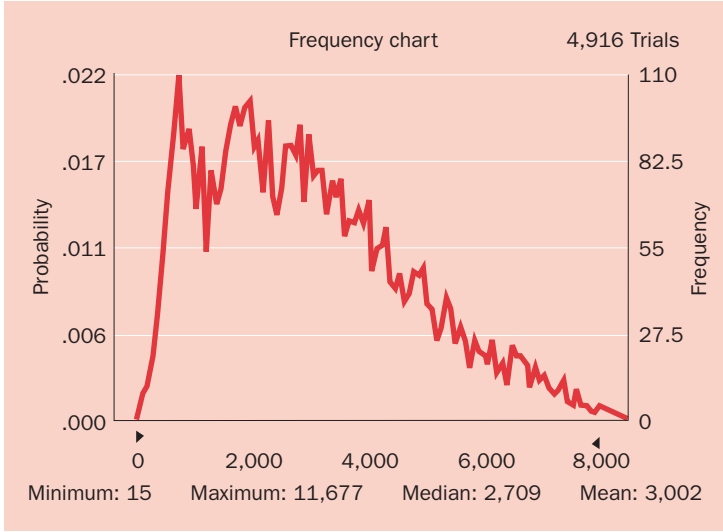
Figure 5.3 **Monte Carlo model: simulated revenue in year 30 ($million)**



you can see the number of drugs that come into the market: on average about seven but, in the worst cases, none at all. In other words, it is possible to run this process with realistic probabilities for 30 years and not have a drug that gets to the market. On the other hand, some scenarios produce as many as 10 or 15, up to a maximum of 17, reaching the market by year 30.

Figure 5.3 shows the distribution of modelled revenues at year 30, going from a minimum of essentially zero up to $3 billion. If you look at that distribution you can see why conventional discounted cash flow analysis based on the most likely outcome does not work in this business. The most likely outcome is far below the mean, because the distribution of revenues is so strongly skewed to the right. The degree of uncertainty is enormous. Note that this refers not to just one drug but to a portfolio of drugs. Think of a small pharmaceutical company that has operated for 30 years.

Figure 5.4 **Simulated market value (NPV) at year 30 ($million)**



We also use this model to calculate how much it costs to bring a new drug to US Food and Drug Administration (FDA) approval. In 1994 dollars we find that it costs about $300 million. That is after tax; before tax it is about $430 million. If you allocate corporate level costs – that is, not the direct costs of the research but some of the costs of running a whole business – back to the individual drugs, you get much higher numbers.

Figure 5.4 shows the market values (NPVs) of our simulated companies at year 30. Again you get an enormous variance in the simulated outcomes and strong right skewness. This chart asserts that I can calculate the true economic value of this business. But in order to do that I have to know the cost of capital. In order to calculate that, I must properly allow for the risk that investors are bearing. Estimating that risk-adjusted cost of capital is the main topic of my paper.

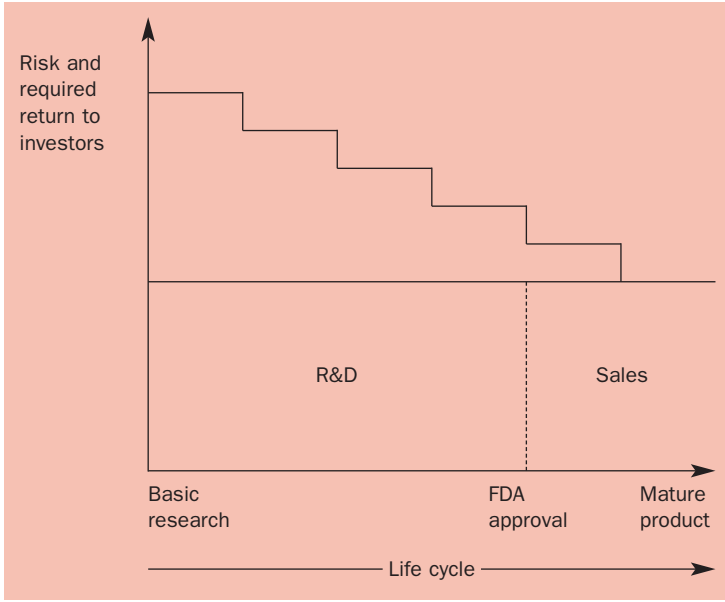
The background I have shown you so far demonstrates that I am not talking about this in the abstract, but with respect to a fairly detailed model that tracks and describes the pharmaceutical business. This

model does not track the business in the same detail as pharmaceutical company executives may do. The model is based on public information and therefore has to simplify; but I would argue that it captures the essence of the pharmaceutical business: high variance and strong right skewness, so that the most likely outcome understates the mean outcome.

How do we talk about the cost of capital in those circumstances? What does it mean? How do we adjust for these risks? Which of these risks matter to investors and which do not?

The cost of capital declines as you go through the R&D and production life cycle. By that I mean that investors want a high rate of return early in the life cycle and are willing to accept a lower rate of return later on. At this point I had better pause and give some definitions.

Figure 5.5 **The risk-return staircase for pharmaceutical products**



By 'the cost of capital' I mean the expected rate of return that you have to offer investors before they rationally put their money into your business. I assert that investors will require a much higher rate of return early on than they will later on. Everybody says 'Okay, that's obvious'. It is obvious in a way, but my guess is that the reason why is not the one you expect. Why do we intuitively think that R&D is riskier in its early stages? We talk about the risk of failure. Indeed if you are the manager or scientist who is on the line, responsible for working on some particular drug candidate, it is the risk of failure you are worried about. However, that is *not* the reason why the cost of capital changes through the life cycle of a drug.

Figure 5.5 provides a stylised illustration of my hypothesis. I have drawn it like a staircase with the steps going down to the right. It demonstrates that there is no single cost of capital for the whole pharmaceutical R&D and production process. Costs of capital estimated for established pharmaceutical companies must be interpreted instead as weighted averages across many drugs, including some very risky ones just emerging from basic research and some much safer ones already on the market.

Figure 5.6 **The cost of capital in the development cycle**

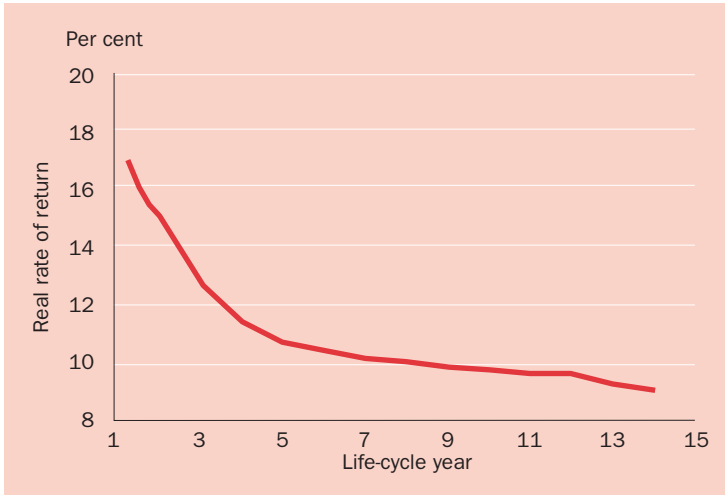


Figure 5.6 shows the actual life cycle costs of capital that result from the Monte Carlo simulation I described earlier. All of the input assumptions together imply that the cost of capital in real terms starts out at about 17 per cent and declines rapidly to a floor of nine per cent. This nine per cent real cost of capital would apply to a mature product: one that is in the market and past the initial heavy-duty marketing expense which often occurs at launch. The 17 per cent cost of capital would apply to a new drug candidate which has been clearly identified but is only just entering pre-clinical testing.

This decline in the cost of capital over the drug's life cycle has nothing to do with the failure rates of R&D. The reason is that those risks are diversifiable. As an investor, I own stocks in many US pharmaceutical companies, but I do not own them directly. I own them through mutual funds and through my MIT pension plan. Consequently, although I am a small investor, I am very well diversified. I own hundreds of different stocks in my portfolio. The failure risks we talk about for drugs – the risk that a drug will not work or that it fails some FDA test – are diversifiable and so constitute merely random noise from my point of view and from the point of view of any other well-diversified investor. I do not care about those risks when it comes to assessing the risk of my overall portfolio. Investors are not worried about diversifiable risk – random noise. The fact that most money is held in diversified portfolios, or can very cheaply be held in diversified portfolios, means that the insurance principle kicks in. You are not worried about uncorrelated risks, which is what these risks are.

If the staircase in Figure 5.5 has absolutely nothing to do with the risk of a drug failing, where then does it come from? It comes from what I call R&D leverage, or in British English 'R&D gearing'. The reason for the staircase is that the future costs of R&D are largely fixed, whereas the pay-offs to R&D are not.

Let me give you an example. Let us suppose we draw an R&D balance sheet. The asset is the present value of the revenues received if the drug gets to the market. The liability is the present value of the R&D costs you have to pay in order to get to the market. The difference

between those two – assets minus liabilities – is the value of the drug at that point. By the present value of net revenues I mean the present value of the profits from the sale of a product that is successful, i.e. reaches the market, multiplied by the probability that it actually will get to the market. Similarly, by R&D costs I mean the present value of the future R&D costs, multiplied by the probability that they will actually be incurred. For example, suppose there are three more stages before you get an approved drug. If the drug fails stage one, you will not have to pay for stages two and three.

These future R&D costs are mostly fixed. They are like debt service. It is as if you own this asset, the PV of net revenues, but have a mortgage loan against it. As you pay off the loan, the risk of your net position declines. In the pharmaceutical business, as a drug proceeds successfully stage by stage through the R&D cycle and so gets closer and closer to being a successful drug, the present value of the future costs declines because you are getting more and more of those costs behind you. At the same time, the present value of the net revenues increases because they are becoming closer and because you also have a higher probability of getting there. Therefore, the total value of the project itself increases. If you think of gearing as a debt to equity ratio, or a debt to asset ratio, then the gearing goes down as you progress through the R&D cycle. As the gearing goes down, the risk of your net position decreases, and so you get the descending staircase of cost of capital.

I have given you a theoretical argument, but what are its practical implications? What do we predict for an actual pharmaceutical company? Such a company is effectively a portfolio of ventures at different steps on the staircase. If I buy into Pfizer, for example, I have some projects or drugs that are just starting up and some that are mature and safe. When I buy Pfizer stock I am getting an average across the curve shown in Figure 5.6. When I observe the risk of Pfizer stock, I am observing the average risk of Pfizer's portfolio of drugs.

Suppose I look at a biotechnology stock. Biotechnology companies are effectively pure plays in R&D. I can therefore test the staircase by looking at the relative risks of biotechnology stocks as against mature

Figure 5.7 **Risk and weighted average cost of capital (WACC) for mature pharmaceutical companies**

	Beta	*WACC*	*WACC (real)*
1976-80[1]	.97	17.2%	9.9%
1981-85[1]	.66	16.1%	10.7%
1986-90[1]	.98	15.1%	10.2%
1990-94[2]	1.08	14.1%	10-11%

1 Myers and Shyam-Sunder, 1996

2 Myers and Howe, 1997

pharmaceutical stocks. Figure 5.7 shows some numbers on risk (beta) and the weighted average cost of capital (WACC) for mature pharmaceutical companies measured at four dates: 1980, 1985, 1990, 1994. The beta value, in the first column, is a measure of risk that financial analysts use. It depends on the correlation, or covariance, between the return on the specific stocks and the return on the overall stock market. Beta has absolutely nothing to do with the technical, scientific or medical risks of the pharmaceutical business because these risks are not correlated with market. Beta represents the risk that cannot be diversified by an investor holding a portfolio of investments in the stockmarket as a whole.

Figure 5.7 shows that the betas have been about one for these mature pharmaceutical companies, at least recently. They are average risk compared to the stockmarket as a whole. I have also calculated the implied weighted average cost of capital (WACC), which, if you take out inflation, is about 10 to 11 per cent. I did not know exactly what inflation rate to put in for 1994, but if you assume three to four per cent inflation in the US economy you come back again to a 10 or 11 per cent real WACC. Remember that this should be interpreted as the average across the staircase shown in Figures 5.5 and 5.6.

My hypothesis implies that biotechnology companies, which are pure R&D plays, ought to have systematically higher betas than the mature pharmaceutical companies. Let us see whether that is the case. The

Figure 5.8 **Betas for biotechnology and large pharmaceutical stocks calculated annually from weekly returns (Sample sizes in parentheses)**

Sample	*1992*	*1991*	*1990*	*1989*	*1988*	*1987*	*1986*	*1985*	*1984*	*1983*
1. Large pharmaceutical	1.12 (11)	1.04 (11)	1.19 (11)	1.02 (11)	1.33 (12)	.89 (13)	1.28 (13)	1.03 (13)	.89 (14)	.70 (14)
2. Biotech traded since 1986, CRSP/NASDQ, (39 companies)	1.50	1.51	1.11	.85	1.44	1.61	2.29			

first row of Figure 5.8 shows the betas estimated for large pharmaceutical companies, in this case year by year for 10 years in the 1980s and early 1990s. They fluctuate around one. The second row shows the betas for a sample of 39 biotechnology companies that have been traded on the stockmarket since 1986. With the exception of 1989, the betas are all far above one and, except for 1989 and 1990, are well above the betas for the mature pharmaceutical companies. I do not know the reason for the low beta for the biotechnology companies in 1989.

To give you another example: Recombinant Capital, which makes a business of keeping track of the US biotechnology industry, has classified biotechnology firms in three tiers. Tier one consists of the mature biotechnology companies which have at least one drug in the market. Tier two is firms with drug candidates that are close to or at advanced stages of clinical testing. Tier three is the firms which are only R&D and are not yet close to having a product. Estimating the betas of these three tiers in 1992 revealed that tier one biotechnology companies still have a higher beta at 1.38 than do the mature pharmaceutical companies (1.12 according to Figure 5.8), but that this tier one beta is significantly lower than in tiers two and three, whose betas are 2.39 and 2.17 respectively. The difference between the value of 1.38 and the numbers above two is highly statistically significant.

If you think of going from tier three to two to one as going down my staircase, it does indeed appear that the left-hand side of the staircase involves higher risk from the investor's point of view. Ideally, I should be able to distinguish between the beta values of tiers two and three, but I cannot do that. Nevertheless, on balance, this supports my explanation for why the cost of capital goes down as you go through the R&D cycle. I reiterate that this estimate of beta has nothing to do with the clinical, medical or scientific risks of the business. It depends instead on the correlation with macroeconomic risks as they are exhibited in the performance of the overall stockmarket.

I would summarise the evidence in this way: that the biotechnology companies have consistently higher risk to diversified investors; that the risk cannot be attributed to scientific or medical uncertainty; and further, we see that the mature biotechnology companies seem to have lower betas than the immature ones. I have also given you some estimates of the cost of capital at different stages of the biotechnology company's life; or of any pharmaceutical R&D programme's life. It probably starts out somewhere in the mid-teens as a product enters clinical testing; it goes down rapidly if and when the project succeeds, and it bottoms out for mature products at around nine per cent real. This is for US companies. I have not looked into estimates for UK companies but experience seems to show similar costs of capital in the UK and USA when you adjust for inflation.

Finally, I should like to add a brief note on how you might approximate the value of R&D. As described earlier, you start by drawing up an R&D balance sheet. On the left you put the present value of net revenues, weighted by the probabilities that you will get those revenues. On the right you put the present value of costs, weighted by the probabilities that you will have to pay them. Because the costs are a fixed obligation they deserve a lower discount rate than the less certain revenues. Again, it is just like buying a house and having a mortgage loan against it. If the mortgage loan is a very high fraction of the value of the house, the risk of your net worth in the house is high. As you pay off the mortgage loan, your net worth increases and the risk of your net worth goes down. That happens because the mortgage loan is a fixed obligation and the future value of the house is uncertain.

To apply this balance sheet approach, you have to have some idea of likely revenue, assuming that the project is going to succeed, and also some idea of the probability of success. In order to identify the liability, that is the present value of the costs to be incurred, you have to have some idea of what those costs are and of the probability of success at each stage. You are not committing today to pay all the future costs between now and approval of the drug; you pay only up to the point when you decide to stop.

To calculate the present value of a drug, you discount the revenues at a rate of discount appropriate for a mature drug, and discount the costs at a somewhat lower rate. Instead of making a single NPV calculation, therefore, you do two: first value the revenues and then the costs; just as if you were estimating the net worth of a house. First figure out what the house is worth; then figure out what the mortgage is worth and subtract it. A worked example of the estimation of the value of a drug is set out in the Appendix to this chapter.

Some US pharmaceutical companies have been experimenting with this balance sheet approach to valuing R&D. They report back that, although it is far from a perfect solution, it is much easier than the complex option pricing model they otherwise might try to use. In other words, the balance sheet approach is a useful approximation.

Why only an approximation? When I write down the present value of the revenues and the present value of the costs, I am fixing the discount rate for one and fixing the discount rate for the other. That works if the major uncertainty is scientific, medical or clinical. Precisely because this uncertainty is uncorrelated and diversifiable, I can set those discount rates without knowing anything about the odds of success, whether or not the drug will get FDA approval, or whatever it is that the scientists or managers involved worry about. However, for a complete solution, I also need to know about the economic risks of a new drug candidate, and my approximation does not fully or accurately pick up these economic risks. Such risks come about in the following way. Let us suppose a drug is in stage two clinical trials. As far as the trials go, the results are great, but at the same time there has been a downturn in the economy: real interest rates

have gone way up, competition is intense, and so the company cancels a scientifically successful drug for purely economic reasons. It is in such a case that my method falls down because it does not allow for those economic risks.

The ideal valuation approach would involve option pricing techniques, which I do not have the space to go into here. On the other hand, I am not proposing that you necessarily use those techniques. I am merely giving you a different way of thinking about ordinary present value calculations.

What are my conclusions? The main point is the idea of the risk-return staircase. Risk declines systematically through the R&D and production cycle. It is not true, therefore, that there is some weighted average cost of capital applicable at every stage of R&D investment. The reason why not is due to the gearing/leverage effect: R&D costs are like a fixed obligation whereas the revenues are less certain. While most of the cost obligation is still in front of you, the risk attached to the residual value of the drug is very high. As you go through the R&D process, however, you in effect pay off the mortgage and so the residual value of the drug becomes more certain.

That is the right way to think about the cost of capital in the pharmaceutical business. Furthermore, the way I have explained the estimation of net present value in terms of a balance sheet, can also be a relatively simple way of approximating present value calculations for the pharmaceutical business.

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Myers SC, Howe CD (1997) *A life cycle financial model of pharmaceutical R&D*, Massachusetts Institute of Technology Program on the Pharmaceutical Industry.

Myers SC, Shyam-Sunder L (1996) 'Cost of Capital Estimates for Investment in Pharmaceutical Research and Development', in Helms R (ed.) *Competitive strategies in the pharmaceutical industry*, American Enterprise Institute.

APPENDIX: Example of Estimating the Net Present Value and Cost of Capital of a Drug

In this example, the drug is assumed to have the following R&D to production cycle of costs, present value net revenues and probabilities:

Period	*0 (Discovery)*	*1*	*2*	*3 (Launch)*
R&D outlay ($m)	50 (Sunk)	100	100	–
Probability of failure	0.2	0.2	0.2	
PV of drug at launch ($m)				500

The overall probability of the drug being successfully launched is therefore:

$0.8 \times 0.8 \times 0.8 = 0.512$ or 51.2%

Revenues are discounted at 9% per annum and costs (which are more certain than revenues) at 6% per annum.

Present value calculations

PV_0

To calculate the NPV of the drug in period 0, just after discovery, and therefore ignoring the sunk cost of 50, set up a balance sheet with 'assets' on the left and 'liabilities' on the right:

$PV_0(\text{Net revenues})$ $= \frac{0.512(500)}{(1.09)^3}$ $= \$197.68$ million	$PV_0(\text{Future costs})$ $= \frac{0.8(100)}{1.06} + \frac{0.8(0.8(100))}{(1.06)^2}$ $= \$132.43$ million

Therefore the **overall NPV_0** $= 197.68 - 132.43 =$ **$65.25 million**

PV_1

To calculate the NPV of the drug in period 1:

PV_1(Net revenues)	PV_1(Future costs)
$= \frac{0.8(0.8(500))}{(1.09)^2}$	$= 100 + \frac{0.8(100)}{1.06}$
= \$269.34 million	= \$175.47 million

Therefore the **overall NPV_1** = 269.34 − 175.47 = **\$93.87 million**

PV_2

To calculate the NPV of the drug in period 2:

PV_2(Net revenues)	PV_2(Future costs)
$= \frac{0.8(500)}{1.09}$	= 100
= \$366.97 million	= \$100 million

Therefore the **overall NPV_2** = 366.97 − 100.00 = **\$266.97 million**

The cost of capital staircase

Each period's cost of capital (r*) is the expected rate of return that investors would demand for them to invest in the project's NPV *for one more period*.

Given that net revenues must earn an expected 9% and future costs are discounted at 6%, the cost of capital (r*) from period 0 to period 1 is calculated as:

$r^*NPV_0 = 0.09PV_0(\text{Net revenues}) - 0.06PV_0(\text{Future costs})$

$r^*(65.25) = 0.09(197.68) - 0.06(132.43)$

$r^* = 0.151$ or 15.1%

From period 1 to period 2:

$r^*NPV_1 = 0.09PV_1(\text{Net revenues}) - 0.06PV_1(\text{Future costs})$

$r^*(93.87) = 0.09(269.34) - 0.06(175.47)$

$r^* = 0.146$ or 14.6%

From period 2 to period 3:

$r^*NPV_2 = 0.09PV_2(\text{Net revenues}) - 0.06PV_2(\text{Future costs})$

$r^*(266.97) = 0.09(366.97) - 0.06(100)$

$r^* = 0.101$ or 10.1%

For all subsequent periods the cost of capital is, by definition, 9% in this example.

Thus the cost of capital declines in steps from an initial 15.1% to a floor of 9%.

Chapter 6
Measuring Pharmaceutical Risk and the Cost of Capital – Discussion

GEORGE YARROW

Stewart Myers has produced a stimulating and admirably clear paper on an issue that is of obvious relevance to current policy concerning pharmaceuticals pricing in the UK. In these comments I will not attempt to discuss the paper as a whole, but will focus instead on those aspects that bear most directly on price regulation in general and on the Pharmaceutical Price Regulation Scheme (PPRS) in particular.

In the work that Professor Myers has described, two major strands of financial analysis, both of which have very wide applicability, are brought together. The first of these is the capital asset pricing model (CAPM), which has long been used to assess costs of capital in regulated industries. The second, and perhaps less familiar, strand, which is covered in the later parts of the paper, is what can be called the options theory of investment (OTI). The OTI evaluates investment projects in terms of a series of option values rather than focusing on a discounted cash flow analysis of a limited number of projected income streams (e.g. a central forecast, buttressed by 'high' and 'low' variants).

Let me start by considering the CAPM. As those who are familiar with UK regulation will almost certainly know, the CAPM has something of the status of a folk religion in pricing reviews. Nobody really believes it, yet its disciplines are widely practised. It is a very tolerant framework in the sense that, depending partly upon which of the priests are consulted, it is capable of producing the answers that are desired. Make one set of assumptions and you come out with a highish cost of capital; make another set of assumptions and you come out with a lowish estimate.

A more attractive feature of the CAPM is that it has a number of intuitive aspects to it and the final answer can be built up from a small number of (relatively) easy to understand components. Nonetheless, the implications of the CAPM are not completely obvious. Take, for

example, the stress placed by the model on *non-diversifiable* or *systematic* risk. Once explained, the logic here is straightforward, but systematic risk is *not* what most people mean when, for example, talking of the risks of a particular investment project. Rather, reference to risk is more frequently made in a context where the concern is with the possibility of things going wrong, with the risks of failure.

I do not, however, think there is necessarily a large gap between these different perspectives on risk when looking at issues of price regulation. Estimating a company's cost of capital is not the bottom line issue in regulatory pricing reviews. It is one stage in the process of establishing allowable prices that stand in some sort of reasonable relationship with costs. Even when restricting the focus to capital costs, there is, in addition to the task of estimating the cost of capital, the problem of determining the value of the asset base to which it will be applied.

In his paper, Stewart Myers has started off from a perspective that is very close to this question of defining the relevant asset base or, as it is often called, the regulatory asset value (or RAV). The view that accounting rates of return produce severely biased measurements of economic rates of return translates easily into a view that asset values are being underestimated.

Let me give an example at this stage. A manager dealing with a large R&D project may, in everyday terms, be worried about the 'risk' of the project going wrong, of things not working out, even if the project is efficiently conducted. Similar, more general concerns also arise in a regulatory context. Capital expenditures may be incurred on a particular project or activity – which may be R&D, or a new pipeline, or simply the marketing of a new product – and, in the event, things go wrong: the project turns out to deliver much lower cash flows that anticipated. This then leads on to a concern that the regulatory process will not allow prices to be set at a level that compensates for the capital expenditures that have gone, not imprudently, into 'failed' projects.

This later point takes us toward the kind of argument that Stewart Myers has developed in relation to valuing R&D, where project 'fail-

ure' is commonplace. Consider, for example, the procedures of the PPRS. The capital values included in the asset base are dominated by those relating to tangible assets, such as manufacturing plant, company offices, and the physical infrastructure of research facilities. A capitalised value for R&D expenditures simply does not appear in those calculations, although, of course, certain provisions for R&D are included in allowable costs. This tends to make incremental investment more risky, in that there are additional things that could go wrong: not only may the projects fail in commercial terms, but even if they succeed there is a danger that the price setting process, based upon an allowable profit equal to the estimated cost of capital multiplied by the value of the asset base, will not remunerate them adequately.

Let me turn now briefly to the OTI. The valuation of R&D is a particular application of this approach, which is also being increasingly used in other contexts. Consider, for example, investment in a power station. In the context of the post-privatisation structure of the electricity industry in Britain, acquisition of a power station can be analysed as the purchase of an *option* to produce and sell electricity when the owner chooses. Thus, when the price of electricity is above the short-run marginal cost of generating and supplying electricity, the power station will usually be operated (the option will be exercised), but when price is below marginal cost, electricity generation will usually cease (the option will not be exercised). The value of the power station can therefore be derived from the value of the options that it provides.

Similar points apply immediately to R&D. Expenditure in the early stages of developing a new product will provide a company with an option to continue with the project tomorrow. If circumstances are favourable, the option will be exercised, but if circumstances are unfavourable (e.g. the research is unproductive), the option will not be exercised (i.e. the project will be abandoned). The value of the initial R&D can therefore be calculated from the value of the options to which it gives rise.

The key point of Stewart Myers' analysis, the 'cascade' or 'staircase'

effect, arises from a combination of this options process and systematic risk. It is assumed that the costs of R&D at each stage of the development process are fixed but that the ultimate returns from successful product launch are correlated with overall market risks. That is, the returns contain non-diversifiable risk.

In the early stages of product development, continuation with a project is, in effect, a highly geared investment. The investment cost is fixed and the expected return from continuation is relatively low because there is a high probability that the project will be abandoned at some point. At later stages, although further fixed investment will be required to continue the project, previous investment will be a bygone and the fact that the project has got so far implies that the expected return will be rather higher. That is, in relation to the decision whether to continue or not, the project's gearing falls, leading to a falling cost of capital.

Whether or not R&D costs are subject to systematic risk is, in the end, an empirical question. In the electricity example given above, for example, the short-run costs of generating power (exercising the option) depend upon fuel prices, which may well be subject to systematic risk. I do, however, think that the argument is plausible in the context of the pharmaceuticals industry and I think the evidence quoted by Stewart Myers is convincing.

This leads me to some final comments. In the evidence quoted, there is a split of companies between mature pharmaceutical companies and biotechnology companies. If, however, we focus on a particular company, it is possible that the portfolio of projects may be shifting either towards or away from the mature end of the spectrum, implying a falling or an increasing cost of capital respectively. Alternatively, if R&D costs are increasing in relative importance over time, there will be a gradual increase in the company's implicit gearing and hence in its cost of capital. More generally, the analysis here points to a positive relationship between R&D intensity and the cost of capital.

Such a link between R&D intensity and cost of capital is of direct relevance to the PPRS. There does appear to be some evidence that R&D intensities in pharmaceuticals are going up over time and, if so, an

implication of the analysis is that this should appropriately be recognised in the price setting process.

I also think that the idea of valuing companies in terms of shifting portfolios of projects is helpful in avoiding some of the less productive debates that tend to occur during pricing reviews. Empirically, the betas of companies, which measure their systematic risk, tend to vary over time, and choice of estimation period is one of the factors that tends to give rise to differences in estimates of the relevant cost of capital. An attraction of Stewart Myers' analysis is that, in the pharmaceuticals case, it offers an account of the factors that might be giving rise to those observed, empirical shifts in betas, which in turn offers the prospect of obtaining more robust estimates of the cost of capital. At the very least, this strikes me as an interesting area for further work.

Chapter 7

Racing to Invest – Patent Races in Pharmaceutical Research?

IAIN COCKBURN

This paper concerns the issue of racing behaviour in pharmaceutical companies' investment in R&D. Let me begin by telling a little story. Let us imagine a 1,500 metres race at the Olympic Games with two runners: the starter fires his gun and they take off and saunter around the track. Because it is the Olympic final, all that matters is to cross the line first. They do not have to run very quickly, until they reach almost the last lap. At that point, the two runners look at each other and one makes a strategic break which they think is at the right time. Both then run much, much faster, in an attempt to cross the line first. Most people have probably seen this type of sporting event quite a few times.

This has quite interesting implications for an industry such as pharmaceuticals. When you think about these athletic races you can imagine all sorts of things happening. Both the runners could start off by walking the first three laps of the 1,500 metres. That would be pretty good news for the people in charge of paying for the amount of effort expended. In pharmaceuticals that effort corresponds to the intensity of R&D expenditure. You could, however, also imagine another version of this race where both runners set off at the maximum speed of which they are capable and run round very quickly. That would correspond to a very costly, intensive level of investment in R&D.

The really interesting issue, however, is what goes on between these two extremes. Typically in such races there is strategic interaction: the runners watch each other; they keep something in reserve; the speed at which they run is a response to what the competition is doing. The economics of this type of problem, and particularly how it relates to pharmaceuticals, are very interesting.

I should now like to discuss some research I have undertaken with Rebecca Henderson at MIT, on analysing this issue in the context of pharmaceuticals. The core question we have tried to address in the research is whether this type of racing behaviour occurs in drug dis-

covery. Why might we think there is this type of behaviour? Most people who have studied economics at some point in their career were told to imagine two drug companies racing to be the first to patent a molecule. It is also the case that the pharmaceutical industry has often been subjected to criticism for producing 'me-too' drugs. For example, there are at least 12 orally active ACE-inhibitors, most of which do not seem to differ significantly from each other in terms of their therapeutic profiles. The topic *du jour* is protease inhibitors for HIV. There are three out in clinical use at the moment and goodness knows how many others in the pipeline. Critics of the industry point to this as evidence that there is some wasteful, duplicative 'me-too' research. Do we really need 12 orally active ACE-inhibitors? We probably do not.

Another piece of interesting evidence is the fact that many companies invest large sums of money in research programmes, which in the end just do not pan out, and realise zero or negative economic returns. One explanation for this observation might be that the companies are, in the race analogy used above, running too fast. Only one person can win the race but all the other people in the race will also have exhausted themselves, i.e. spent a lot of money on R&D, and that is wasteful.

If we think of the case of the ACE-inhibitors, in 1977 Squibb patented the compound which was then marketed as Captopril. Following that we had Enalapril, Lisinopril, Alacepril, Perindopril, Quinapril, 'Me-tooapril', 'Knock-offapril', etc. So, can we infer from cases like this that racing between pharmaceutical companies exists? Can we conclude from looking at episodes like this that it is a widespread problem and something people need to worry about when thinking about calculating returns to investment in R&D? Probably not, is the answer implied by the results of the work Rebecca Henderson and I have done on this.

There is a body of economic theory, which is mathematically elegant and very interesting, that looks at this problem of strategic interaction in R&D, i.e. how do I respond if we are engaged in this winner-takes-all type of competition and my competitor accelerates? A very strong conclusion which comes from this line of literature is that, for 'Prisoner's Dilemma' type reasons, if your competitor accelerates then

you have to as well. All that matters is to get across the line first and this instantaneous strategic response results in people wastefully over-investing in order to win these types of races.

In the extreme, these types of economic models predict that this over-investment in R&D will end up completely dissipating any returns to the activity. Although this is an extreme proposition, it nevertheless bears entertaining. It is particularly problematic if you consider regulatory regimes which try to reward companies on the basis of their R&D costs; or have tiered levels of stringency of price regulation, where somehow companies identified as producing products which are breakthroughs or winners will be allowed to charge higher prices (or increase their prices more quickly) than those who have been identified as producing 'me-too' follow-on types of compounds.

Despite the reams of economic textbooks which say 'imagine two pharmaceutical companies racing to get a patent….', people who are familiar with the industry and the nature of doing R&D find this a bit hard to swallow and feel that reacting to the competition is probably not the major motivating force. Armed with this knowledge and with a lot of quite detailed data, which Rebecca Henderson and I gathered on investment behaviour and investment outcomes in pharmaceutical R&D, we decided to test statistically for the presence of this racing phenomenon.

The existing research literature on this issue is rich. This means that, as usual in economics, if you ask a direct question such as 'what determines the level of a company's R&D investment?' the literature provides an enormous variety of responses.

In thinking both about testing the economic theory against the reality and trying to come up with some implications for policy, we tried to keep this study very simple. This theory ought to be able to explain the situation which might be called the Klondike model of investment. Imagine that somebody announces that gold has been found in the Yukon. What behaviour would you then expect to see? You would expect to see a couple of things, one of which is lots of people jumping onto ships and trains, heading for the Yukon. In pharmaceutical research you would expect to see that as a surge of concerted investment in a particular technology when there has been a shock to tech-

nological opportunity. Thus, if this racing analogy is appropriate you would expect to see lots of investment when, for example, a university uncovers a new enzyme pathway or identifies a set of receptors, or something like that.

The second feature you would expect to see is that, when everybody gets to the Klondike and starts digging, the probability of uncovering a nugget starts to go down. In the language of economics, there is an 'exhaustion externality'. The more nuggets that my competitors have found, the fewer are left for me.

If pharmaceutical R&D is characterised by this behaviour, so that the crude Klondike characterisation of strategic interaction is correct, we ought to see these effects in the data. We ought to see concerted effort, i.e. correlation in investment across companies working in the same area. When your competitor starts running faster, you start running faster too. We ought also to see the exhaustion feature: that the more successful your competitors are at exploiting the angiotension conversion enzyme system the less successful you ought to be in your follow-on attempts to do this.

To understand the research strategy of our study, it is worth taking a moment to describe the data we used. This is one of a series of studies by Rebecca Henderson and myself which uses the same data. Ten companies participated in this study and provided us with extremely detailed confidential internal data on their investments, expenditure on R&D and outcomes over 20 years. Unfortunately, I may not tell you which these companies are but I can say that they cover five US and five European manufacturers which together provide about 25 per cent of world-wide pharmaceutical R&D and a similar percentage of world-wide sales. We tried to span a spectrum of large, small, successful and unsuccessful firms, but you might still want to remain cautious about the representativeness of this sample.

We measured investment in R&D simply by R&D expenditures at the level of narrowly defined research programmes, for example ACE-inhibitors, or SSRIs for treatment of depression. We put a lot of effort into making this data comparable across companies, to deal with and net out consistently things like corporate overheads. We used the

resultant figure for R&D expenditure on a research programme as our measure of investment.

We used patents as a measure of output. This is a problem. After all, the pharmaceutical industry is in the business of producing drugs, not patents. Also there are all kinds of noise in the data, generated by the patenting process. We attempted to overcome this by, for example, only counting patents which were filed in two out of the three major jurisdictions: the USA, Europe and Japan. We are, therefore, focused at the very top level of the R&D process: purely looking at discovery. Nothing I have to say here is about development, where there might be quite different investment dynamics and strategic interaction.

To go back to the Klondike analogy, we first looked to see whether or not, when somebody announces the discovery of gold in the Yukon, lots of people do get on trains and head for Canada. Does investment correlate across firms? Using a very simple reduced-form regression approach, we asked 'does my investment correlate with my competitors' investment?' In our analysis we included other factors which we thought might drive investment in R&D, such as demand conditions and, in particular, shocks to the technology. We tried a variety of strategies to identify somebody who was effectively firing the starter's gun in the race. Perhaps the most successful of these approaches was tracking down the 100 most cited papers in life sciences every year, to see what they were about, and treating the publication of a paper which turns out to be highly cited as being a technological event which would wake people up in the industry and start them investing.

When we ran these regressions we found that almost the sole determinant of a company's level of investment is how much it was spending last year. Spending is highly auto-correlated and very stable over time. After all, pharmaceutical companies do not start up and shut down programmes very often. Funding for research programmes is typically fairly smooth over time horizons of three to five years. Thus if you want to predict a company's research investment this year, all you need to know is how much it was spending last year. Other factors such as what the company's competitors were doing, what was happening in downstream demand, and so forth, turn out to be not

very important statistically.

We found that a company's sales in the relevant class of drugs also had a significant effect on research investment, but a small one. There was no correlation at all with the level of competitors' investment. Thus there was no evidence for simple, strategic interaction of the type: the more you spend the more I spend, because we are both in this race to get to the finish line first.

The second thing we did was to look for the 'exhaustion effect'. If firms are engaged in wasteful, duplicative research, you would expect at the very least to see that competitors' success should undermine your own success. We examined this by estimating a statistical model of research productivity, measured as important patents per research dollar. We constructed a fairly detailed model and controlled for many factors we thought were important: the presence of economies of scale or economies of scope in doing R&D; the product mix in a particular company's portfolio; a measure of how successful the firm had been in the past. Using a variety of possible explanatory variables like these, we tried to build up the best predictive model of pharmaceutical R&D productivity we could. Then we added in those variables which we hoped would describe the phenomenon of spill-overs (or cross-fertilisation).

We looked at spill-overs in a variety of dimensions, both internal to a company and between companies in the industry. A company's programme on heart disease looking at prostaglandin metabolism and its role in treating cardiology might come up with something which is really interesting to people elsewhere in the firm who are working on arthritis, or something else which involves inflammation. Success in prostaglandin research directed at cardiology might therefore turn out to give the company a boost elsewhere, such as in arthritis. In analysing this, we found evidence for statistically quite significant effects from such within-company spill-overs from one research programme to another. Moving from one of the least diversified companies to one running twice the number of programmes was found to increase productivity (important patents per research dollar spent) by 20 per cent.

More interestingly, from the perspective of the racing strategic inter-

action, we looked for evidence of the effect of rivals' research successes on own research success. We found a very strong statistical result: that the more successful my competitors are in a narrowly defined therapeutic class, the more patents per R&D dollar I get too, even after controlling for a large number of variables which might be thought to lead to spurious joint causation, in particular technology shocks. A company whose competitors are 10 per cent more productive than average will be roughly two per cent more productive than average itself.

That is the nitty-gritty of the research study. Let me sum up by saying a little about what we learned about the presence of racing behaviour, and why we might care, and also by making some cautionary remarks about why you might want to be sceptical about our results.

If you characterise racing behaviour by the crude Klondike model, then we do not think there is much statistical support for it, at least in our sample of 10 companies and looking at 20 years of investment. In aggregate, firms do not appear to race with each other. Investment levels are driven almost overwhelmingly by historical experience, both in terms of prior investment and in terms of a firm's historical market success in the area. Pharmaceutical R&D has numerous prizes rather than one single winner-takes-all prize.

On the flip side, we find strong evidence for the presence of spillovers. In the language of economics: for the racing situation to apply so that people would be justified in being worried about the existence of dissipative, over-intense competition, competing research projects have to be substitutes. On the contrary, however, we seem to find that, if anything, competing research projects are complements. Thus the arrival of another company pursuing a similar research project is not necessarily wasteful, and may even be socially beneficial. There are, however, a variety of reasons for being careful about this.

Firstly, my characterisation of this body of theoretical literature is indeed very crude and there are all sorts of models of strategic interaction which generate results that could be consistent with some of the things we see. For example, to return to the story of the foot race, if instead of starting both competitors off at the same starting line we

let the first runner start off 20 metres ahead, and if the two competitors are relatively evenly matched, we know what is going to happen. Provided the one in the lead looks over his shoulder, the person behind will never catch up. As soon as he starts running, the person in front will start running. A rational response to this situation for the competitor who must start 20 metres behind is to give up. Indeed, there are theoretical models which predict precisely this kind of behaviour. If somebody gets too much of a head start then others will not try to play this chasing-each-other-across-the-finish line game, but just give up. That might explain the fact that we see the very weakest type of correlation in investment levels across firms.

A second reason for caution about our results is that we only looked at 10 firms. Gathering this data was a very difficult, costly and lengthy process. We would have liked to have looked at more but, in order to make sensible statements, you have to look at the level of very narrowly defined therapeutic classes and gathering this data is extremely difficult.

There are a number of other issues too. When you stop and think about the so-called problem of 'me-too' drugs in actual therapeutic practice, it might be that we do need lots of different ACE-inhibitors; and we might need lots of SSRIs for depression. The reason for this possibility is that there are variations in patient response and in side effect profiles. There are many areas of drug therapy where there is both titration in doses and titration across molecules. The physician and the patient experiment to find out which drug works best for them. In order to make strong statements about duplicative over-investment you have first to take this into account and that is extremely difficult.

In terms of policy prescriptions, the lesson I have learned from the study is that thinking about rates of return for R&D in terms of dollars per drug can be pretty misleading. It is very easy to come up with the wrong answer. In particular, if there is racing behaviour going on, then the dollars per drug figure will be too high. If you were looking for the true rate of return to pharmaceutical R&D, you would therefore need to net out that which is simply strategic interaction and does not represent the return to R&D in a production function sense.

Conversely, if, as our results suggest, racing does not happen and there

is the spill-over phenomenon described above, then you will come up with an underestimate of the amount of resources needed to generate a new drug candidate – because you need to take into account the inputs from other projects inside your firm; from the research projects of all of your competitors; from universities upstream; and from feedback from physicians. There are all sorts of research outputs from elsewhere which will go into your research process, and you will probably need to take some account of those when you arrive at the estimate of the cost of a new drug.

A world characterised by spill-overs also has some interesting implications for the presence of large diversified companies engaging in apparently duplicative research. One view is that this is not actually a wasteful duplicative type of activity but rather that it is resources being invested, which are generating a return. It might not be a private return to the company investing, but it might generate a significant social return. Statements about what has been the rate of return to R&D and whether there is over-investment or under-investment in R&D, ultimately hinge on the problem of defining social returns – whether narrowly defined in terms of the world-wide industry as a whole, where the output is greater than the sum of the parts because of this spill-over and cross-fertilisation, or more broadly defined as the total benefits to producers plus the total benefits to consumers. The presence of the wider variety of drugs, whilst it may be driving down the profits of individual companies, is giving consumers of the end product a much greater choice and variety. It allows an experimentation process which ends up better matching patients to therapies.

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Chapter 8
The Changing Nature of NCE Pricing of Second and Subsequent Entrants

ADRIAN TOWSE and TREVOR LEIGHTON

This paper addresses the issue of whether there is increasing price competition in the UK pharmaceuticals market and, if there is, the likely reasons why.

To answer this we draw on our work analysing trends in pricing, timing, and the numbers of second and subsequent entrants into the UK market place over a more than 30 year period.[13] The analysis is based on a sample of 19 'modes of action' listed in Figure 8.1 below. There were 100 new products launched in these 19 categories during the study period, of which 19 were the first entrant and 81 were followers. A full list with launch dates and prices is set out in the Appendix to this chapter. Our analysis focuses on the pricing behaviour of the followers relative to the price of the initial entrant. The sub-categories analysed in this exercise are narrowly defined to ensure that only directly competing products are included in each one. The third mode of action on the list, for example, is the introduction of non-selective beta-blockers. Cardio-selective beta-blockers appear further down the list as a separate mode of action.

The 19 categories and 100 products were selected by focusing on oral solid therapies with single active ingredients, a launch date after 1960, and multiple entries within the mode of action. Pack prices were translated into the cost per day of therapy using modal doses. This allowed a relative price index to be constructed of the cost per day of therapy of the follow-up compound as compared with that of the market leader at the time of introduction of the follower compound. The results are summarised in Figure 8.2. Full details are included in the Appendix. There is a steady reduction in followers' relative prices over the period, starting from the late 1960s. The

13 We have updated the results presented at the 1996 conference to take into account more recent product launches. The structure of the paper is in other respects as presented.

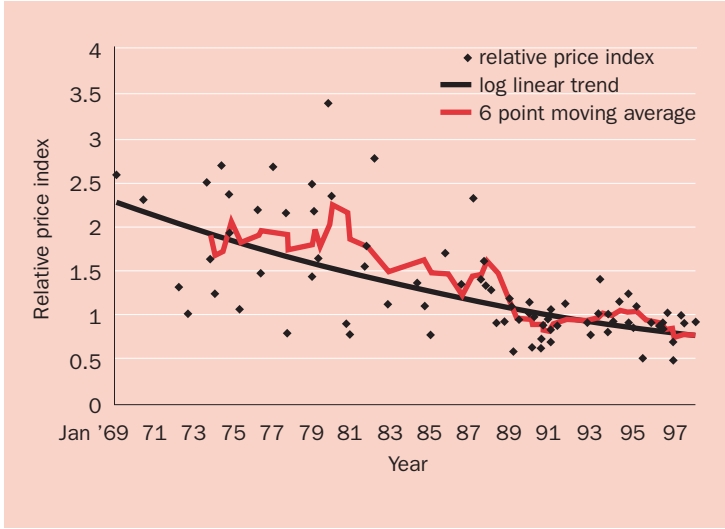
Figure 8.1 **Modes of action included in the study**

Launch year of first entrant	*Mode of action*	*New chemical entities*
1961	Broad spectrum penicillins	5
1965	NSAIDs	18
1965	Non-selective beta-blockers	6
1967	Calcium ion antagonists	7 (angina)
1969	Cephalosporins	8
1975	Cardioselective beta-blockers	5
1976	H2 antagonists	4
1981	ACE inhibitors	9
1981	Nucleoside analogues	3
1987	Quinolones	3 (UTI)
1987	5HT reuptake inhibitors	7
1988	Triazole systematic antifungals	2
1989	Proton pump inhibitors	3
1989	Statins	5
1990	5HT3 antagonists	3
1992	5HT1 agonists	3
1995	A2 antagonists	4
1995	Continuous combined oestrogen and progestogen	3
1997	Acetylcholinesterase inhibitors	2
	TOTAL	100

graph starts at 1969 because although the first product entrant was in the early 1960s, the first follower did not arrive until the end of the 1960s. This first follower came in at two and a half times the price of the market leader; whereas in the 1990s the new entrants were coming in, on average, at a discount to the market leader.

To gain further insight, three sub-periods corresponding to the 1970s, 1980s and 1990s were identified. In each of these, all follower products were grouped as to whether they were priced more than two and a half times, more than twice, more than one and a half

Figure 8.2 **Trends in relative prices of follower products 1969-1998**



times, up to one and half times or at parity or below the price of the market leader. The results are set out in Figure 8.3. In the first period, 1969 to 1979, 14 of 21 follower entrants (66 per cent) were priced at more than one and a half times the market leader's price, (columns (1) – (3)) whereas during the third period (1990 to 1998) none were priced so highly relative to the market leader. During 1969 to 1979, only two of the 21 follower entrants (10 per cent) were priced at parity or below (column (5)). By the period 1990 to 1998, 26 of the 37 follower entrants (70 per cent) were priced at or below parity to the market leader[14]. The results show differences in performance between the decades that are significant at a 1 per cent level with a χ^2 value of 42. This analysis demonstrates that there have

14 No second or third entrant in our data set introduced in the 1990s was priced above the market leader. The 11 products introduced in the 1990s priced above parity were later entrants. Of these, three had prices less than 5 per cent above the market leader.

Figure 8.3 **Trends in follower pricing**

Period covered	*Number of follower entrants*	*Priced above 2.5 × market leader (1)*	*Priced between 2.0-2.5 × market leader (2)*	*Priced between 1.5-2.0 × market leader (3)*	*Priced between 1.0-1.5 × market leader (4)*	*Priced at parity or below market leader (5)*
1969-79	21	4	7	3	5	2
1980-89	23	1	2	5	9	6
1990-98	37	0	0	0	11	26
Total	81	5	9	8	25	34

been quite dramatic changes in the behaviour of follower entrant pricing over the 30-year period analysed.

The data were also analysed with respect to the average time to follower entry (Figure 8.4). The average time from the initial entrant to the first follower entry and the average time after that to the second follower entry were determined. Two numbers appear for the 1980 to 1984 period due to the distorting impact of one outlier, Zovirax, where second entry did not occur for 12.3 years. The lower number excludes Zovirax. Although Figure 8.4 does not suggest a strong downward trend in average time to first follower entrant over the 30 year period, in practice the regression is strong, with a co-efficient of 0.41 which is significant at the 1 per cent level. As Figure 8.4 would suggest, the downward trend in average time from second to third entrant has an even stronger regression co-efficient (0.55) which is also significant at the 1 per cent level. The full data set is included in the Appendix. In summary, the time to entry of both second and third products into a new mode of action has been falling over the 30 year period, such that in the 1990s breakthrough innovations in our sample (i.e. those which create new modes of action) have had on average only two years before facing a second entrant and only another year before a third product enters.

We attempted to look at the trends in the total numbers of follower

Figure 8.4 **Trends in time to follower entry**

Average time (years) for:	*First to second entry*	*Second to third entry*
1960s	6.5	4.6
1970s	2.5	5.3
1980s	2.6/4.0*	3.7†
1990s	2.0	1.2†

*The nucleoside analogue, Zovirax (aciclovir), is an outlier with 12.3 years to second entry. If included, the average is 4.0 years.

†One product with a second entrant in each of these decades has had no third entrant to date.

entrants within modes of action over the 30 year period. However there are two difficulties. One is the necessity of adjusting for the numbers of active classes. In other words, at some point old therapeutic classes of products become therapeutically redundant and nobody introduces any further new products. The second is the time period for which we have data. For the new modes of action introduced in the 1990s we have only a few years of data. All of the new modes appearing in the 1990s have had a second entrant and all but one a third entrant. However it is not possible to make comparisons of overall 'class' numbers over, say, a 10 year period with those introduced in earlier decades. As it is likely that the second and third entrants will have a much greater impact on the market than subsequent entry, (although this will of course depend on the clinical profiles of the entrants) we have not looked at other ways of pursuing this analysis.

To make sense of the price and speed of entry data we need to consider the impact of both demand and supply factors. Taking demand first, we might expect prescribers to be more interested in prices if they were subject to budget constraints. Such constraints may take the form of prescribers having their own budgets or their being tied to an overall NHS pharmaceutical budget that if not met would result in some penalty such as constraints on clinical freedom. An improvement in the information that prescribers have on the price and quality of products might also change their price sensitivity. There may

also be a 'hassle factor' of pressure from peers, health authorities, or whomever, if they do not take price into account. This is also likely to increase the price sensitivity of prescribers.

It is easy to see all of these things happening since the NHS internal market reforms of 1990, which included the introduction of fund-holding for some GPs and target prescribing budgets for non-fund-holders. It is harder to see why demand price sensitivity would have changed over the preceding two decades. Trends influencing price sensitivity of GPs' demand over this period may have included: improvements in the quality of clinical information, more rigorous pharmaceutical industry promotional standards, and improvements in the professional training of GPs. One might therefore conclude that not only has there been a transformation of the cost pressures on, and the price sensitivity of, prescribers since 1990, but there has also probably been a general trend over a longer period in terms of the quality of information GPs have received on the costs and benefits of medicines and their willingness and ability to use it in making comparisons between products.

On the supply side, there is little evidence of a significant shift in the supply curve over time, although there are indications that the increased scientific understanding provided by the biotechnology and genomics revolutions and the impact of changes in discovery technology, notably the use of combinatorial chemistry, will increase the flow of products in the future. What is more likely to have occurred over the last decade is that cost containment pressures from health care payers around the world have forced companies to cut costs and to improve their research and development 'time to market'. In the UK, our analysis suggests that the demand side changes in GP behaviour mean that the NHS has been successful in translating cost containment pressures into price competition from new entrants in established modes of action.

We looked at the consistency of our findings with those of Reekie's study of six countries, (Reekie, 1996) which looked at 80 therapeutic sub-markets for the seven-year period, 1989 to 1995. Reekie's analysis took the average price of the top five products – although the pack sizes may be quite different – as the incumbent price. The study

looked at innovation in a broad sense: including all new products coming into the market. This definition extended to branded generics, but not to unbranded generics. Reekie compared the price of the new entrant, or 'innovator', for whatever pack size the innovator was selling most of, with the average price of the top five packs. Figure 8.5 is taken from his results for the UK market.

For each year from 1989 to 1995, Reekie counted the number of sub-markets which had innovations. The numbers of those sub-markets are listed in column A. Column B shows the proportion of those sub-markets where innovations were on average launched at a discount. This shows, that in sub-markets where innovations were introduced, they were introduced at a discount on around two thirds of occasions. Column C sets out the percentage of sub-markets with innovations where the average discount of the new products exceeded 25 per cent. In approximately half of the sub-markets over the seven year period where there was at least one innovation the average price discount exceeded 25 per cent. In the case of 1995, the number of sub-markets experiencing new entry was relatively low, but all such discounted entry as did occur was at a price discount of more than 25 per cent to the market leader.

Figure 8.5 **Impact of innovations on price reductions**

Year	*A* *Sub-markets with innovations*	*B* *% of sub-markets where innovations were launched at a discount*	*C* *% of sub-markets where discount exceeded 25%*
1989	33	70	42
1990	30	60	47
1991	35	60	43
1992	29	66	55
1993	36	58	39
1994	24	54	46
1995	11	73	73

Source: Reekie, 1996. Taken from Table 3E, p58

Although the Reekie study uses different definitions of innovation, of the sub-market, and of the market leader price, its results are consistent with the behaviour of our sample in the 1990s, i.e. new product entry being associated with price discounting against the market leader.

Summary

We have presented data covering 19 novel 'modes of action' with 100 product entries over a 30 year plus period. Our analysis provides evidence that speed of entry of second and third entrants into new modes of action has increased over the period and that the relative price of new entrants to the price of the market leader has declined over the period, such that most new entrants now price at or below the market leader.

Both our study and the Reekie (1996) study are consistent with the view that there has been a qualitative transformation of the NHS market place since 1990. Changes in demand are likely to be the most important factors driving this as there have been qualitative changes in the pressures to which prescribers have been subject since 1990. There are caveats, however, where we plan to undertake further analysis.

Firstly, this does not mean that GPs all switched to using lower-priced products. It simply means that lower-priced products were available, although it is unlikely that companies would continue to introduce new products at a discount if this was not a successful way of gaining market share. This is particularly important for companies, as the UK regulatory environment in most cases only gives them pricing freedom at the point of launch. The second caveat is that there have been some examples of market leaders cutting prices in response to new entry. To that extent, therefore, the study is underestimating the overall impact on pricing of followers coming in with lower prices. The final caveat is a reminder that we are not looking at trends in the prices of the first entrants in a novel mode of action. These will, we expect, be constrained by the prices of the modes of action they seek to displace.

With these three important caveats in mind, it seems to us that the evidence demonstrates that the UK market is much more price com-

petitive than it was. As price competition is driven by new entry, the greater speed of second and third entry that is occurring in the 1990s is adding to competitive pressure. The logical explanation for the changes would appear to be primarily on the demand side: prescribers have become more price sensitive. If that is the case, it is likely that the market place will become even more price competitive in the future.

REFERENCE

Reekie WE (1996) *Medicine prices and innovations. An international survey.* IEA Health and Welfare Unit, London.

Appendix **Details of product database**

Category	*Brand name*	*Drug name*	*Launch date*	*Dosage used*	*Days treatment per pack*	*Cost (launch price £)*	*Cost per day (launch price £)*	*Launch order*	*Market leader*	*Market leader price*	*Ratio to market leader*	*Years to sub-sequent entrant*
Broad-spectrum penicillins	PENBRITIN	ampicillin	Nov-61	250mg qds	25	13.80	0.55	1	1	–	–	10.4
Broad-spectrum penicillins	AMOXIL	amoxycillin	Apr-72	250mg tds	33	5.30	0.16	2	1	0.12	1.30	8.5
Broad-spectrum penicillins	PONDOCILLIN	pivampicillin	Oct-80	500mg bd	50	20.53	0.41	3	2	0.46	0.89	0.2
Broad-spectrum penicillins	AMBAXIN	bacampicillin	Dec-80	400mg bd	50	17.92	0.36	4	2	0.46	0.78	0.8
Broad-spectrum penicillins	AUGMENTIN	amoxycillin/ clavulanic acid	Sep-81	375mg tds	33	25.00	0.76	5	2	0.49	1.53	–
NSAIDS	INDOCID	indometacin	Jan-65	75mg	167	10.25	0.06	1	1	–	–	4.1
NSAIDS	BRUFEN	ibuprofen	Feb-69	400mg tds	83	12.00	0.14	2	1	0.06	2.56	4.6
NSAIDS	NAPROSYN	naproxen	Sep-73	250mg bd	125	17.50	0.14	3	1	0.06	2.48	0.2
NSAIDS	ORUDIS	ketoprofen	Nov-73	50mg bd	250	22.80	0.09	4	1	0.06	1.62	0.3
NSAIDS	FENOPRON	fenoprofen	Feb-74	300mg tds	33	2.75	0.08	5	1	0.07	1.23	2.2
NSAIDS	RHEUMOX	azapropazone	Apr-76	1/2g	25	5.88	0.24	6	2	0.11	2.17	0.8
NSAIDS	CLINORIL	sulindac	Jan-77	200mg bd	50	19.40	0.39	7	2	0.15	2.65	0.7
NSAIDS	FROBEN	flurbiprofen	Sep-77	100mg bd	50	15.65	0.31	8	2	0.15	2.14	1.3
NSAIDS	VOLTAROL	diclofenac	Jan-79	100mg	25	9.00	0.36	9	2	0.15	2.46	0.3
NSAIDS	TOLECTIN	tolmetin	May-79	200mg tds	33	7.88	0.24	10	2	0.15	1.63	0.5
NSAIDS	LEDERFEN	fenbufen	Nov-79	300mg tds	33	16.24	0.49	11	2	0.15	3.36	0.2
NSAIDS	FELDENE	piroxicam	Jan-80	20mg od	28	9.24	0.33	12	2	0.14	2.32	2.2
NSAIDS	SURGAM	tiaprofenic acid	Mar-82	200mg tds	33	15.76	0.48	13	2	0.17	2.75	3.6

Notes: od 'once daily'; bd 'twice daily'; tds 'three times daily'; qds 'four times daily'.

Appendix **Details of product database (*continued*)**

Category	*Brand name*	*Drug name*	*Launch date*	*Dosage used*	*Days treatment per pack*	*Cost (launch price £)*	*Cost per day (launch price £)*	*Launch order*	*Market leader*	*Market leader price*	*Ratio to market leader*	*Years to sub-sequent entrant*
NSAIDS	LODINE	etodolic acid	Oct-85	200mg bd	30	16.80	0.56	14	12	0.33	1.70	1.4
NSAIDS	RELIFEX	nabumetone	Mar-87	1g od	28	15.68	0.56	15	3	0.24	2.31	1.6
NSAIDS	MOBIFLEX	tenoxicam	Oct-88	20mg od	28	16.52	0.59	16	3	0.64	0.93	2.3
NSAIDS	EMFLEX	acemetacin	Feb-91	60mg bd	45	22.50	0.50	17	9	0.71	0.71	5.6
NSAIDS	MOBIC	meloxicam	Sep-96	7.5mg od	30	10.00	0.33	18	11	0.38	0.89	–
Non-selective beta-blockers	INDERAL	propranolol	Aug-65	80mg bd	250	4.17	0.02	1	1	–	–	4.9
Non-selective beta-blockers	TRASICOR	oxprenolol	Jul-70	80mg bd	50	5.20	0.10	2	1	0.05	2.28	3.9
Non-selective beta-blockers	BLOCADREN	timolol	Jun-74	30mg od	33	4.00	0.12	3	1	0.05	2.66	0.3
Non-selective beta-blockers	VISKEN	pindolol	Oct-74	15mg od	33	4.58	0.14	4	1	0.06	2.35	0.1
Non-selective beta-blockers	SOTACOR	sotalol	Nov-74	160mg od	100	8.70	0.09	5	1	0.05	1.91	4.2
Non-selective beta-blockers	CORGARD	nadolol	Jan-79	160mg od	28	4.20	0.15	6	1	0.11	1.42	–
Calcium ion anatagonist	CORDILOX	verapamil	Jun-67	120mg tds	33	9.72	0.29	1	1	–	–	10.3
Calcium ion anatagonist	ADALAT	nifedipine	Oct-77	10mg tds	33	10.29	0.31	2	1	0.39	0.80	6.6
Calcium ion anatagonist	TILDIEM	diltiazem	May-84	60mg tds	33	16.67	0.51	3	2	0.37	1.35	2.3
Calcium ion anatagonist	CARDENE	nicardipine	Aug-86	30mg tds	33	16.33	0.49	4	2	0.37	1.34	2.5
Calcium ion anatagonist	PRESCAL	isradipine	Feb-89	2.5mg bd	28	11.39	0.41	5	2	0.37	1.10	0.9
Calcium ion anatagonist	ISTIN	amlodipine	Jan-90	5mg od	28	11.85	0.42	6	2	0.37	1.15	3.6
Calcium ion anatagonist	MOTENS	lacidipine	Aug-93	4mg od	28	14.50	0.52	7	2	0.37	1.40	–
Cephalosporin	CEPOREX	cefalexin	Dec-69	500mg bd	50	35.50	0.71	1	1	–	–	2.8
Cephalosporin	VELOSEF	cefradine	Oct-72	500mg bd	50	26.56	0.53	2	1	0.53	1.00	6.3

Notes: od 'once daily'; bd 'twice daily'; tds 'three times daily'; qds 'four times daily'.

Appendix **Details of product database (*continued*)**

Category	*Brand name*	*Drug name*	*Launch date*	*Dosage used*	*Days treatment per pack*	*Cost (launch price £)*	*Cost per day (launch price £)*	*Launch order*	*Market leader*	*Market leader price*	*Ratio to market leader*	*Years to sub-sequent entrant*
Cephalosporin	DISTACLOR	cefaclor	Feb-79	250mg qds	25	23.27	0.93	3	1	0.43	2.15	3.8
Cephalosporin	BAXAN	cefadroxil	Nov-82	500mg bd	50	30.15	0.60	4	1	0.54	1.12	5.0
Cephalosporin	ZINNAT	cefuroxime axetil	Nov-87	250mg bd	25	45.00	1.80	5	3	1.36	1.32	2.8
Cephalosporin	SUPRAX	cefixime	Sep-90	200mg od	50	64.00	1.28	6	3	1.74	0.74	2.3
Cephalosporin	ORELOX	cefpodoxime	Dec-92	200mg bd	5	9.50	1.90	7	3	2.06	0.92	1.7
Cephalosporin	CEDAX	ceftibuten	Aug-94	400mg od	7	17.50	2.50	8	3	2.17	1.15	–
Cardioselective beta-blockers	SECTRAL	acebutolol	Apr-75	400mg od	125	16.50	0.13	1	1	–	–	0.1
Cardioselective beta-blockers	BETALOC	metoprolol	May-75	100mg bd	25	3.50	0.14	2	1	0.13	1.06	1.1
Cardioselective beta-blockers	TENORMIN	atenolol	Jun-76	100mg od	28	5.71	0.20	3	3	0.14	1.46	8.3
Cardioselective beta-blockers	KERLONE	betaxolol	Sep-84	20mg od	28	7.70	0.28	4	3	0.25	1.10	3.4
Cardioselective beta-blockers	MONOCOR	bisoprolol	Feb-88	10mg od	28	8.96	0.32	5	5	0.25	1.28	–
H2-antagonists	TAGAMET	cimetidine	Nov-76	800mg od	125	70.00	0.56	1	1	–	–	4.9
H2-antagonists	ZANTAC	ranitidine	Oct-81	300mg od	30	27.43	0.91	2	1	0.52	1.77	5.8
H2-antagonists	AXID	nizatidine	Aug-87	300mg od	28	23.04	0.82	3	1	0.59	1.39	0.1
H2-antagonists	PEPCID	famotidine	Sep-87	40mg od	28	26.60	0.95	4	1	0.59	1.60	–
ACE inhibitor	CAPOTEN	captopril	Apr-81	25mg bd	50	21.40	0.43	1	1	–	–	3.8
ACE inhibitor	INNOVACE	enalapril	Jan-85	10mg od	28	10.40	0.37	2	1	0.48	0.78	3.4
ACE inhibitor	ZESTRIL	lisinopril	Jun-88	10mg od	28	12.13	0.43	3	1	0.48	0.91	1.1
ACE inhibitor	ACCUPRO	quinapril	Jul-89	10mg od	28	11.48	0.41	4	1	0.43	0.95	0.5

Notes: od 'once daily'; bd 'twice daily'; tds 'three times daily'; qds 'four times daily'.

Appendix **Details of product database (*continued*)**

Category	*Brand name*	*Drug name*	*Launch date*	*Dosage used*	*Days treatment per pack*	*Cost (launch price £)*	*Cost per day (launch price £)*	*Launch order*	*Market leader*	*Market leader price*	*Ratio to market leader*	*Years to sub-sequent entrant*
ACE inhibitor	COVERSYL	perindopril	Jan-90	4mg od	30	13.00	0.43	5	1	0.43	1.01	0.2
ACE inhibitor	TRITACE	ramipril	Mar-90	5mg od	28	7.79	0.28	6	1	0.43	0.65	0.8
ACE inhibitor	STARIL	fosinopril	Jan-91	10mg od	28	12.04	0.43	7	1	0.43	1.00	0.4
ACE inhibitor	VASCACE	cilazapril	Jun-91	2.5mg od	28	10.67	0.38	8	1	0.43	0.89	2.1
ACE inhibitor	GOPTEN	trandolapril	Jul-93	2mg od	28	12.28	0.44	9	1	0.43	1.02	–
Nucleoside analogue	ZOVIRAX	aciclovir	Sep-81	800mg 5 times daily	7	140.00	20.00	1	1	–	–	12.3
Nucleoside analogue	FAMVIR	famciclovir	Jan-94	250mg tds	7	107.35	15.34	2	1	15.33	1.00	1.0
Nucleoside analogue	VALTREX	valaciclovir	Jan-95	1g tds	7	98.50	14.07	3	1	15.33	0.92	–
Quinolones	CIPROXIN	ciprofloxacin	Jan-87	250mg bd	10	15.00	1.50	1	1	–	–	3.2
Quinolones	TARIVID	ofloxacin	Apr-90	400mg od	10	14.75	1.48	2	1	1.50	0.98	0.3
Quinolones	UTINOR	norfloxacin	Aug-90	400mg bd	7	6.72	0.96	3	1	1.50	0.64	–
5HT reuptake inhibitor	FAVERIN	fluvoxamine	Jan-87	100mg od	30	25.00	0.83	1	1	–	–	2.0
5HT reuptake inhibitor	PROZAC	fluoxetine	Jan-89	20mg od	30	29.40	0.98	2	1	0.83	1.18	1.9
5HT reuptake inhibitor	LUSTRAL	sertraline	Dec-90	50mg od	28	26.51	0.95	3	2	0.98	0.97	0.2
5HT reuptake inhibitor	SEROXAT	paroxetine	Feb-91	20mg od	30	33.90	1.13	4	2	1.07	1.06	3.9
5HT reuptake inhibitor	EFEXOR	venlafaxine	Jan-95	37.7mg bd	28	23.97	0.86	5	2	0.69	1.24	0.2
5HT reuptake inhibitor	DUTONIN	nefazodone	Apr-95	100mg bd	28	16.80	0.60	6	2	0.69	0.87	0.2
5HT reuptake inhibitor	CIPRAMIL	citalopram	Jun-95	20mg od	28	21.28	0.76	7	2	0.69	1.10	–

Notes: od 'once daily'; bd 'twice daily'; tds 'three times daily'; qds 'four times daily'.

Appendix Details of product database (*continued*)

Category	*Brand name*	*Drug name*	*Launch date*	*Dosage used*	*Days treatment per pack*	*Cost (launch price £)*	*Cost per day (launch price £)*	*Launch order*	*Market leader*	*Market leader price*	*Ratio to market leader*	*Years to sub-sequent entrant*
Triazole systematic antifungals	DIFLUCAN	fluconazole	Sep-88	50mg od	7	16.61	2.37	1	1	–	–	0.6
Triazole systematic antifungals	SPORANOX	itraconazole	Apr-89	100mg od	15	21.43	1.43	2	1	2.37	0.60	–
Proton pump inhibitor	LOSEC	omeprazole	Jun-89	20mg od	28	36.36	1.30	1	1	–	–	4.8
Proton pump inhibitor	ZOTON	lansoprazole	Apr-94	30mg od	28	33.36	1.19	2	1	1.27	0.94	2.5
Proton pump inhibitor	PROTIUM	pantoprazole	Oct-96	40mg od	28	29.76	1.06	3	1	1.27	0.84	–
Statin	ZOCOR	simvastatin	May-89	10mg od	28	18.29	0.65	1	1	–	–	1.3
Statin	LIPOSTAT	pravastatin	Sep-90	10mg od	28	16.18	0.58	2	1	0.65	0.88	3.3
Statin	LESCOL	fluvastatin	Jan-94	20mg od	28	14.90	0.53	3	1	0.65	0.81	3.0
Statin	LIPITOR	atorvastatin	Jan-97	10mg od	28	18.88	0.67	4	1	0.65	1.03	0.2
Statin	LIBOBAY	cerivastatin	Apr-97	100mcg od	28	12.95	0.46	5	1	0.65	0.71	–
5HT3 antagonist	ZOFRAN	ondansetron	Mar-90	8mg bd	5	90.00	18.00	1	1	–	–	1.7
5HT3 antagonist	KYTRIL	granisetron	Nov-91	1mg bd	5	91.43	18.29	2	1	16.20	1.13	1.3
5HT3 antagonist	NAVOBAN	tropisetron	Feb-93	5mg od	5	63.37	12.67	3	1	16.20	0.78	–
5HT1 agonist	IMIGRAN	sumatriptan	May-92	100mg	6	48.00	8.00	1	1	–	–	4.9
5HT1 agonist	ZOMIG	zolmitriptan	Apr-97	2.5mg	6	24.00	4.00	2	1	8.00	0.50	0.1
5HT1 agonist	NARAMIG	naratriptan	May-97	2.5mg	6	24.00	4.00	3	1	8.00	0.50	–
A2 antagonist	COZAAR	losartan	Feb-95	50mg od	28	17.23	0.62	1	1	–	–	1.7
A2 antagonist	DIOVAN	valsartan	Oct-96	80mg od	28	15.75	0.56	2	1	0.62	0.91	0.9
A2 antagonist	APROVEL	irbesartan	Sep-97	150mg od	28	17.22	0.62	3	1	0.62	1.00	0.2
A2 antagonist	AMIAS	candesartan	Nov-97	8mg od	28	15.75	0.56	4	1	0.62	0.91	–

Notes: od 'once daily'; bd 'twice daily'; tds 'three times daily'; qds 'four times daily'.

Appendix **Details of product database (*continued*)**

Category	*Brand name*	*Drug name*	*Launch date*	*Dosage used*	*Days treatment per pack*	*Cost (launch price £)*	*Cost per day (launch price £)*	*Launch order*	*Market leader*	*Market leader price*	*Ratio to market leader*	*Years to sub-sequent entrant*
Continuous combined oestrogen & progestogen	KLIOFEM	oestradiol/ norethisterone	Mar-95	2mg od	84	39.60	0.47	1	1	–	–	0.6
Continuous combined oestrogen & progestogen	PREMIQUE	conjugated oestrogen/ medroxyprogesterone	Oct-95	0.625mg od	84	20.55	0.24	2	1	0.47	0.52	0.4
Continuous combined oestrogen & progestogen	CLIMESSE	oestradiol/ norethisterone	Mar-96	2mg od	84	23.70	0.28	3	1	0.31	0.91	–
Acetylcholinesterase inhibitors	ARICEPT	donepezil	Apr-97	5mg od	28	68.32	2.44	1	1	–	–	1.2
Acetylcholinesterase inhibitors	EXELON	rivastigmine	Jun-98	3mg bd	28	63.00	2.25	2	1	2.44	0.92	–

Notes: od ‘once daily’; bd ‘twice daily’; tds ‘three times daily’; qds ‘four times daily’.

Chapter 9
The Biotechnology Industry: Diversifying Risk, Raising Capital and Takeovers

IAN SMITH

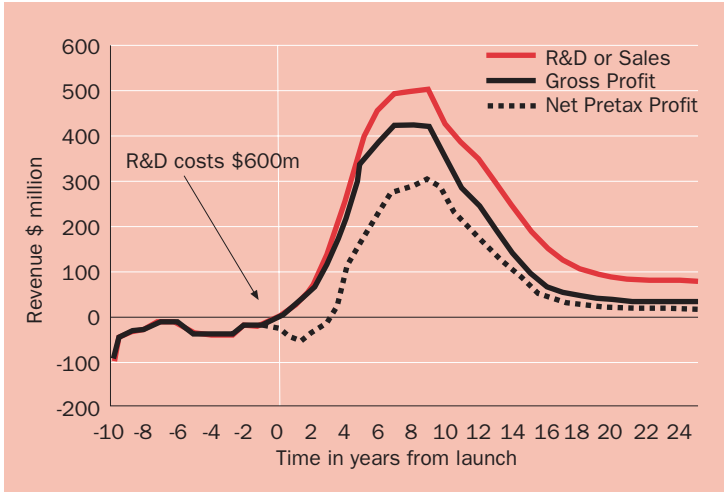
This paper will discuss issues relating to the fact that it is becoming harder to get a return on pharmaceutical R&D. It will use that theme to point out how the biotechnology industry can alter the dynamics in favour of the pharmaceutical industry. Finally, it will include some of the valuation work we do at Lehman Brothers, for our investing clients, on biotechnology and pharmaceutical companies.

It is getting harder to get a return on R&D for a variety of reasons. Sales growth is being constrained by purchaser pricing pressures, patent expiries and competition, whereas R&D costs continue to rise. Putting these two things together creates a margin squeeze in the middle. The increasing difficulty in getting a return on R&D is the reason why so much consolidation is going on in the industry at the present time, and why that will continue.

Figure 9.1 shows the theoretical pharmaceutical product life cycle we use at Lehman Brothers. This details the R&D spend through the development period, followed by the likely sales of an average drug when it comes to the market, and the operating profit you can get from that product once it is on the market. The point I wish to emphasise is that out of the post-tax operating profit earned after this product comes to the market must be recouped all the development costs, otherwise the money might as well have been put into a building society.

What are the development costs for a drug? Data from Zeneca, illustrated in Figure 9.2, indicate that on average around 4.7 products need to go into phase one to get one product onto the market; 3.3 go into phase two to get one product onto the market; and so on. This gives a starting point for calculating the probabilities of success for getting products onto the market, taking into account the cost of doing all of these stages for both the successful products and the unsuccessful products. If you include the cost of capital and the cost of developing failures to the point at which they fail, Lehman

Figure 9.1 **Product life cycle theoretical sales and profit progression**



Source: Lehman Brothers Pharmaceutical Research

Brothers' view of the current cost of bringing a new chemical entity (NCE) to the market is around $600 million.

About a third of this is what could be regarded as a fixed cost. The way I justify this is by citing, for example, Glaxo Wellcome's billion-dollar establishment in Hertfordshire which has to be depreciated every year. In other words, even if Glaxo Wellcome never put anyone in that facility it would still cost between $50 million and $100 million a year just to have it sitting idle. If Glaxo Wellcome does put scientists in it, the cost goes up, whether or not they discover anything. There is therefore a huge fixed cost base involved in doing R&D, which is sometimes overlooked and which makes a substantial contribution to the $600 million cost of bringing each drug to the market.

If you do not believe this $600 million figure, I will prove it to you in a slightly different way. The industry is now spending something in excess of $25 billion in bringing NCEs to the market, and we know

Figure 9.2 **$600m to get an NCE to market (1995 $m, including failures)**

	Drug discovery	*Preclinical*	*P1*	*P2*	*P3*	*Approval*	*Total*
Number of compounds entering stage	many projects →	11.8 →	4.7 →	3.3 →	1.7 →	1.1 →	1
		↓	↓	↓	↓	↓	
Number of compounds failing		7.1	1.4	1.6	0.6	0.1	11
Cost ($m) per compound completing stage		6	12	12	100	40	170
Cost ($m) of all failures	230	65	44	28	70	4	441
Total cost ($m)	230 (discovery and infrastructure costs)	71	56	40	170	44	611

Source: Lehman Brothers Pharmaceutical Research. (Data from Zeneca. Decision Support Group)

that the number of NCEs brought to the market each year is about 40. Simple arithmetic that tells you that our assumption of a $600 million cost of bringing a drug to the market at 1995 dollars is in the right range. And we believe that the cost is going up. That is a lot of money invested in R&D which has to be recouped.

I would like to touch on the issue of achieving a return on that R&D spend. A few years ago, many people were concerned about the rate of pharmaceutical market growth around the world, ourselves included. We were noted as being more bearish than most on where the pharmaceutical market growth would go through to the end of this

decade. Happily, it seems that pharmaceutical market growth is running at a higher level than we had anticipated, not least in the USA. One of the reasons why the market is now growing at something approaching double digits again in the USA, is that rationality is now coming into prescribing. That is because the decision-making has moved away from single GPs acting in isolation, towards bulk purchasers, such as Pharmaceutical Benefit Managers (PBMs) and Health Maintenance Organisations (HMOs), who are able to make more rational assumptions as to whether or not a drug is worth prescribing.

Drugs can save not only lives but also money. The more cost you take into account, the more money successful drugs can save. Figure 9.3 shows an example for a septic shock drug. There are none on the market at the moment, but I have used this example in connection with Celltech to assess the sort of price they might get when they and Bayer launch their first septic shock drug. In this example, a drug priced at just $5,000 can save on average $55,000 per patient treated, if it is successful. That takes into account not just possible savings in hospitalisation costs but also in indirect costs. For example, there is an employer cost in having one of your employees die of septic shock. I should mention also that there is a 50 per cent probability of dying within 28 days if you have septic shock, so this is not a minor syndrome!

Figure 9.3 **Septic shock: economic benefits of effective drug therapy[a]**

	Saving $'000
• Extra hospitalisation costs	5.0
• Employer costs ($10K × 25%)	2.5
• Life insurance payout (3 × $30K × 25%)	22.5
• Spouse pension NPV (20 years × $10K × 25%)	25.0
Average saving	$55.0

(a) For a 40 year old person on a $30,000 annual salary, on the basis that a drug reduces the risk of death by 25 per cent.

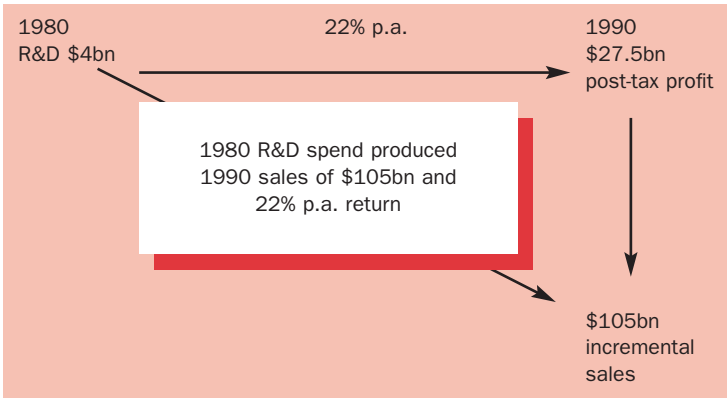
Source: Lehman Brothers Pharmaceutical Research

Other issues like life insurance come into play. At the moment, a life insurer first gets to hear that a person's life has expired when he gets a bill for three times the person's salary floating across his desk. This is one of the reasons why the evolving rationality of prescribing in the US market is starting to lead to more drugs being prescribed, or a willingness on the part of health care payers to allow relatively expensive drugs to be prescribed – because they are picking up, in some cases at least, the full cost of the life not continuing.

You would think that in Europe, where governments pay for drugs, we would have an ideal situation where all the costs would be added into the equation. However, such is the way that governments work, this does not tend to happen. When we start getting rationality into prescribing and some recognition of all the costs of successful drugs, then the industry can hope to get prices for its drugs which bear some relationship to their true value.

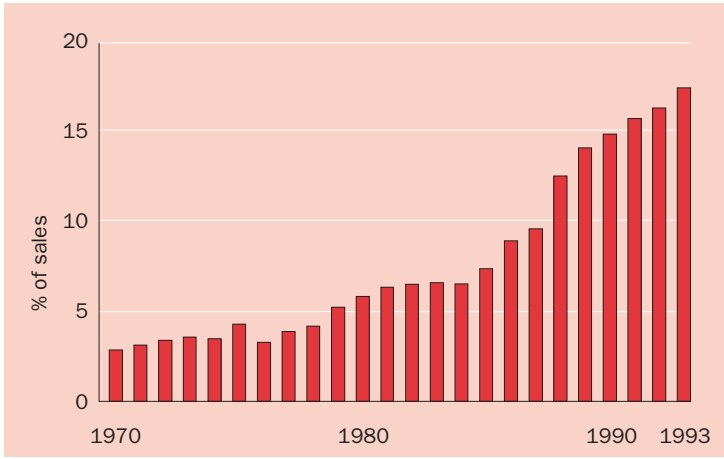
To get that price you have to have something which is unique. If there are five companies marketing septic shock drugs you can bet which way price is going to go. Indeed, that is one of the major arguments: that the survival of this industry depends on bringing cost-effective and truly innovative drugs to the market.

Figure 9.4 **R&D spend produced a 22% p.a. return**



Source: Lehman Brothers Pharmaceutical Research

Figure 9.5 **Glaxo: R&D percent of sales**

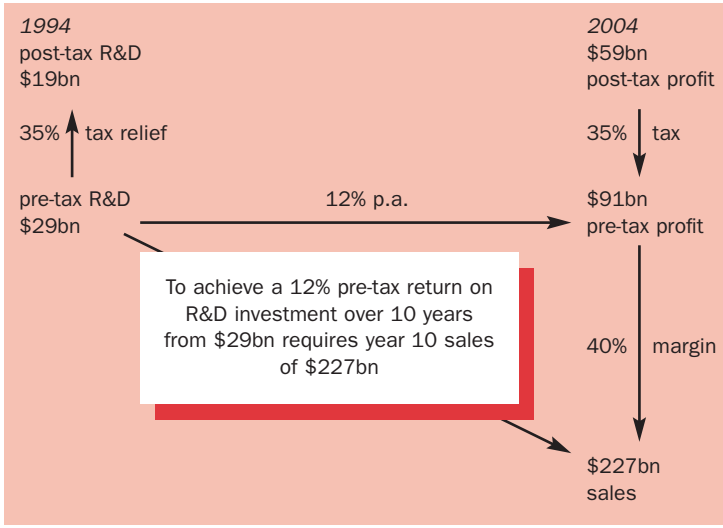


Source: Lehman Brothers Pharmaceutical Research

Figures 9.4 and 9.5 demonstrate why getting a return on R&D has become harder. Figure 9.4, using Lehman Brothers' analysis, shows that the industry spent around $4 billion on R&D in 1980. We calculate that 10 years later, in 1990, that led to incremental sales of $105 billion, on which the industry in aggregate made around $27.5 billion post-tax profit. In other words, on this 10-year lag analysis, the industry made a 22 per cent per annum return on its $4 billion investment in R&D costs in 1980. The 1980s were a high inflation decade, but not that high. I suggest that the industry got a very good return on its R&D spend during that decade.

In the meantime, however, the proportion of sales being spent on R&D has increased from something like five per cent in 1970 to around 15 per cent now. Figure 9.5 shows the example of Glaxo, but a similar trend would be seen in virtually all pure play drug companies. Even in the Zantac development days, Glaxo was only spending around seven per cent of its sales on R&D. It is an arithmetic fact that if you are spending 15 per cent of your sales on R&D it will be a lot harder to get a return on that R&D investment than if you were spend-

Figure 9.6 **Adequate return on $29 billion* unlikely**



*$29bn = $26.5bn from 65 pharma/biotech company Lehman universe + $2.5bn from otherwise uncovered biotechnology companies.

Source: Lehman Brothers Pharmaceutical Research

ing 5 per cent of your sales on R&D. This return has to be recouped in a pharmaceutical market which is growing at half to two-thirds of the rate at which it was growing a few years ago. Hence my point that it is becoming much harder to get a return on R&D, and hence the need for companies to look at ways in which they can enhance that return.

Figure 9.6 shows that with the industry's total R&D spend in 1994 of $29 billion, based on a group of companies that Lehman Brothers follow, then just to get a return of 12 per cent per annum would require a rate of market growth of about 10 or 11 per cent per year. This in turn implies sales of $227 billion by year 10, which is barely achievable. The industry in aggregate, therefore, will not get an adequate return on its R&D spend as we go forward, and has indeed not had it over the last few years. That is why we are seeing consolidation in the industry. That is why some companies have decided to pull out alto-

gether. Boots sold its R&D arm. Fisons pulled out of R&D. Companies are merging so that they can cut their R&D costs. Put simply, not everyone can now afford to play in this game.

The basis of innovation is in-house usable and enabling technologies, like molecular biology and combinatorial chemistry, but complemented by networking with smaller organisations – universities, biotechnology companies, small research organisations and so on. The model used by Lehman Brothers for working out return on R&D spend is shown in Figure 9.7. Year zero is launch year. Years minus 10 to zero are development years for a drug. By putting a cost on the development of an average drug, including the cost of failures and the time value of money, you can arrive at a fully capitalised cost of about $400 million for bringing an average drug to the market. That is $400 million post-tax as compared with $600 million pre-tax.

At the point of launch and for years subsequent to that you can also calculate the NPV of the drug at various points in its life cycle. At the stage where you bring it to the market, or indeed at any other stage, you can calculate the return on your R&D spend from that drug development. In this hypothetical example, for a $500 million per annum peak sale drug, it happens to be 52 per cent.

Using a model like that, you can look at various strategies that big drug companies and biotechnology companies can use to bring drugs to the market. In other words, does a big pharmaceutical company get a better return on its R&D spend by in-licensing a product that is now in phase two with a biotechnology company? Or should it start up its own 'me-too' follow-on research programme so that it can have its own product? Similarly, you can model whether smaller companies should license out or develop in-house and pay for all the costs for the full phase one to phase three development of that product.

This type of analysis shows, in our view, that it is better for pharmaceutical companies to in-license products at the phase two stage from biotechnology companies than to start up their own in-house research project which will be several years behind the biotechnology market leader. The advantages are that the pharmaceutical company: can increase the sources of its innovation or innovative technology beyond

Figure 9.7 **NPV analysis of drug development. In-house discovery/development**

Year from launch	*R&D (pass)*	*R&D (fail)*	*R&D/ sales*	*Growth rate*	*Gross profit*	*Promotion cost*	
	$m	*$m*	*$m*	*%*	*$m*	*% of sales*	*$m*
	X	*Y*	*A (X+Y)*	*B*	*C*	*D*	*E (AxD)*
–10			–115*		–115		
–9	–3	–35	–38	p/c	–38		
–8	–7	–26	–33	p1	–33		
–7	–4	–8	–12	p2	–12		
–6	–4	–9	–13	p2	–13		
–5	–23	–17	–40	p3	–40		
–4	–25	–18	–43	p3	–43		
–3	–25	–18	–43	p3	–43		
–2	–19	–2	–21	r	–21		
–1	–19	–2	–21	r	–21		
0			0	r	0		–20
1			25		19	200%	–50
2			63	150%	50	100%	–63
3			138	120%	117	75%	–103
4			248	80%	223	45%	–111
5			396	60%	337	30%	–119
6			455	15%	387	25%	–114
7			501	10%	426	20%	–100
8			501	0%	426	18%	–90
9			501	0%	421	15%	–75
10			426	–15%	353	12%	–51
11			383	–10%	287	10%	–38
12			345	–10%	241	10%	–34
13			293	–15%	191	10%	–29
14			249	–15%	137	5%	–12
15			187	–25%	93	5%	–9
16			150	–20%	60	5%	–7
17			120	–20%	40	3%	–4
18			102	–15%	41	2%	–2
19			86	–15%	35	2%	–2
20			78	–10%	31	2%	–2
21			74	–5%	30	2%	–1
22			74	0%	30	2%	–1
23			74	0%	30	2%	–1
24			74	0%	30	2%	–1
25			74	0%	30	2%	–1

Source: Lehman Brothers Pharmaceutical Research. *Discovery and ancillary costs. p/c=Pre-clinical testing. p1=Phase 1; p2=Phase 2;

and marketing

General + admin + overhead $m	*Pre-tax profit* $m	*Pre-tax margin* %	*Post-tax profit* $m	*NPV @8%* $m	*Cum. R&D cost @8%* $m	*% return on R&D* %
F	*G (C+E+F)*	*H*	*I (0.65xG)*	*J*	*K*	*L (J/K)*
	–115		–75		–75	
	–38		–25		–105	
	–33		–21		–135	
	–12		–8		–154	
	–13		–8		–175	
	–40		–26		–215	
	–43		–28		–260	
	–43		–28		–309	
	–21		–14		–347	
–4	–25		–16		–391	
–8	–28		–18	669	–440	52%
–21	–53		–34	741		
–23	–36	–57%	–23	836		
–27	–13	–10%	–9	926		
–32	79	32%	51	1010		
–40	178	45%	116	1040		
–43	230	51%	150	1008		
–45	281	56%	182	940		
–45	291	58%	189	834		
–45	301	60%	195	712		
–41	261	61%	170	575		
–39	210	55%	138	452		
–37	170	49%	110	352		
–35	127	43%	82	271		
–22	102	41%	86	211		
–19	65	35%	42	183		
–17	35	23%	23	134		
–16	28	24%	18	123		
–15	24	23%	15	115		
–14	19	21%	12	110		
–14	16	20%	10	107		
–14	14	19%	9	105		
–14	14	19%	9	104		
–14	14	19%	9	103		
–14	14	19%	9	102		
–14	14	19%	9			

p3=Phase 3; of clinical testing. r=Regulatory approval.

its in-house expertise; can support a franchise in a chosen core area; can get a product candidate which is closer to the market than an in-house alternative they have not yet started to invent; and can get an enhanced, risk-adjusted return on its R&D spend. Indeed, we are seeing increasing evidence of big drug companies being inclined to in-license rather than start their own follow-up R&D projects.

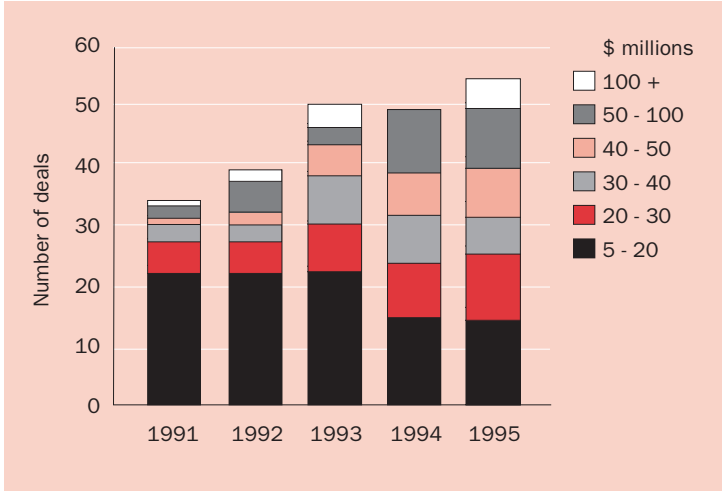
What this implies is that it is statistically unlikely, no matter how good a pharmaceutical company's scientists are, that it will come up with all the best ideas to support any chosen core area. Everyone wants to be in Alzheimer's disease, for example, but it is statistically unlikely that Glaxo Wellcome, Merck, Bristol Myers or Pfizer, etc. will come up with the best idea and the real breakthrough for the treatment of Alzheimer's. So they might as well be scouring what is going on in biotechnology companies and in-licensing at the phase two stage, where at least they have an opportunity to see some clinical data.

The advantages to the biotechnology company are that there are very attractive terms available for innovative products. Biotechnology companies tend to be quite good at coming up with innovations, i.e. the drug discovery process, but less good at the development process. A biotechnology company is therefore likely to be slower in the development process and so may try to cut corners, which inevitably leads to mistakes and failures. Biotechnology companies will be less good at the development process than a pharmaceutical company which is already an expert in developing an asthma drug, a depression drug, or whatever.

As far as the biotechnology company's shareholders are concerned, this approach can produce a superior return on R&D spend. It reduces the cash-burn rate and therefore shareholder dilution, and indeed offers a risk/reward profile to investors that they feel comfortable with. Figure 9.8 shows the number of deals between big and small drug companies from 1991 through to 1995. Not only is the number of deals going up but the sizes of the deals are also increasing.

More and more pharmaceutical companies are doing more and more deals at higher prices with biotechnology companies because they are implicitly accepting this type of analysis. Figure 9.9 shows what Glaxo

Figure 9.8 **Biotechnology out-licensing: the number and size of deals are increasing**



Source: Windhover's Pharmaceutical Strategic Alliances for the PC

was doing prior to the Wellcome acquisition. Glaxo was spending around a quarter of its research budget, as opposed to its R&D budget, on external collaborations with biotechnology companies. The drugs which will save Glaxo Wellcome's earnings from completely cratering over the next few years are those which were obtained through that collaboration process. Drugs like Numibudine-3TC from Biochem Pharma; a flu' drug from Biota; and others. The company's sales and earnings momentum over the next few years owe a lot to what Glaxo did in setting up a lot of these collaborations five-plus years ago.

I will switch tack now onto the valuation work we do at Lehman Brothers. We use two methods valuing biotechnology companies. One is an aggregate net present value of projects and is just a shorthand method. The other is probability adjusted cash flows, which is the proper way to do it. In each case, however, you have to be able to relate a future value to a current valuation. The connecting factor is

Figure 9.9 **Glaxo: some key research collaborations ($60m p.a.; not including approx. 50 early stage technology collaborations)**

Partner company	*Field of interest*	*Therapeutic area*
Gilead Sciences	Genetic blocker compounds	Cancer and other
Glycan Pharmaceuticals	Chemokine binding	Inflammation
ICOS Corporation	Phosphodiesterase inhibitors	Cardiovascular disease and other
Ligand Pharmaceuticals	Intracellular receptors	Cardiovascular
Megabios Corporation	Gene therapy	Cystic fibrosis
NeuroSearch	Calcium-activated membrane potassium channel blockers	Central nervous system disorders
Regeneron Pharmaceuticals	Neurotrophins	Neurological and psychiatric disorders
Sequana Therapeutics	Genetics	Type II diabetes
Spectra Biomedical	Genetics	Migraine
Vertex Pharmaceuticals	Protease inhibitors	HIV disease

Source: Lehman Brothers Pharmaceutical Research

the discount rate, which relates to the perceived probability of success. One of the things which is very poorly understood in financial markets amongst investors – not only in London, where biotechnology is quite new, but even in the US where biotechnology has been going for 15 years – is the relationship between probability of success and discount rates. Luckily, there is a simple but little-known equation which gives it to you. That is, the appropriate discount rate for a given project is given by the safe rate or an alternative rate for the firm – so you could use bond rates, although most investors want to use 10 per cent because that is what they think they can make in the market elsewhere anyway – divided by the 'n'th root of the probability, where 'n' is the number of years you are at risk (see Figure 9.10).

For example, a project that is going to run over three years (n=3), which you perceive to have 50 per cent probability of success (p=0.5),

Figure 9.10 **Higher risk investments: what discount rate?**

Key factors:

- Likelihood of success
- Alternative (e.g. safe) rate of return
- Time (years)

$$\text{discount rate} = \frac{\text{safe rate of return}}{\text{n(yrs)}\ \sqrt{\ \text{probability}}}$$

$$d = b/p^{1/n}$$

Source: Lehman Brothers

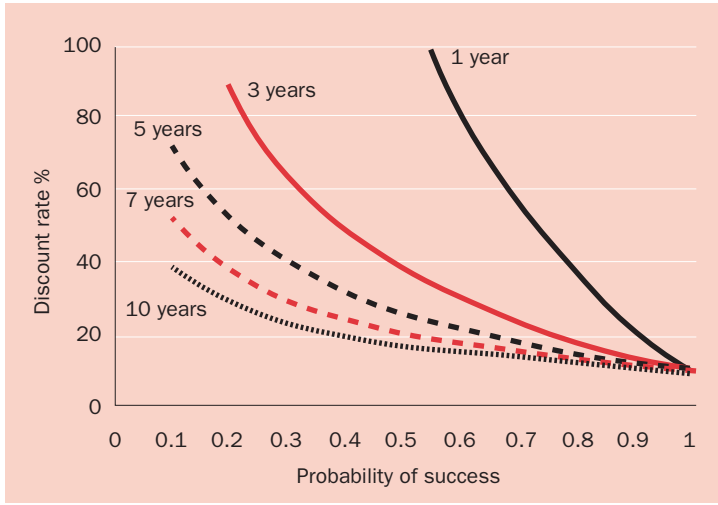
compared with a bond rate equal to 10 per cent (b=1.10) requires that you use a 40 per cent per annum discount rate (d=1.40) (see Figure 9.11). That is how we choose our discount rates. It gives you a valuation on a company or on a project which is exact; but it is only as good as the assumptions that went into it, principally the probability of success that you perceive to be the case.

Figure 9.12 shows an NPV table for Celltech. It lists all the projects, one underneath the other, along with a peak sales estimate, an NPV factor – what proportion of peak sales will the project be worth at that peak? – and a probability of success. Those factors then allow you to calculate a discount rate. You can then work out an NPV in pence per share per project, aggregate the lot, and that gives you a current valuation by this method of 436p per Celltech share.

If you roll that forward for 12 months, you can change the probabilities for each of the projects – on the assumption that things will continue to move forward satisfactorily. For example, the septic shock product mentioned earlier has a probability of something like 50 per cent, although it is now in the last three months of its phase three studies. In 12 months' time, if everything is going forward satisfactorily, it will have something like a 90 per cent probability of coming to the market. In fact it may even be on the market, or at least approved.

In this way one can arrive at a valuation target for the end of next year which comes out at 865p. So when we say to investors 'We think you

Figure 9.11 **Discount rates**



Source: Lehman Brothers

should be buying Celltech', that is because we have taken a view that the septic shock drug is going to work and, by this time next year, this stock will be worth not 436p, its current valuation, not 500p, its price today, but 865p, which is the price we expect it to be at in 12 months' time.

It is interesting to note the variation in what you pay for R&D spend in big drug companies versus small drug companies. Figure 9.13 shows the NPVs of the existing businesses in a range of the world's drug companies. Using the product life cycle outlined above and the example of Glaxo Wellcome, a pure play drug company that does not have cyclical operations like chemicals, we calculate that the NPV of the company's current portfolio of marketed drugs comes to 50 per cent of the current stock price for the NPV of all the marketed products (market capitalisations have been adjusted to the 100 per cent level). What are you paying the rest for? The rest is being paid for all the things that are not valued in here. In Glaxo Wellcome's case you are paying for its R&D portfolio.

In other words, since Glaxo Wellcome has a market capital of something like $45 billion, you are currently paying $22.5 million for their R&D portfolio: the products in phase two and phase three, and those that are currently in filing or just-launched phase. Those products have projected, undiscounted, aggregate peak annual sales of $8.4 billion, but that has to be discounted because some of them are only in phase two and some of them are in phase three. We therefore do some discounting for time, which gives us $5.7 billion of sales, risk and time adjusted, for Glaxo Wellcome's phase two and later development projects. But you are paying $28 billion for that. In other words, you are paying $5 per $1 of future sales for Glaxo Wellcome's R&D. If you do this same calculation for Smith Kline the figure is about 3.5; for Zeneca it is 4.2; for Pfizer it is about 5; and so on (Figure 9.14).

What about the UK biotechnology companies? There are in total 27 phase two, phase three and final products for the UK biotechnology industry. No matter what you might think of any particular one of those products, that is not a bad R&D development portfolio. If any drug company had that, investors would be pretty pleased with it. What are you paying for that? If you add up the market capitalisations of all the companies that produce those drugs, it is $4.3 billion. The products themselves have a time and risk adjusted value of $4 billion. In other words, you are paying not $5, as you are paying for Glaxo, but $1.1 per $1 of future sales, time and risk adjusted, in 'UK Biotechnology plc'.

This is slightly misleading as some of these products will be licensed out. An adjustment will therefore need to be made to allow for the fact that they will not get a full trading profit on that portfolio. I calculate that you may have to increase the $1.1 value to about $2. However, I can still confidently say that in biotechnology companies you are only paying about half what you would pay in a large drug company to access their pharmaceutical R&D. In other words, as things stand at the moment, UK biotechnology companies are a very cost-efficient way into investing in pharmaceutical R&D.

Figure 9.12 **Celltech: individual product contributions to current (1996) NPV**

Drug	*Indication*	*Status*	*Launch year*	*Peak sales $m*
B-1351/CDP571	sepsis	P3	1998	350
CDP771	acute myel. leuk.	P2	1998	150
CDP671	ovar./lung cancer	P1/2	2000	125
CDP833	colorectal cancer	discontinued		
CDP833 follow-up	colorectal cancer	pre-clinical	2001	200
CDP845	solid tumours	pre-clinical	2002	350
CDP571	severe rheum. arth.	P2	1999	150
CDP835	severe asthma	P1/2	2001	75
CDP840	asthma	suspended		
CDP??	asthma	pre-clinical	2002	500
CDP571	Crohn's/IBD	P2	1999	125
CDP571	ulcerative colitis	P2	1999	75
CDP850	psoriasis	P1/2	2001	150
CDP??	transplant rejection	pre-clinical	??	
Other research (early pre-clinical work not separately valued)				
Royalty from Centocor/Lilly's ReoPro (year 2000 sales $200m)				
Aggregate NPV				

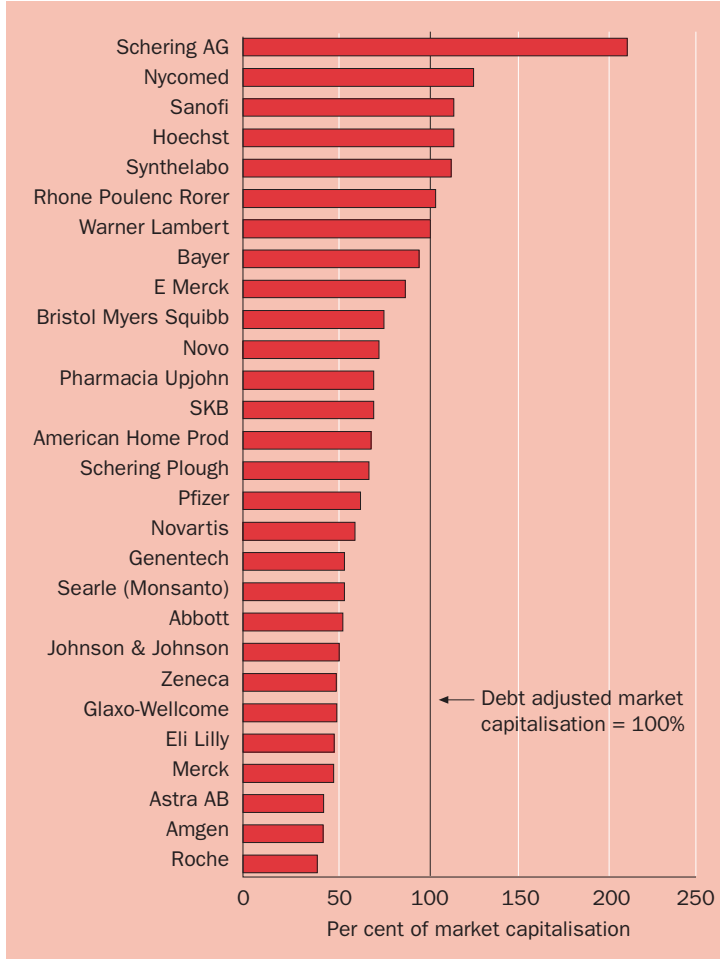
Assumptions: Product NPV = 1-2x peak sales; $/£ exchange rate = 1.50; full dilution (79m shares).

Discount rate based on perceived probability of success and years to be discounted.

(assuming 10 per cent Treasury bond rate)

NPV at peak $m	*Peak sales year*	*Years to peak sales*	*Probability of success %*	*Discount rate %*	*NPV (pence per share)*
525	2002	5.5	50	25	131
225	2002	5.5	50	25	56
187.5	2003	6.5	20	41	17
					0
300	2005	8.5	10	44	11
350	2006	9.5	15	34	18
225	2004	7.5	35	27	33
75	2004	7.5	20	36	6
					0
750	2007	10.5	15	32	35
187.5	2003	6.5	35	29	30
75	2003	6.5	35	29	12
300	2005	8.5	15	38	17
					55
	2000	3.5	100	10	16
					436 pence

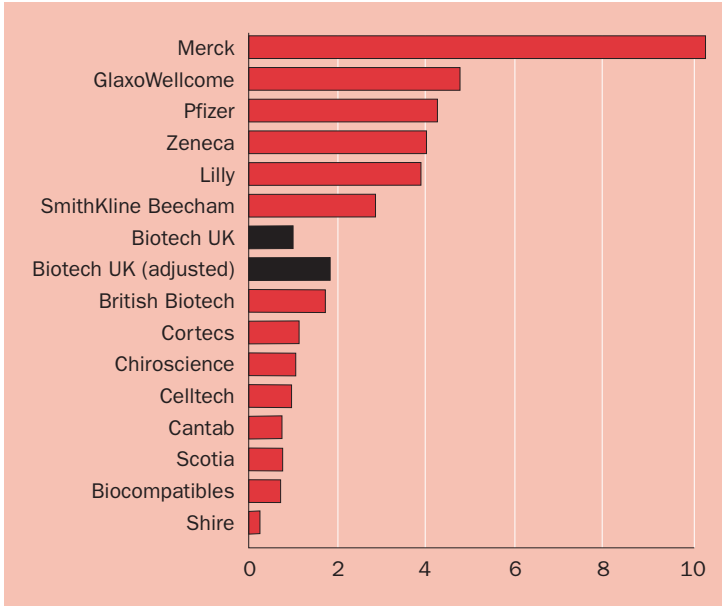
Figure 9.13 **Net present values at 4 September 1996* (ex-R&D)**



*Existing drugs and other businesses. Ignores R&D and infrastructure. Excluding Japanese companies.

Source: Lehman Brothers

Figure 9.14 **Cost per $ of sales**



Source: Lehman Brothers

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