

**CONSOLIDATION AND COMPETITION  
IN THE PHARMACEUTICAL INDUSTRY**

Based on papers delivered at the OHE  
Conference, London, 16 October 2000

Edited by Dr Hannah E Kettler



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Office of Health Economics  
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## **Office of Health Economics**

The Office of Health Economics (OHE) was founded in 1962. Its terms of reference are to:

- commission and undertake research on the economics of health and health care;
- collect and analyse health and health care data from the UK and other countries;
- disseminate the results of this work and stimulate discussion of them and their policy implications.

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## **LIST OF CONTRIBUTORS**

**Professor Louis Galambos**

Professor of Economic and Business History, Johns Hopkins University, USA.

**Professor Henry Grabowski**

Professor of Economics and Director of the Program in Pharmaceuticals and Health, Duke University, USA.

**Professor John Kay**

Writer, lecturer and broadcaster, johnkay.com.

**Dr Hannah Kettler**

Research Associate, Office of Health Economics, UK.

**Dr Bernd Langeheine**

Head of Unit, General Competition Policy – Economic and Legal Aspects, Directorate General for Competition, European Commission.

**Mr Roy Levy**

Deputy Assistant Director, US Federal Trade Commission.

**Professor Fabio Pammolli**

Associate Professor of Economics and Management, University of Siena, Italy.

**Dr Massimo Riccaboni**

Faculty of Economics, University of Siena, Italy.

**Professor John Vernon**

Professor of Economics, Duke University, USA.

**Ms Jo Walton**

Pharmaceutical Analyst, Lehman Brothers, London, UK.

**Mr Abraham Wickelgren**

Economist, US Federal Trade Commission.

LIST OF CONTRIBUTORS

**Professor George Yarrow**

Regulatory Policy Institute, Oxford, UK.

## Introduction

HANNAH KETTLER

A number of potentially important structural developments are taking place in the pharmaceutical industry. On the one hand, we are witnessing a large number of mergers and acquisitions between companies across countries, suggesting a move towards a small number of large global players. On the other hand, a large number of new companies have entered in the industry over the past 15 years. Many are biotechnology companies that specialise in research and/or developing technologies for the discovery and pre-clinical stages of the research and development (R&D) process. Many new contract sales organisations (CSO) and contract research organisations (CRO) have also been created, a number with global reach, to provide specialised services to the large pharmaceutical companies.

Empirical analyses of these trends highlight a series of important questions of particular interest to industrial economists and policy makers. What changes in the industry are motivating the major companies to become larger but at the same time allowing new groups of small, specialised companies to flourish? Are the global leaders and the small specialist biotech rivals or collaborators? Is there a move away from the traditional vertically integrated model of R&D towards something new? What role do scale and scope play in this move? Finally, do policy makers need to rethink how they assess competitive conditions in the pharmaceutical industry?

On October 16th, 2000, the Office of Health Economics hosted a conference entitled 'Consolidation and Competition in the Pharmaceutical Industry' which set out to debate these questions, drawing on the expertise of representatives from academia, industry, investors and government. This volume of papers draws on the presentations made at that conference. The participants presented a broad range of information and opinions but a number of key themes did emerge.

There was a general consensus that the traditional large pharmaceutical companies are undergoing a transformation but to

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what end was less clear. To explain the move towards 'global oligopoly', Galambos focuses on the major changes in the innovation process over time, while Walton identifies the growth in both R&D and marketing costs relative to the growth in markets as a key motivator for companies to seek larger scale. Grabowski shows that returns from new pharmaceuticals are highly skewed, with only 30 percent of products launched in the early 1980s recovering average R&D costs. The skewness in net present value for products launched in the 1990s may be even greater given estimates of increases in R&D costs. Grabowski suggests that only large companies can afford the investment needed to bring innovative blockbusters to market.

It is unclear, however, whether larger companies are more effective than smaller ones at R&D. Galambos argues in favour of important scale and scope economies in R&D but Walton's empirical analysis found significant economies only in marketing.

At the same time as larger pharmaceutical companies are merging, they are also increasing their expenditure and involvement with biotechnology and other specialised research companies by way of alliances and licence deals. Kettler analyses the nature and the implications for R&D of the growing interactions between these segments. She finishes by investigating whether the increasing amounts spent on external partnerships represent a temporary strategy by major companies, undertaken while they catch up with the new technologies and fill temporary gaps in their R&D pipelines. This is a position supported by Galambos. Or does the increase in external partnerships represent a real shift towards a new R&D model?

Pammolli uses data and analysis of the alliances and networks between universities, major companies, and biotechs to show that there are key performance advantages in conducting R&D via a network rather than solely in-house. Kay also predicts a substantive transformation where technological developments mean that large companies increasingly act in the manner of book publishers: co-ordinating the process, financing production and marketing the output; with most of the value added coming from the 'originators' – the discovery companies.

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In the final three chapters, competition policies in the US and EU are explored. In addition to assessing the competitive implications of traditional merger and acquisition activity, both Levy and Langeheine point out that regulators on both sides of the Atlantic are increasingly having to tackle competitive issues relating to new types of research collaborations and sales arrangements. Assessing the impact on competition of innovation is becoming a key policy issue alongside the traditional concern with competition between existing products in final markets. Yarrow makes another key point, which is that the need for the additional layers of sector specific regulations in pharmaceuticals that exist in most EU countries is not proven. It may well be that competition policy on its own provides a comprehensive framework for the regulation of new and existing activity within the sector.

## Chapter 1

# Changes in Market Structure: the Economic Issues

JOHN KAY

'The trouble with people is not that they don't know but that they know so much that ain't so'. That is why this paper starts, not with pharmaceuticals, but with other industries and other businesses. My reasoning is that when I discuss an industry that people know about, they already have views about how its structure is changing. So I hope to use an analysis of the book business to provide a new context and perspective for thinking about how industrial structures are changing generally and might change in the pharmaceutical business.

Three types of activity are needed to create books. Authors are the people who write them. There is – as there must be in any media business – a delivery mechanism. This delivery mechanism is provided partly by printers and partly by booksellers. In between, co-ordinating the process, financing production, marketing the output, are publishers. An important element of that co-ordination function is selecting from the range of material originated. The publisher finances both the originating authors and a part of the delivery process. But the essential role of the publisher is as manager and coordinator. So the book industry is divided into origination, publishing and delivery. The skills required to do each of these things are very different. The capabilities that are required to be good at one are typically rather different from the capabilities that are required to be good at the others.

The manufacture of books is the result of several distinct activities, like most complex products in the modern economy, and the structure of any industry is defined by the distinct activities its products require. The financial relations between these activities are determined by the nature of the capabilities needed in these activities and the economic rents associated with scarcities of these capabilities. In the book business, both the nature and the scarcity of the capabilities required are distinct at each different part of the value chain.



Economic rents are derived from scarce distinctive capabilities, so to find the most profitable sections of the value chain we need to identify those areas where talents are rare. In the book industry, this is obvious enough. The greatest scarcity of talent is in authorship. To a lesser degree, origination also requires distinctive capabilities. There are good and bad publishers and so rents are generated in publishing.

The delivery activities of printing and book selling are substantial businesses. But the characteristics of these businesses are easy entry, no scarcity of relevant capabilities, and no very strong distinctive capabilities. In consequence, although there is substantial turnover in the printing and selling of books, these are not particularly profitable businesses.

In this value chain the further back in the chain we go the higher is the return on capital employed. For an author with his pen or his word processor, the return on capital employed can be very large indeed and – here we might note already a read across to pharmaceuticals – most capital employed is actually uncompleted R&D.

There is no advantage to vertical integration in the book business. Nor is there much vertical integration in practice. Publishers do not own authors, authors do not own publishers, and publishers own neither printers nor booksellers. Vertical integration is inappropriate because there are no large barriers to entry at any point in the value chain, and because the sources of competitive advantage and the activities that make up the business at each point are different.

Sometimes there is another business advantage from vertical integration. That advantage comes from asset specificity – the need for investments to be dedicated to a particular supplier or customer – or from the problems of passing information, either about which products are selling or about product quality and reliability, to firms at different points in the value chain. Vertical integration has often been justified to secure these kinds of idiosyncratic investments, or to facilitate information flows.

These relationships can be equally achieved by contract – often an implicit contract rather than legal contract – without requiring

integration. The most illuminating example was the Japanese reconfiguration of the automobile industry. Toyota's keiretsu<sup>1</sup> proved more effective than the integrated structures of Ford and General Motors in securing product quality and rapid response to changing market conditions.

Sometimes vertical integration is used to leverage dominance. A strategic position in one market can be used to gain competitive advantage in another. But there is little vertical integration in the book industry because nobody has sufficient dominance to motivate it. If HarperCollins bought Waterstones, then maybe HarperCollins and Waterstones would go on running themselves as they always had and there would be no advantage to vertical integration. Or they could try and use the vertical integration they had created to leverage their market power; pushing HarperCollins books through Waterstones' outlets with Waterstones giving priority to the promotion of HarperCollins books. But so long as both firms have relatively small market share then pursuing this exclusivity will actually reduce the value of both companies. There are incentives to seek to corrupt intermediary processes, i.e. for HarperCollins to pay Waterstones to put HarperCollins books at the front of the store, and indeed that is what they do. But ownership is neither necessary nor useful in bringing about this result.

It has become increasingly clear both as a matter of theory and of practical business management that one can extract value from dominance without involvement in other parts of the value chain. This is what Microsoft and Nike both do. Service providers do not have to manufacture computers to extract most of the rents that are earned in the computer business. Nike can enjoy the rents from its brands even though it outsources the production of its shoes.

<sup>1</sup> Starting in the 1980s, rather than integrating all automobile supplies and parts in-house as Ford and General Motors did, Toyota moved to use a core set of independent suppliers and 'pull in' parts and products as needed to complete their automobile assembly. The configuration with Toyota at the centre and its set of suppliers and subcontractors is called the keiretsu.



So asset specificity or leverage in dominance sometimes justify vertical integration, but not often and certainly not in the book industry. Other media industries are organised along lines very similar to books. If we look at the music business, we see the same split of origination, publishing and delivery. Artists and composers are the originators. There are two different mechanisms for delivery: recorded music and the live performance. Music publishers and promoters take on the activities of selection, coordination and financing, the same functions as publishers undertake in the book industry.

Films are organised in the same way. There is originating talent, stars and directors. There are delivery mechanisms. Three kinds of distributors work here: the exhibition sector; video distribution; and television. There are also the misleadingly named studios. They retain this name although the one thing they do not have any more is a studio. Studios are publishers of films, and, as in other media businesses, the functions of publishers are coordination, marketing, financing and selection. This pattern of division into origination, publishing and delivery is common across all media. Vertical integration is sometimes tried in these businesses, but there is no underlying industrial logic to it and it does not, in the main, last.

I have talked about media businesses at some length because I think they provide the closest analogy to the pharmaceutical industry. The central requirements for getting pharmaceutical products successfully to market are very similar to the requirements of getting a media product to market. There is a creative activity involved in origination. There is a delivery process of manufacture and distribution. Then there is a publishing function, which incorporates the same requirements of coordination, selection, marketing and finance.

Perhaps the pharmaceutical industry is a bit more complex. The list of distinct activities needed to make pharmaceutical products is quite long. It includes: fundamental research; selection within and from that fundamental research; development and testing; financing; the management of regulation; marketing; manufacturing; product distribution; and finally there are requirements for prescribing and

retailing activities. Right in the centre, there is the activity of co-ordinating the whole variety of these functions.

The pharmaceutical industry is similar to media industries, but there are two important differences. First, the boundaries between the activities of originating, publishing and delivery are fuzzier in the pharmaceutical business than they are in the media business; and indeed these fuzzy boundaries may themselves be undergoing change with the advances in technology and changes in market structure. The editor will often improve the work of an author. But there is rarely any real doubt whose creative talent dominates the final product. The boundary between research and development is less sharp. An established printer can use the same technology for all books. Manufacturing pharmaceutical products is not quite so simple.

The second difference is that the delivery process in the pharmaceutical business is organised in what seems to be an almost unique way. All manufactured goods, including pharmaceuticals, need to be retailed. From an economic standpoint, there are three reasons why retailing is needed: because consumers are small; because consumers are ignorant; and because consumers are immobile. Small customers need someone to negotiate with manufacturers. Ignorant customers need someone to select the range of products that are most appropriate for their needs. Lastly customers do not want to go to the factory to collect the product; they want someone to bring the product to a location nearer by. Retailers resolve these problems.

Tesco handles these three functions for the food shopper. They have negotiated with manufacturers and used their bulk purchasing power to get discounts on the price. They have selected from the wide range of products that are available and the wider range that is potentially available the ones that they think their customers will buy. They have performed the logistic function of bringing the product to some nearby superstore. In this industry, and most others, one agent conducts all the three functions of retailing.

What makes the pharmaceutical business special is that separate agents perform these three retail functions. Governments (or in some

countries intermediaries) try to negotiate better prices for consumers. Doctors do the product selection. Pharmacists bring the products closer to the patient.

No analogy is ever exact and it is important to understand the differences as well as the similarities. Still, I believe the fundamental division into distinct activities of origination, delivery and coordination is as relevant to the pharmaceutical industry as it is to media. It is a guide to the underlying industrial logic of its organisation and a framework for analysing how it might change.

I am aware of at least two groups of factors driving structural change in pharmaceuticals. There are changes in the technology of pharmaceutical research. From a business economist's standpoint (and I emphasise that my perspective is that, rather than the scientist's), the relationship between fundamental research and pharmacological development seems to be in flux. Historically my economic model of pharmaceutical research shows skilled and lucky people dipping into a very large pot that contained a very large number of coloured balls, hoping that one or two will turn out to have winning numbers on them. That discovery process is changing. We are much closer to exploiting a common base of fundamental knowledge accessible to all companies. The identification of compounds is more systematic, aimed at finding those that are most appropriate for the exploitation of that fundamental knowledge. So the boundary between the process of origination and the process of development is changing, and clarifying itself. In this way, the analogy with media businesses becomes closer. There will be increasing tension over attempts to appropriate the fundamental knowledge that is the basis of research. The competitive development of the mapping of the genome is the high profile public face of a wide-ranging issue.

Changes in capital markets are also driving changes in the structure of the pharmaceutical industry. Those who are close to fundamental research have greater capacity and determination to extract the rents that are associated with their activities. For example, the person who has probably made most money for shareholders in British business



over the last 50 years is not Richard Branson, or even James Hanson. My nominee for that position is not a businessman at all but James Black, who first at ICI and then at SmithKline was responsible for discoveries which produced extraordinary shareholder value first, directly, for ICI and SmithKline, and second, indirectly, for Glaxo. Black was content to do that for what would by current standards be regarded as an extremely modest salary. While he is a comfortably off man, he is not what my friends in the City would call seriously rich.

In the framework I described above the economic rents generated by Black's activities mostly accrued to the companies where he was employed. We should not be surprised that that was what happened in the early stages of the development of the modern pharmaceutical industry. No one then envisaged the magnitude of the rents that such abstract science could create. In many ways the remarkable thing – and it did not happen often in the development of British business immediately after the Second World War – was that ICI was able to attract people of Black's ability to undertake industrial research.

The trend is for the originators of ideas to retain a more substantial part of the economic rents they generate. The growth of venture capital and private equity has made it possible for individual innovators and small teams to capture the rewards of their activity, in a manner which was possible a century ago but which seemed to have died as the modern economy became dominated by large corporations. A more individualistic society has reduced the force of public service as a motive, while people with exceptional scientific talent can hardly have failed to notice the large returns which investors in some pharmaceutical companies have obtained and the very substantial remuneration that executives who run pharmaceutical businesses have received. Changes in the moral climate have made it far more acceptable for individuals to expect a large share of the rents they create; changes in the business climate have made it far more possible for them to do so.

So the rents which accrued in such large measure to some major pharmaceutical companies in the centre of the value chain in the post-war era come under attack both from the front and the rear. The

pharmaceutical majors' share of these rents is under pressure from those who are closer to the production of fundamental knowledge. These firms must license or sell knowledge from spin-off companies or buy the spin-off companies themselves. At the same time, purchasers – governments and intermediaries – are increasingly organising themselves to quarrel over the distribution of rents.

So the rationale for vertical integration seems to diminish. At first sight, this seems paradoxical: how can I talk of a decline in vertical integration when we see every day a process in which major pharmaceutical companies buy and invest in research businesses and in research sponsorship. But there is no paradox at all: this is also precisely what publishers do. No one should anticipate that these transactions will eliminate independent research, because new focuses for it will emerge as others disappear. It is like a computer game: as soon as you zap the players on the screen, more come over from the left-hand side. They will keep coming.

The future I am describing for the major pharmaceutical companies is a role analogous to publishers: the providers of marketing, finance, selection and coordination skills. If that is right, there should probably be fewer companies than in the days when there was more need for vertical integration, in which companies could differentiate themselves more effectively by their different capabilities. But less differentiation means lower profitability. There will be fewer rents available and, as part of the same process, these rents will come under pressure from those at both earlier and later stages of the value chain. It is hard to imagine that the pharmaceutical industry's traditional position at or close to the top of the profitability league can be sustained.

It is one thing to anticipate the future. It is quite another to act appropriately with the right strategy at the right time. We hear much today in business strategy about the importance of correctly predicting changes in industrial structure. Yet the lesson of business history is that it is rarely the case that people who saw the future more clearly than others in their particular business were most successful in building sustained, competitive advantages.

Take the restructuring of AT&T after the break up of the company in the early 1980s. AT&T announced that they saw the future of their business as lying in the convergence of computing and telecommunications. They were right. They were far more right than anyone could have then reasonably imagined. What they actually did in pursuit of that strategy was to buy a computer company called NCR – a business they disposed of five years later at a loss. Although AT&T's vision of the future was absolutely right, the company is not a major player in that convergence.

It is still worth visioning the future. The restructuring I have discussed here will take place over decades not years. In that timeframe, predictions of which companies will survive and who will take the lead are difficult, if not impossible, to make. We need to think about how technological and market changes are affecting the structure of all our industries. But we should not think that success in doing that is the source of competitive advantage. Competitive advantage comes with the rents that can only be earned from scarce factors and distinctive capabilities.

## Chapter 2

# Global Oligopoly, Regional Authority and National Power: Crosscurrents in Pharmaceuticals Today and Tomorrow

LOUIS GALAMBOS

It is difficult these days to avoid thinking about the global economy. The vast number of books and articles that discuss the pros and cons of the globalization process is truly heartbreaking to any scholar determined to keep up with the literature on this aspect of political economy.

To some, the proper response to these developments is a weary 'ho hum'. It has happened before, this line of reasoning goes. The sceptics, drawing on statistical evidence of world flows of trade, investment and labour from the nineteenth century, maintain that contemporary levels of economic interdependence are by no means historically unprecedented. In their view, globalization is a myth. It is, moreover, a myth with a clear purpose, that of rationalizing a world economy in which a sharp north/south split and traditional economic inequalities are being sustained. By accepting the myth, we are left with little choice but to accept the policy dictates of Chicago School economics.

Arrayed against the sceptics are the 'hyperglobalists', who see nation-states as outmoded, even 'unnatural', and applaud 'the emergence of a single global market and the principle of global competition as the harbingers of human progress'. These are the words of authors Held, McGrew, Goldblatt, and Perraton, whose book *Global Transformations* provides one of the best available excursions through the vast literature and often contradictory data of globalization. The 'hyperglobalists' look to a future in which the traditional nation-state will no longer hold a central role in the world political economy.

If you do not want to seem 'hyper' and you are too positive to be a 'sceptic,' you are not left out of the analysis by these four authors (who come, incidentally, from four different academic sub-disciplines). Their middle position, which is the position of this paper, is that of the 'transformationalists'. The transformationalist sees



globalization as 'a powerful transformative force', which is changing our most basic economic and political institutions. In their account and mine, however, the direction of change is a 'contingent historical process'. It is this process that is explored here, with particular but not exclusive reference to our main subject, the pharmaceutical industry.

### **Global oligopoly**

One of the most important transformations taking place in pharmaceuticals and many other industries in the recent past is the trend toward global oligopoly. The original subtitle for the OHE conference was 'consolidation or competition', implying a choice between one or the other. In the final version, however, that subtitle has been changed to 'consolidation and competition'. The change is telling, allowing for an environment of both consolidation and competition.

There is considerable evidence that consolidation in the 1980s and 1990s has changed the structure of the industry decisively. The Pfizer/Warner Lambert combination has been finalised and the Glaxo Wellcome/SmithKline Beecham deal finally closed. Monsanto is joined to Pharmacia & Upjohn, as is Zeneca Group to Astra AB, Hoechst to Rhone Poulenc, Ciba Geigy to Sandoz, and Bristol Myers to Squibb. While the pharmaceutical industry has lagged far behind other modern, high tech industries in the process of consolidation, it has been rapidly catching up during the last two decades. Oligopoly in various therapeutic categories of medicines is a reality.

The biotech industry, which seemed for a time to move things away from the common pattern of twentieth century industry, or at least of high tech industry, has experienced its own form of consolidation with pharmaceuticals in the recent past. For the first time in the past 100 years or so, pharmaceuticals is following the same pattern of structural evolution as other leading industries, including those in metals, industrial chemicals, automobiles, electronics (software and hardware) and financial services, to mention only a few.

So why did pharmaceuticals not evolve decisively toward national oligopoly during most of the twentieth century; and why is it now



rapidly shifting toward global oligopoly? We can start to provide tentative answers to both of these questions by exploring the special role and nature of product innovation in this industry and its relationship to realized and potential economies of scale and scope.

From the perspective of innovation, there have been four rather clearly defined eras in the industry's development since the early twentieth century. During the first era, which ended in the early 1930s, the pharmaceutical industry had three important characteristics: a relatively low level of scientific knowledge; batch production with few opportunities for economies of scale; and economies of scope only in that part of the industry synthesizing compounds along lines perfected in the German industry. For much of the second half of the nineteenth century, the search for synthetic substitutes for natural substances was central to pharmaceutical innovation. During the early twentieth century, the link to natural substances began to give way to the use of animal models in a relatively random search for chemical entities effective against disease.

During the second major era of discovery, which extended from the 1930s through to the 1960s, advances in organic chemistry made a higher level of scientific innovation possible despite the fact that there was still little understanding of the disease process or the precise targets of therapeutic intervention at the molecular level. There were now greater opportunities for economies of scale in the production of pharmaceuticals, as well as opportunities to benefit from economies of scope due to the importance of building and maintaining a first-rate research establishment with capabilities that could extend across a broad range of therapeutic categories. While a relatively small number of leading organic chemists could still run a highly successful laboratory employing hundreds of less talented researchers, the nature of the economies of scope in R&D began to lead toward a higher degree of concentration in particular therapeutic categories. Dominant firms within categories began to emerge on the basis of their capabilities in R&D, as well as in distribution. This was true in antibiotics, where Pfizer established a powerful position on the basis of its capabilities in fermentation chemistry, as well as for more standardized products such as vitamins – consider Hoffman-La Roche's dominance in this market.

Product innovation was so crucial for success during this second era that it seems to have overshadowed a drive to realize scale or scope economies that characterized structural evolution in many other industries. The beginnings of concentration can be traced to the beginnings of a higher level of scientific capability in drug discovery and to the related improvements taking place in pharmaceutical distribution but the goal was not large, dedicated facilities, at least not for human pharmaceuticals<sup>2</sup>. In the production of drugs still covered by patent, improvements in the efficacy of the therapies worked in the opposite direction, fostering modular plants that could be quickly shifted from one product to another. Production runs were not going to be so long any more.

In the third era of pharmaceutical innovation, during the 1970s and 1980s, when biochemistry and enzymology began to reshape the industry by drastically altering the innovation process, these trends accelerated. Instead of making the established style of medicinal chemistry obsolete, the new medical sciences forced firms that desired to remain at the industry's cutting edge to maintain their existing capabilities while adding new personnel and new specialties to their laboratories. As enzyme inhibition became central to the process of discovery, scale and scope efficiencies in pharmaceutical R&D steadily became more important. The contest to be first or second to market became more intense, and the requirements of successful marketing and sales in now global markets began to drive merger and acquisition activity throughout the industry in the 1980s. Regulatory and distribution capabilities also became important chips to play in consolidation or in the development of strategic alliances. In the very large US market for prescription drugs, health maintenance organizations and pharmaceutical benefits managers (PBMs) restructured the wholesaling and retailing of drugs. Today, the leading PBM (Merck-Medco) operates an automated pharmacy that can dispense more than 5,000 prescriptions an hour!

Close on the heels of targeted enzyme research came molecular genetics and rDNA technology, followed by combinatorial chemistry

<sup>2</sup> Developments in the agricultural wing of the industry were different.

and bioinformatics. Again, the new capabilities had to be added to and blended with the existing matrix of scientific talent and programmes. It is little wonder, therefore, that the large pharmaceutical firms sought licensing and other alliance strategies during the first phase of the biotech revolution in medical science. This was the first wave of change since the 1930s which was not initially dominated by the large pharmaceutical firms. In fact, these companies appeared for a time to have lagged behind their smaller biotech competitors in the process of innovation employing the new science and technologies. Galambos and Sturchio (1998) have written on the issue of why major companies entered these technological areas relative late and have argued that most of the firms were still reaping tremendous benefit from the prior era of research. At the time, it was not clear how biotech was going to pay off. Some people are still not clear today exactly how it is going to pay off and how much.

Over time, however, superior resources and economies of scale in the regulatory process, production, and especially in global distribution, allowed the large pharmaceutical companies to enhance their own capabilities in biotech and to bring the small specialized firms into their orbits through a variety of strategies. These included close strategic alliances, licensing agreements and acquisitions, which have together transformed the biotech sector in recent years. Here too the pattern of global oligopoly in therapeutic classes seems to be the way of the present and future.

To many, oligopoly along these lines might seem to present a threat to the public interest, but the history of this industry, and indeed of most of the high tech industries in the world, suggests otherwise. In recent history, all of the industries that have driven growth have been highly concentrated. Competition has been changed by consolidation, but certainly not eliminated. Oligopolistic or strategic competition has sustained innovation and promoted operating efficiency over the long run. Mainstream, industrial organization theory suggests that we should be suspicious of oligopoly, but the economic and business history of the twentieth century indicates otherwise. The dynamics of innovation have been particularly evident



in pharmaceuticals, an industry in which R&D is extremely expensive, introduces substantial risk and takes place over a very long period of time. By means of consolidation and the development of oligopolistic industrial structures, firms have been able to work with these conditions. There is no reason to believe that the economic performance of global oligopoly in pharmaceuticals will be significantly different than that of national oligopoly has been for many decades (Galambos, 1994).

### **Regional authority**

While the industry is thus becoming increasingly global, the most important change in the political economy of pharmaceuticals appears to be the growth of regional authority. Three major regional entities have emerged or are emerging: one in Europe, another in the Western Hemisphere, and a third in Asia. Most completely developed to date is the European Union, which has already become a powerful entity, guiding the regulatory, antitrust, and fiscal and monetary policies of its member states. Now, and for the foreseeable future, the executives guiding the development of any global pharmaceutical firm must give substantial consideration to the goals and specific policies of an authority controlling access to one of the largest markets in the world.

The regional politics of the Western Hemisphere are still in an early stage of development. The North Atlantic Free Trade Area (NAFTA) has brought the US, Canada, and Mexico into closer economic alignment, and there is potential to extend that agreement to other nations in the hemisphere. 'Dollarization', which is going on right now, is likely to become the first step in the next wave of change. It is under consideration in a number of Latin American countries, all of which are seeking to promote trade and investment by removing doubts about the value of their respective currencies. The swiftness with which currency fluctuations take place in the present global economy is promoting serious consideration of 'dollarization', just as it is promoting serious reconsideration of the role, structure and governance of the International Monetary Fund.

Least adumbrated and institutionalized at present is the Asian regional bloc. It is not clear which of the leading Asian economic powers, Japan or China, will become the centre of this regional entity or whether the Asian pattern of regionalization will be similar to that of either the EU or the Western Hemisphere economic region. Rapid market integration, rather than strong institutional integration, is currently the most significant centralizing force in this third region, and that phase of development may continue for several decades. If the EU and the Western Hemisphere entities continue to coalesce, however, they will place increasing pressure on the Asian nations to seek closer economic relations with one another and to achieve bargaining power against Europe and the Americas.

Regionalization introduces one of those important 'contingent historical processes' mentioned at the beginning of this paper. While pharmaceutical firms are rapidly coming up to scale for global competition and have to a considerable extent coalesced with the new biotech sector, the political side of political economy is moving far more rapidly toward regional than global orientation. The rift can be seen in regulatory as well as antitrust and subsidy policies, where the contrasting styles of the EU, western hemisphere and incipient Asian systems have the potential for generating significant inter- and intra-bloc struggles in the next few decades. This may merely be a transitional phase in institutional development, but if that is the case, one would expect to see more substantial signs of change in global institutions than is currently the case. The beginnings may be there in the structure of international organizations created after World War II, but I cannot see much creativity there right now. They seem to be fighting a holding action.

### **National power**

Instead, what seems most evident is the manner in which national goals and national power, leading elements in the traditional world of international affairs, have retained their hold on our imaginations and our perceptions of the world. In the US at the present time, one of the hottest political issues is the price of pharmaceutical products. The issue is highlighted by the contrast between prices in other coun-

tries and in the US market. One way to look at this issue is in global terms. The US is a wealthy nation that, since its remarkable recovery in the 1980s and 1990s, has one of the most successful and competitive economies in the world. Surely its citizens can afford to pay higher prices than citizens in New Zealand for their pharmaceuticals. Since the margin between US prices and those in other countries helps enable the US industry to crank out a majority of the world's innovative pharmaceuticals, it could also be argued that this imbalance in price levels helps the US economy. It attracts foreign investment in pharmaceuticals and helps sustain the US's most innovative pharmaceutical firms. The New Jersey economy would certainly suffer without them! So too would all of the US patients who benefit from new therapies.

But of course the rub is that patients in New Zealand benefit from the same new therapies at a lower price. Here the political imagery is extremely powerful. We see a grey-haired American couple tottering into the pharmacy. They are clearly living on social security and they are going into the local drug store and shelling out a large percentage of their monthly income to buy the newest and most effective drugs – maintenance pharmaceuticals – which their physicians have prescribed. With that image in mind, it does not take much imagination to come to the conclusion that there is a free rider problem in global pharmaceuticals. Is it equitable to force the elderly American couple to pay for the innovations that benefit patients in New Zealand and much of the rest of the world? The nationalistic answer is of course 'no'!

Having said 'no' loudly, we are faced with two possible political responses, one global and one national. Hoping to preserve and encourage a highly innovative pharmaceutical industry, nations around the world could 'see the light' and move their health care systems toward the US semi-market model and thus equalize global conditions. There would be some secondary benefits from this choice, including in the national case a more innovative and thus globally competitive pharmaceutical sector in nations other than the US. But the nationalistic solution probably has more political appeal. In that case the free riders will continue to ride free and the US will use some



form of monopsony to bring the retail prices of its pharmaceuticals down closer to global averages. This is what appears to be happening right now (Galambos, 2000).

There are other ways in which the tensions between globalism, nationalism, and regionalism are being played out in pharmaceuticals. Within the EU, there is substantial interest in spurring innovation in this and other high tech, high science industries. That goal is laid out very clearly in the British government's 1998 White Paper on competitiveness and the subsequent report 'Our Competitive Future: UK Competitiveness Indicators 1999'. Read from a US perspective, both reports are extremely interesting. It is of course heartening to see so much attention in both documents devoted to the US. In that regard, the British reports closely resemble US commentaries from the 1970s and 1980s, which spent many of their pages looking over their shoulders at what the Japanese and Germans were doing. But that is no longer true in the US, which seems to have found ways to be competitive without creating a national institution like MITI, the Japanese Ministry of International Trade and Industry.

One of the lessons to be learned from the US recovery is that each nation needs to chart its own distinct path to economic progress, a path dictated by its resources, culture, and political system. Applying that lesson to the British government's reports, one might conclude that they devote too much attention to imitating the US and too little attention to distinctive British factors, including those that have made British services so successful in global competition.

The British reports also use a national, not a regional EU approach to innovation. Thus, one assumes, each of the national economies will strive to duplicate the US experience in recent years. Instead of specialization framed in terms of national competitive advantage, they will, in pharmaceuticals and other advanced industries, each try to mimic the much larger US innovation system. Currently, several EU nations seem to be adopting this goal in biotechnology. Fearful of being left behind, Germany is subsidizing the biotech sector, playing catch-up with a US sector that is very well advanced by now. In this case, too, a private sector is being promoted even though the kind of

research – university based basic research – that fostered US biotechnology is much smaller and less diverse in Germany than in its US counterpart.

The point is a simple one. The traditional approach to national competition is still very much alive – a sort of national Olympics in economics – and is likely to remain an important factor shaping public policy and economic performance for many years to come. Within the EU, there is thus tension between the regional policy of free trade and regulation of drug adoptions, and the retention of national systems of purchase and pricing for pharmaceutical products. This is the kind of on-going tension that I believe is characteristic of our current day, global political economy. While we have seen national power conditioned by, for instance, the activities of the World Trade Organisation (WTO) and the EU, we are a long way from a situation in which we can use words such as ‘atrophy’ to describe the nation-state. Nation-states still have all of the armies and, as long as they do, they are unlikely to consider themselves ‘unnatural’ forces in a competitive world system.

## **Conclusion**

The ‘transformationalist’ perspective on pharmaceuticals today and tomorrow thus looks to a long transitional phase in which regional, rather than global, institutions become the most important factors shaping the political environment for economic activity in this industry. In each case, however, regional institutions will have to fight their way to power, ridge by ridge, issue by issue, against national institutions and leaders who have shown little inclination to yield their power gracefully. There will also continue to be tensions between regions. We do not currently have effective political institutions for resolving problems like the free-rider issue mentioned earlier. Nor do we have the means of developing common approaches to antitrust and regulatory problems.

If increasing regionalization does not foment intense struggles between these three large blocs, we may see the long period of rapid economic expansion envisioned by the most ardent supporters of the



WTO and free trade. In the meantime, we will have to deal with the tensions that arise between global oligopoly, regional authorities and still powerful nation-states.

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## Chapter 3

# The Role of the External Network in the Pharmaceutical R&D Process: Alliances and Licensing Strategies

HANNAH KETTLER

This paper addresses two key issues: the integration of biotechnology within the pharmaceutical industry's R&D process; and the impact of these new technologies and methods of discovery on the structure of that process. I turn an assertion made by Louis Galambos in the preceding chapter into a question: are the pharmaceutical and the biotech industries really coalescing? The ideas and data included draw on a study underway by Gabby Ashton of CMR International and myself that looks at the biotech and the pharmaceutical companies' perceptions of the interactions between their two industries. We have survey results from 26 research-oriented pharmaceutical companies and interview material from 20 public biotechnology companies in the UK and the US<sup>3</sup>.

In general there is considerable evidence that points towards increased interaction between the pharmaceutical and the biotech industries. The 'so what?' questions are more difficult to assess. We consider two. First, did the major pharmaceutical companies that moved early, with significant commitment, into the biotech industry, gain first mover advantage in terms of new products and R&D productivity? Or is this industry one where late entrants, by watching the field and learning from it, have been able to leap-frog the leaders? Second, by learning how to interact with the biotech companies through alliances and licensing deals, have pharmaceutical companies developed a new, more effective way of conducting R&D? This learning is potentially important if the pharmaceutical industry is in fact moving towards a new model of R&D which depends on

3 The first report from this study, the CMR International publication *External Collaboration and Licensing in Pharmaceutical R&D* by G.A. Ashton, H.E. Kettler, E.J. Saunders and J.A.N. McAuslane, was published in May 2001.

extensive use of external networks and it suggests that companies may gain a structural as well as a scientific advantage by moving into biotechnology.

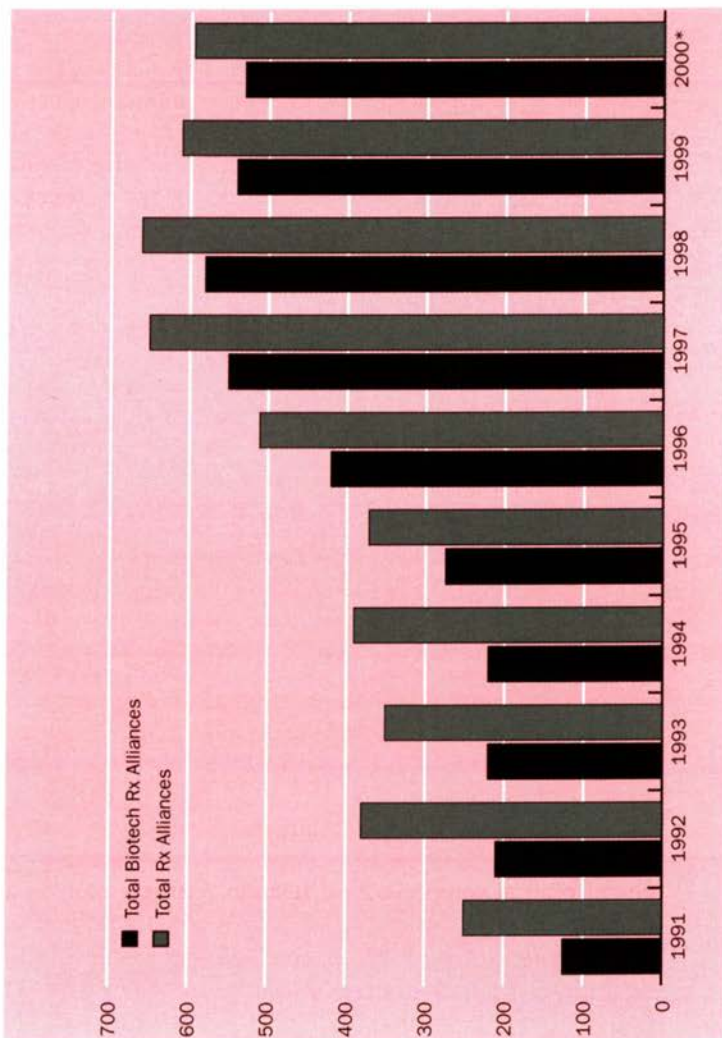
First let us consider the evidence of the interaction between the two industries. Pharmaceutical companies spend somewhere between 20 and 30 percent of their research budgets outside their in-house capacity and a considerable share of that goes towards alliances with biotechnology companies. Pharmaceutical companies responding to our survey spent about 15 percent of their discovery budgets on biotech alliances. Figure 3.1 shows an increasing trend in alliances throughout most of the 1990s, with some levelling off towards the end of the decade. What is not clear is whether this levelling off represents a turning point, or just a temporary blip in the upward trend due to a spate of mergers between the large pharmaceutical companies that are involved in many alliances. If those companies that underwent mergers between 1996 and 2000 are excluded, the number of alliances initiated annually remains uniform.

There is evidence to suggest, again from our survey, that the major pharmaceutical companies<sup>4</sup> plan to continue to spend a large amount of their budgets on alliances. Three-quarters of respondents plan to increase the share spent on alliances over the next five years.

Those alliances are concentrated at the early stages of the R&D process. Figure 3.2 shows that the share of alliances that were at the discovery end of the R&D process increased from 42 percent at the beginning of the 1990s to 62 percent in 1998. According to our survey, which focused on discovery alliances only, the major companies use alliances mainly to identify and screen the development of new products. 'Other', i.e. small and medium sized pharmaceutical companies, use alliances relatively more at an even earlier stage in the discovery process to conduct exploratory research and provide enabling technologies. See Figure 3.3.

4 The companies in our survey were categorized according to R&D spending in 1999. *Major* companies spent more than \$1 billion on R&D that year, *medium* companies spent between \$300 million and \$1 billion and *small* companies spent less than \$300 million (Ashton et al., 2001).

Figure 3.1 Pharmaceutical alliances, 1991-2000



Note: \*2000 estimated based on January-April data.

Source: Windhover Information Inc. (2000)

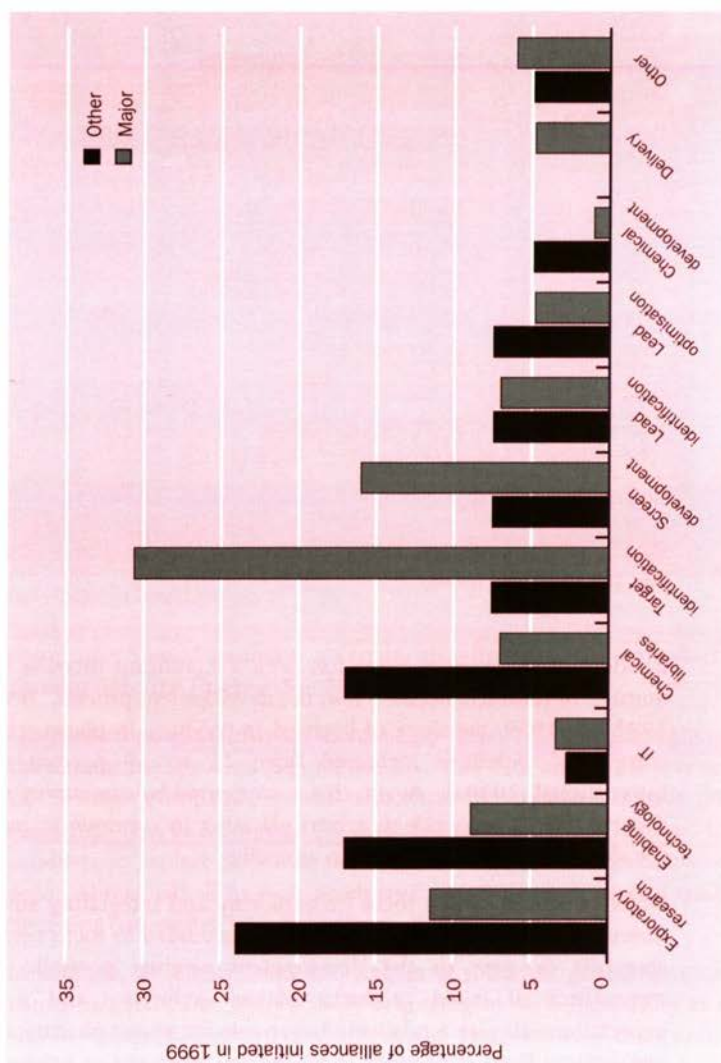
Figure 3.2 Alliances between the top 20 pharmaceutical companies and biotech firms by R&D stage



Source: Recombinant Capital (2000).

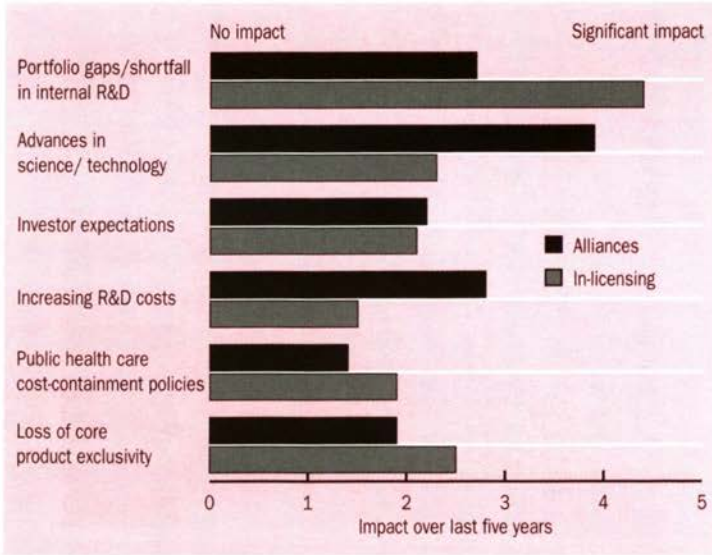


Figure 3.3 Alliance goals of pharmaceutical companies



Source: CMR International.

Figure 3.4 Drivers of alliances and in-licensing activities

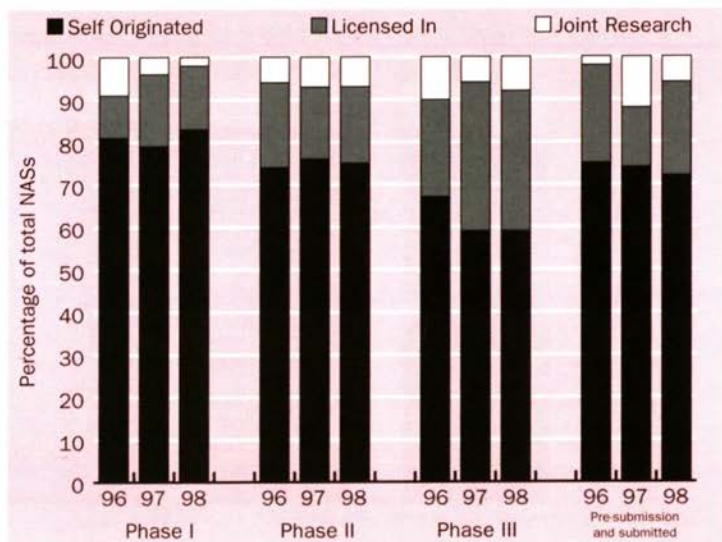


Source: CMR International (2000b).

In addition to alliances, there has been a significant increase in the number of products licensed into the development process. Between 1992 and 1999, the share of licensed-in products in pharmaceutical companies' pipelines increased from 11 to 20 percent (CMR International, 2000a). Again, this is supported by our survey where the majority of respondents report planning to continue to increase the share of products licensed-in annually.

Unlike alliances, which focus on exploring and integrating advances in science and technology, licensing-in has tended to focus on filling shortfalls or gaps in the development product portfolio. The importance of failed products, patent exclusivity and investor expectations all play a relatively larger role for major pharmaceutical companies. There is pressure to fill the gap when major products are about to go off-patent and there is also an expectation that major

Figure 3.5 Trend in origin of major companies' new active substances (NASs) by phase of clinical development



Source: CMR International (2000a).

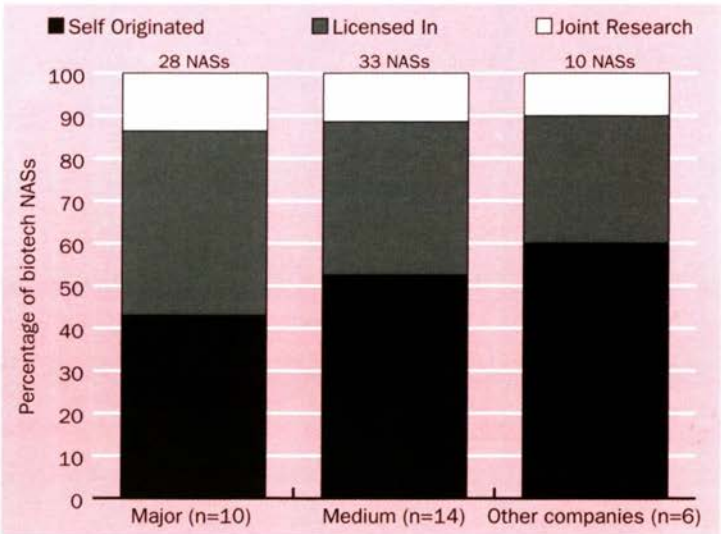
companies should maintain a certain growth rate in new products coming onto the market. See Figure 3.4.

Licensed-in products play an increasingly important role throughout the clinical trial process. See Figure 3.5. In 1998, almost 40 percent of the major companies' products in Phase III originated outside the company. This fact supports the idea that companies use licensed-in products to replace in-house product failures and fill unanticipated gaps. About half of biotech products moving through clinical trials by major companies have been licensed-in (Figure 3.6).

In addition to alliances and licensing-in of products, pharmaceutical companies have also been actively acquiring biotech companies as a way to move into the biotechnology arena. The number of companies acquired increased over the late 1990s (Figure 3.7). Spending on biotech mergers and acquisitions peaked at \$2.3 billion in 1998.



Figure 3.6 Origin of biotech new active substances (NAS) by type of developer

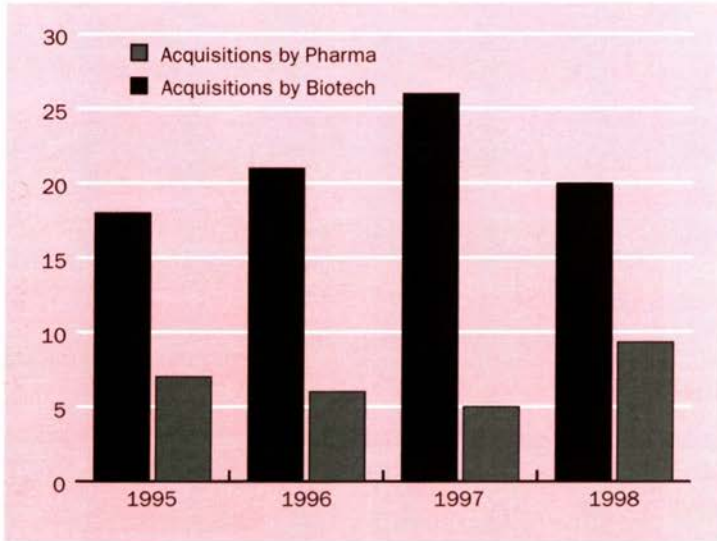


Source: CMR International (2000a).

It is important to keep in mind that different companies use biotech acquisitions for different purposes. Pharmacia’s purchase of SUGEN was focused in particular on gaining access to products in late-stage clinical trials. That compares with Glaxo Wellcome’s purchase of Affymax, which was to integrate a specific range of platform technologies. Roche’s long-term shareholding arrangement with Genentech is a broad alliance that covers technology and products in a range of therapeutic categories.

While there has been a general move towards integrating biotech businesses by pharmaceutical companies, there are considerable differences between companies in terms of the types and sizes of the investments made. The companies initiating the most alliance deals between 1988 and 1998 – Roche, SmithKline Beecham, and American Home Products – are also among the top five in-licensors,

Figure 3.7 Number of announced biotech mergers and acquisitions



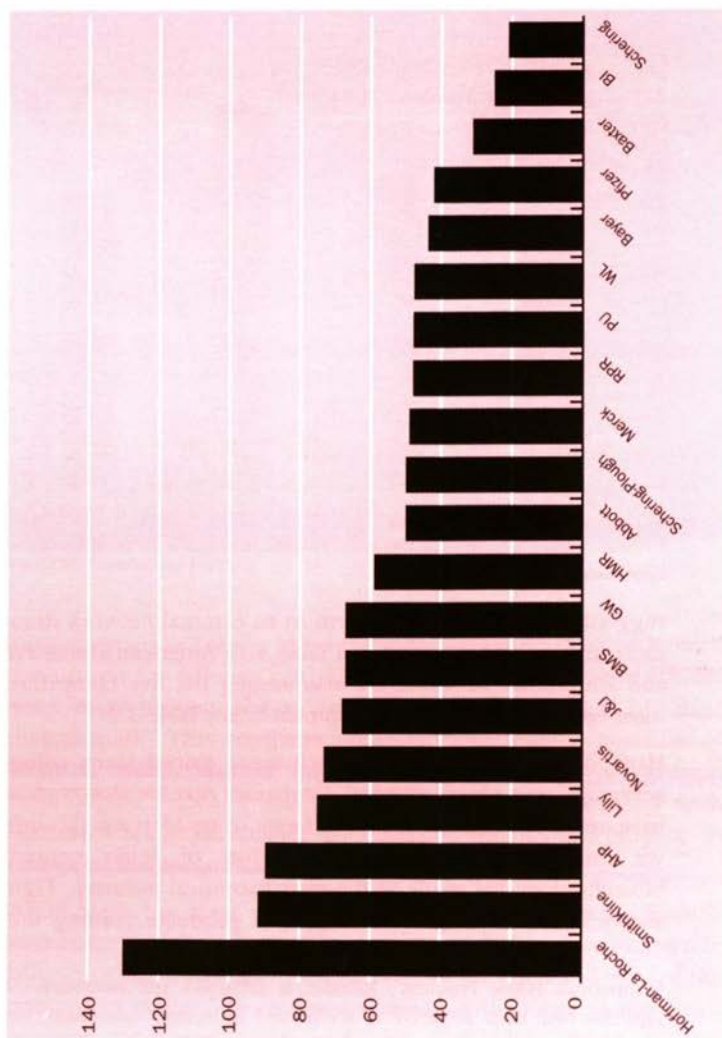
Source: Recombinant Capital (2000).

suggesting a greater commitment to an external network strategy by these firms. See Figure 3.8 and Table 3.1. American Home Products and SmithKline Beecham are also among the five companies with most biotech projects in development<sup>5</sup>. See Table 3.2.

Have first movers into the biotech arena gained some competitive advantage over pharmaceutical companies that are slower movers or have opted not to enter at all? To begin to try to assess this question, we must first explore the question of what contribution biotechnology has made to the pharmaceutical industry. Figure 3.9 shows the increasing rate of biotech products coming onto the

<sup>5</sup> American Home Products', Johnson & Johnson's and Pharmacia's biotech pipelines have been 'acquired' or are housed in biotech subsidiaries. American Home Products, for example, has purchased a controlling share in Immunex and the Genetics Institute and most of its biotech activity is taking place there.

Figure 3.8 Biotech alliances initiated by major pharmaceutical companies, 1988-1998



Source: Recombinant Capital (2000).

Table 3.1 Top five in-licensors, 2000

Company	Number of projects	Percent licensed in
Roche	35	74
SmithKline Beecham	39	72
American Home Products	33	67
Bristol-Myers Squibb	38	66
Boehringer Ingelheim	30	60
Average of top 5 companies	35	68
Average of top 30 companies	31	34

Note: Includes biotech and non-biotech projects.

Source: CMR International (2000a).

market. They made up 22 to 25 percent of all new molecular entities (NMEs)<sup>6</sup> launched worldwide in 1998 and 1999. A handful of these products are among the top selling medicines. See Table 3.3<sup>7</sup>.

There is a clear division of labour in the biotech industry between the specialised biotech companies and the traditional players, the major pharmaceutical companies. Biotech companies and pharmaceutical companies have each discovered about 45 percent of the biotech products now on the market. Academic and public research institutions discovered the remaining 10 percent. But biotech companies have brought to market only 20 percent of all biotech products, or fewer than half of those they discovered. Thus, the majority of biotech products on the market are the result of a network of cooperative partnerships with pharmaceutical companies and other organisations.

Biotech companies' contribution to the pharmaceutical industry extends beyond biotech products however, as investments into bio-based science and technologies have had spill-over effects into R&D

6 NMEs include both chemical and biology based products (NCEs and NBEs respectively).

7 It is worth noting that these top sellers are also among the first biotech products to have come to market. Further research is needed to establish the key differences in development times, success rates, scientific barriers and market prospects between these early successes and products coming onto the market now.



Table 3.2 Biotech projects in major pharmaceutical companies' development portfolios

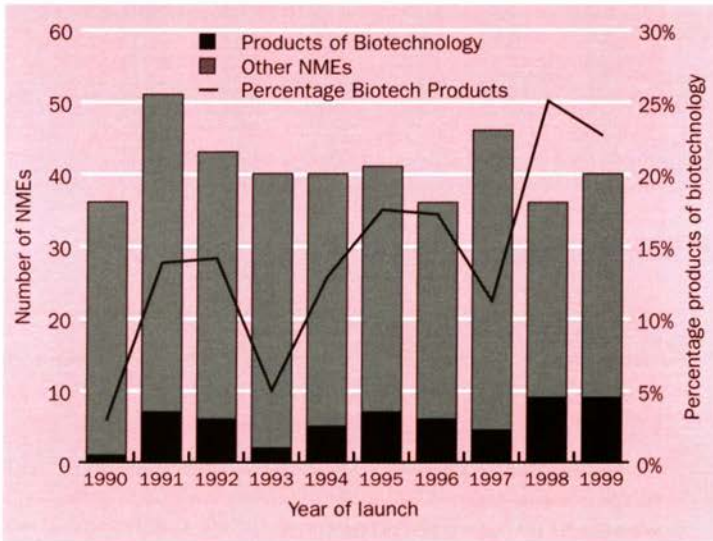
Company	Number of disease areas	Number of projects
AHP*	6	14
Serono Labs	8	14
Schering Plough	7	12
Genentech	6	11
SKB	2	10
Chiron	6	8
Pharmacia*	4	8
Pfizer*	5	6
J&J*	4	4
Aventis	2	3
Merck	3	3
Roche*	2	3

Notes: Seven other top 20 pharmaceutical companies have 1 or 2 biotech projects in development.  
 \*AHP includes Immunex, Genetics Institute and Wyeth; Pharmacia includes Searle and SUGEN; Pfizer includes Agouron and Warner Lambert; J&J includes Centocor; Roche includes Boehringer Mannheim.  
 Source: PhRMA (2000).

for new chemical entities (NCEs) as well. The organisation Recombinant Capital estimates that biotech companies have contributed to at least 30 percent of all NMEs (NCEs + NBEs) launched onto the market in 1998 and 1999.

So, given that the biotech sector is making a small but growing contribution to the industry as a whole, have the first movers had any advantage by way of their investments in biotech? More generally, do companies gain advantages by applying an external rather than entirely in-house approach to R&D? Table 3.4 shows the ranking of companies by number of products coming on to the market between 1962 and 1998. The first column was put together by DiMasi (2001). He was looking strictly at NCEs. In column two, the new biotech products have been added to the product totals. According to the new rankings, for NCEs plus NBEs, Roche, Aventis and Johnson & Johnson have been able to boost their positions in terms of numbers

Figure 3.9 **Biotech products and other NMEs launched worldwide, 1990-1999**



Source: CMR International (2000a).

of products by making an investment and bringing biotech products to market. Further work is needed to establish whether these additional products have translated into higher sales and profits as well.

Less clear is the issue of whether pursuing an external network strategy brings clear benefits. For the case of NCEs, DiMasi finds that companies that rely on self-originated output as opposed to licensed-in products out-perform their competitors in terms of products to market. These companies with 'in-house strategies' have also dominated three of the five largest therapeutic categories and earned 75 percent of the FDA's priority approvals issued in the 1990s. While licensing-in may seem a strategically weak position for NCEs, these findings may not carry over to biotech products, given that more than 60 percent of the biotech products currently on the market are the result of partnerships.

Table 3.3 Sales of top NMEs – top 10 NCEs and top 4 NBEs compared

Product	Company	1998 global sales, \$m
Losec	Astra	4,444
Zocor	Merck	2,945
Prozac	Lilly	2,588
Norvasc	Pfizer	2,331
Lipitor	Warner Lambert	1,926
Renitec	Merck	1,784
Seroxat	SKB	1,687
Zoloft	Pfizer	1,668
Augmentin	SKB	1,547
Claritine	Schering Plough	1,459
<b>Epogen</b>	Amgen	1,380
<b>Neupogen</b>	Amgen	1,120
<b>Procrit</b>	OrthoBiotech (J&J)	1,000*
<b>Humulin</b>	Lilly	959

Notes: \*Estimated sales.

Products in bold are NBEs.

Sources: Grindley and Ogden (1999) and IMS (1999).

The evidence available about the success of alliances to move products forward is also mixed. According to CMR International, only five percent of products launched on the market between 1995 and 1999 were the product of joint research between biotech and major pharmaceutical companies. It is important to point out, however, that most alliances do not focus exclusively on bringing one product to market and therefore this figure may understate the extent that alliances have successfully produced products.

According to our survey, 32 percent of all alliances fail and for the most part those failures are due to problems with the science and technology that were unanticipated when the alliances were undertaken. But according to Andersen Consulting this failure rate is low compared to other industries: 'Success rates for alliances are higher in pharmaceuticals (>60 percent) than in just about any other industry, in part because of the high volume of similar and relatively simple deals'

**Table 3.4 Top producers of NCEs and NBEs by current parent company, 1999**

	<b>NCEs</b>	<b>NCEs + NBEs</b>	<b>Rank for NCEs + NBEs</b>
AHP	45	52	1
BMS	43	43	4
Roche	41	46	2*
Aventis	38	44	3*
P&U	38	39	6
Merck	36	37	8
Novartis	36	38	7
GW	35	36	9
SKB	34	36	9
J&J	32	40	5*
Lilly	31	34	11
Pfizer	27	27	12
SP	21	24	13
WL	21	21	14
Abbott	18	19	15

Notes: \*Companies gaining rank with the inclusion of NBEs.

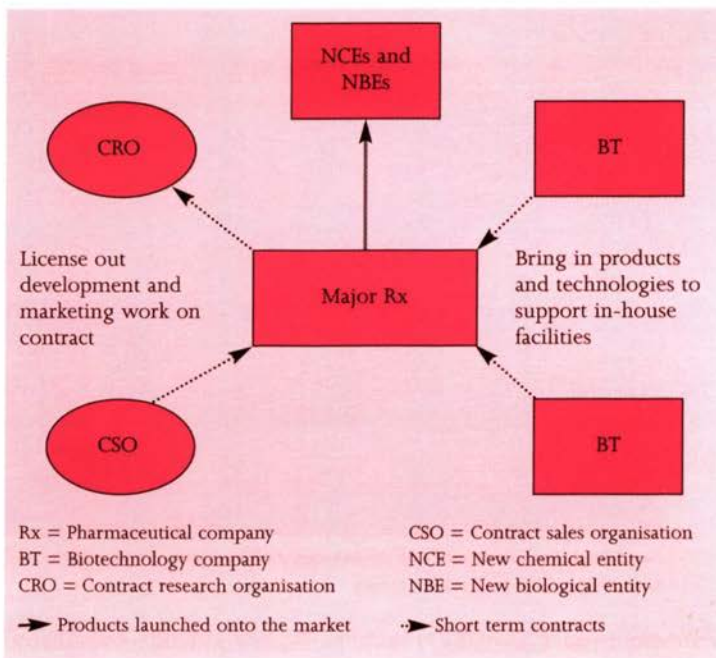
Sources: DiMasi (2001) and PhRMA (2000).

(Andersen Consulting, 1998). Professor Pammolli investigates in detail in the next chapter the comparative merits of the network versus the in-house approach to developing new technologies.

The final question considered here is whether, by learning how to work externally by way of alliances, in-licensing companies are moving towards a new model of R&D. How should R&D best be organized: as a vertically integrated structure or as a horizontal network of independent, specialized units? According to the 'traditional model', illustrated in Figure 3.10, the major pharmaceutical companies use alliances and licensing to catch up with new technologies. But once they have caught up, the major companies continue to be the dominant players, using biotechs and other external entities to fill gaps, learn new technologies prior to then integrating them, and 'cherry picking' the ones that they need to move their own agenda and products forward. So under this



Figure 3.10 **Traditional model**

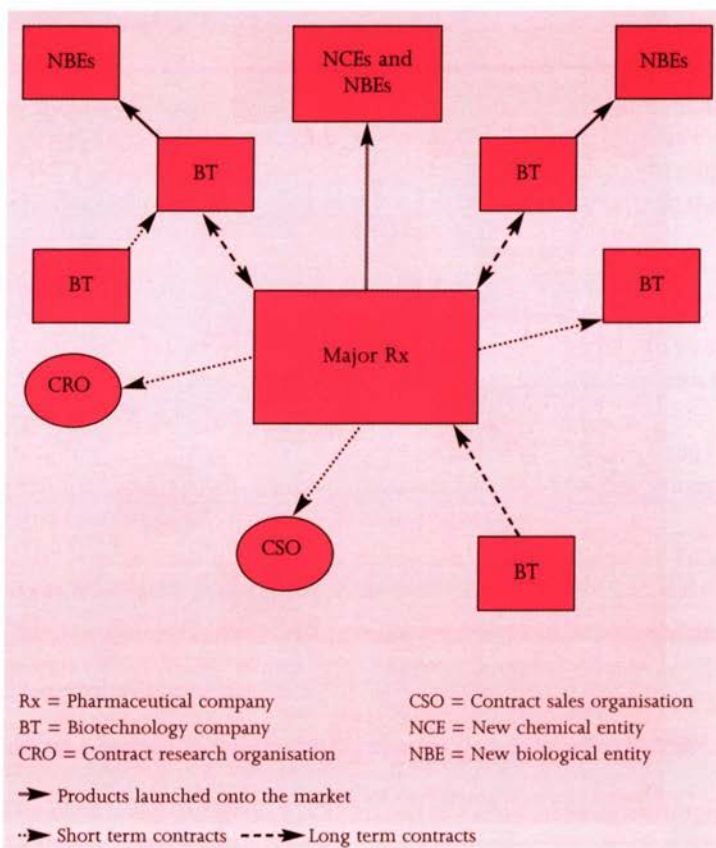


scenario, the large integrated company is capable of learning and maintaining competitive dominance.

A second possible model, which was described by biotech company managers in a number of interviews, is where the major pharmaceutical company continues to be the focus or centre of the network but it establishes long term relationships with biotech companies, either by way of renewable contracts or by acquiring shares in them. Then there is a stable relationship of small discovery entities feeding into the larger development process of the major company (see Figure 3.11).

A third scenario involves a dynamic network. The R&D process might differ depending on the therapeutic category and the product. There are cases of biotech companies developing products, perhaps through

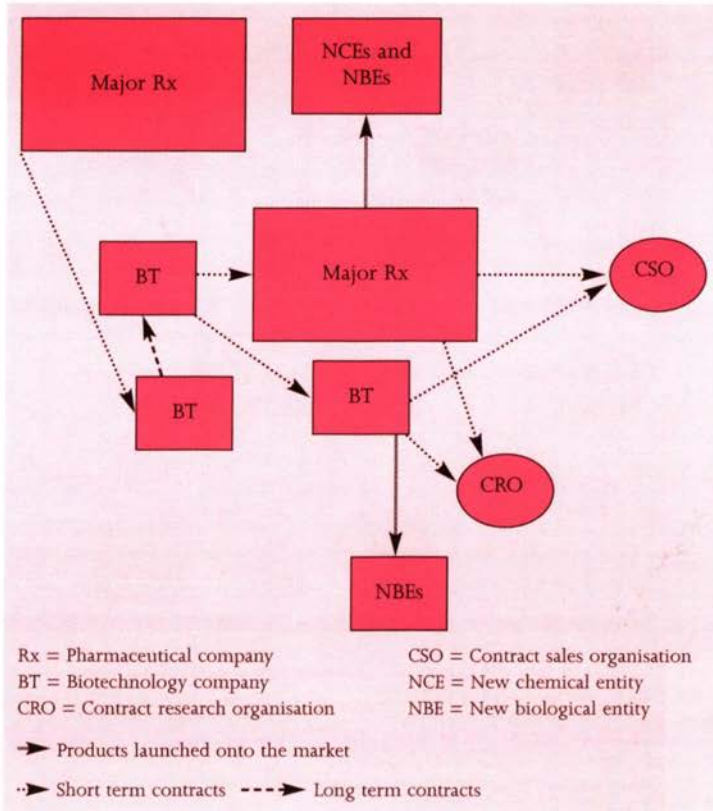
Figure 3.11 **Satellite model**



collaborations or alliances with each other, sometimes with a major pharmaceutical company, sometimes not. In the latter case they rely on contract research organisations and contract sales organisations to do work that major pharmaceutical companies have done in the past (see Figure 3.12).

Our survey results seem to support the second arrangement (Figure 3.11), where there is continued reliance on the external network but

Figure 3.12 **Dynamic network model**



major pharmaceutical companies play the central role overall in coordinating and bringing products through development to market.

In conclusion, there is evidence to point towards the important role of the biotech industry in the process of new pharmaceutical discovery and development, where the biotech industry is defined broadly to include bio-based products as well as platform technologies and genomics. Major pharmaceutical companies are using external networks to move into biotechnology but the extent to

which any one company is externally oriented varies significantly. Some have relied upon acquisition and in-house investment to move into biotechnology. Others continue to pick occasional products that fit into their pipeline, rather than make a major commitment.

What is less clear is the pay-off for companies making a significant investment in biotech and in the external network. More evidence is needed to ascertain whether this way of doing R&D is setting the stage for a fundamental model shift or if it is a short-term arrangement that companies will use to catch up with changes in technology.

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## Chapter 4

# Innovation and Markets for Technology in the Pharmaceutical Industry

FABIO PAMMOLLI and MASSIMO RICCABONI

Empirical analysis of the pharmaceutical R&D process reveals a relatively recent phenomenon of a growing division of labour between the companies and organisations that discover the new products and the companies that develop and market them. In this paper the evolution of this new R&D model is described, as is an explanation for why a market for technologies has developed and how this specific market contributes to economic growth and innovation. To that end we investigate whether R&D undertaken by way of this network, through licence deals, outperforms R&D conducted in-house. The analysis draws on a database of collaboration agreements that were signed at the discovery stage, before the start of clinical trials.

The facts contributing to the development of markets for technology and the division of innovative labour across companies (as opposed to within them) go beyond the specifics of the pharmaceutical sector. In general, these markets for technologies grow ever more prominent with the rise of specialised technology producers and the increased use of outsourcing of technological activities by major companies. But economic theory continues to lag these real world developments.

Drawing on historical fact, the theoretical literature tends to focus on reasons for not having markets for technologies or a division of innovative labour. According to this literature, innovative activities depend on companies realising increasing returns to scale and scope through in-house investments, due to steep learning curves and high fixed costs in the production of technology (Nelson and Winter, 1982; Teece, 1980). Even if scale could be realised by way of numerous contracts instead of in-house transactions, it is argued that these contracts for 'technological knowledge' are difficult to package and write up. There is still a huge debate on what is 'commercial' and what is 'public' about technology (Nelson, 1992). At one extreme, some argue that knowledge is a public good that cannot or should not

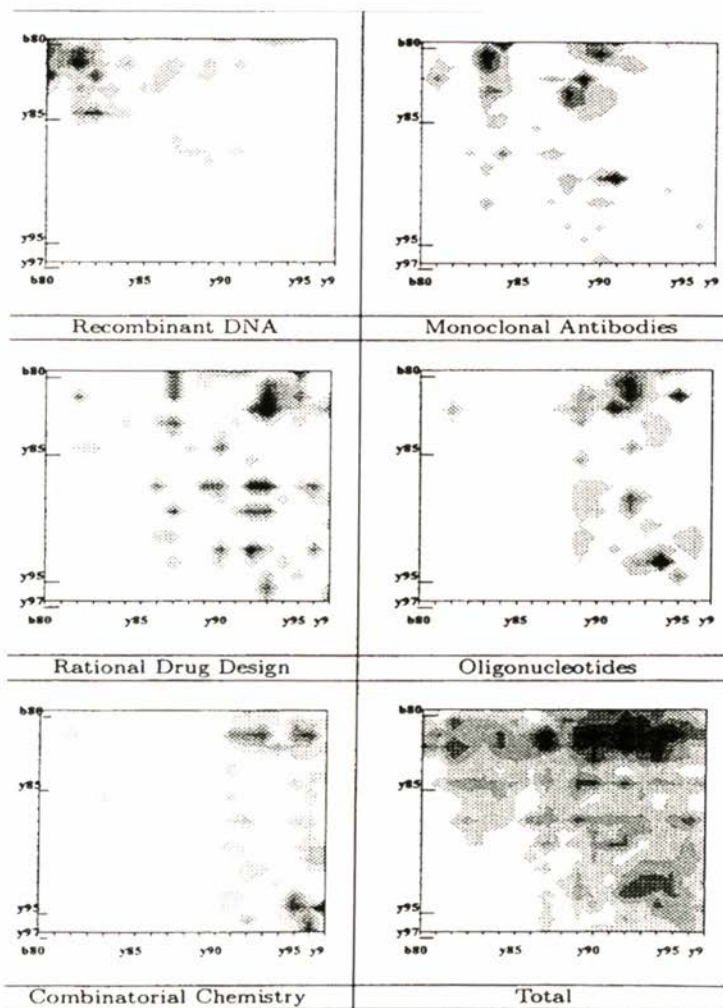
be controlled and patented by a single for-profit firm. Others argue against a division of labour for precisely the opposite reason. As knowledge tends to be tacit and produced in the context of learning environments, it tends to be incubated within a given organisation. As a consequence, a great deal of the technological content has to be revealed in order to convince the potential partner of the effective value of a contract (Arrow, 1962; Teece, 1986).

Our work addresses the literature gap with a detailed analysis of the factors that determine the increasing diffusion of innovative labour in the pharmaceutical industry R&D process (see: Orsenigo, Pammolli and Riccaboni, 2001; Pammolli, Orsenigo and Riccaboni, 2001; Pammolli and Riccaboni, 2001; Riccaboni, 2000). This analysis is based on a data set that tracks more than 20,000 R&D projects over time, covering several hundreds of biological actions and therapeutic classes. It covers more than 1,000 firms worldwide and represents a detailed analysis of the R&D activities carried out within the pharmaceutical industry.

There are two scientific developments that we identify as potential drivers of a division between 'originators' and 'developers' in this industry. One is the increased 'scientification' of R&D information following the molecular biology revolution in the 1970s. The second is the emergence in the 1990s of what we call 'general-purpose technologies', a second wave of technologies that includes combinatorial chemistry and genomics. Specialised technology suppliers can focus on the production and eventual sale of general-purpose technologies that can be applied downstream in the R&D process to a wide range of applications and disease areas.

Figure 4.1 captures the collaborative activity that is taking place in five different technologies. These cases are selected to illustrate specific patterns of collaborations for older and newer technologies. In general, in our analysis, a firm is classified at the moment at which it first subscribes to a licensing contract with another participant in the industry. For each technology, the agreements signed in the 1980s and 1990s are tracked, a total of 9,000 agreements in all. The X-axis shows the date when the originator of the technology in a specific deal entered into the 'network', that is when it made its first collaborative agreement.

Figure 4.1 R&D deals for different technologies



Note: The X-axis shows the date when the originator in a specific deal entered the network, i.e. joined their first collaboration. The Y-axis shows the date when the developer in a specific deal entered the network, i.e. joined their first collaboration.

## INNOVATION AND MARKETS FOR TECHNOLOGY

The Y-axis shows the date when the developer, i.e. the company licensing the product or technology, first entered into the network. Taking an example from recombinant DNA, a deal marked by a dot in the top left corner of that graph would involve an originating company that made its first deal (as recorded by our database) in 1980 and a developing company that also first entered into a deal in 1980. The point does not tell us the date when this specific deal was made, but rather the vintages of the participating companies.

Our technology examples are selected from two major technology regimes that have developed in the industry since the molecular biology revolution. The first regime, including recombinant DNA and monoclonal antibodies, is characterised by firms that are biologically based and enter the industry with a specific technology and a specific set of biological targets. Starting around 1990 we also find the development of a second type of technology, including oligonucleotides and combinatorial chemistry, where the originator firms develop general-purpose technologies.

As a result, our network, which covers both types of technology regimes, includes three kinds of actors. First, we have incumbent firms. These are often major pharmaceutical companies which enter the network (engage in the technology market) as drug developers buying technologies and licensing-in products. Second we have biotech firms that sell molecules which are based on specific biological hypothesis targets and technologies, by way of licensing agreements with these developers. Third we observe, after 1992, the entry of the aforementioned generalist companies which are based on general-purpose technologies. These firms occupy a different structural position within the market for technologies than the other type of biotech firms and their risk profiles are also completely different. In particular, this third set of firms does deals with the established incumbent firms and the product-based biotech companies.

To illustrate the differences in network partners across the types of technologies, compare the deal patterns for monoclonal antibodies and oligonucleotides in Figure 4.1. For monoclonal antibody technologies, almost all the deals are between new 'originator firms'



that enter the market for technology between 1981-1991 and older developers that entered the market before 1985, many of them before 1980. Thus, most of the deals are concentrated in the north west corner of the chart. By contrast, the new originator companies licensing-out platforms based on oligonucleotides, from 1989 onwards, are doing deals with companies that have a range of entry dates from before 1980 right through to companies doing their first deal (entering the technology market) in 1996. Combinatorial chemistry is also characterised by this second kind of deal pattern.

Table 4.1 Top 20 firms/institutions ranked by number of agreements made

Network ranking	Number of ties	Firms and institutions	R&D projects <sup>1</sup>	Sales rank <sup>1,2</sup>
1	145	Novartis	224 <sub>(2)</sub>	1 <sub>3</sub>
2	141	Hoffmann-LaRoche	112 <sub>(12)</sub>	1 <sub>6</sub>
3	88	Smith Kline	152 <sub>(7)</sub>	1 <sub>9</sub>
4	81	Merck and Co	207 <sub>(4)</sub>	1 <sub>2</sub>
5	77	Bristol-Myers Squibb	209 <sub>(3)</sub>	1 <sub>4</sub>
6	74	American Home Products	124 <sub>(10)</sub>	1 <sub>8</sub>
7	69	Lilly	138 <sub>(8)</sub>	1 <sub>12</sub>
8	62	Abbott	93 <sub>(13)</sub>	1 <sub>18</sub>
9	60	Pfizer	77 <sub>(19)</sub>	1 <sub>7</sub>
10	52	Schering-Plough	113 <sub>(11)</sub>	1 <sub>15</sub>
11	51	Pharmacia and Upjohn	174 <sub>(6)</sub>	1 <sub>11</sub>
12	46	Glaxo Wellcome	204 <sub>(5)</sub>	1 <sub>1</sub>
13	45	Centocor	22 <sub>(101)</sub>	NBF
14	43	Genentech	45 <sub>(13)</sub>	NBF
15	41	Incyte	10 <sub>(257)</sub>	NBF
16	40	Bayer	44 <sub>(35)</sub>	1 <sub>16</sub>
17	39	Parke-Davis	88 <sub>(16)</sub>	1
18	37	Genetics Institute	19 <sub>(123)</sub>	NBF
19	36	NIH	131 <sub>(9)</sub>	P
20	34	Chiron	64 <sub>(24)</sub>	NBF

Notes: 1. The subscripts in columns four and five indicate the company's ranking in terms of R&D projects and sales respectively.

2. I = incumbent; NBF = new biotechnology firm; P = public research institution.

Table 4.1 shows the 20 organisations that have made the greatest numbers of collaborative agreements. The top deal makers are also among the top pharmaceutical companies in terms of sales and R&D projects in the pipeline. It is not surprising, perhaps, that with the exception of Incyte, major pharmaceutical companies own a controlling stake in all the top deal making biotech companies<sup>8</sup>.

Having identified the different types of actors and their collaboration patterns, we sought to identify attributes that help explain the ability of individual companies to sign agreements either as originators or as developers in the technology market. We use the number of agreements a firm signs as a proxy for its ability to generate knowledge and participate in the learning processes within the industry. In general, developers tend to be large firms, experienced in specific therapeutic areas and targeting large final product markets. Originators have either a general-purpose technology with which they can target a range of therapeutic categories, and/or have a niche focus and can sell a specialised product. We also found, in all the technologies, first mover advantages for originators that entered early into the market as suppliers.

There are other important attributes that distinguish a developer (licensee) and an originator (licensor). For developers, the major buyers of products and technologies (in this case the top 80 firms in terms of sales worldwide), it is important to have a clear strategy about the therapeutic classes that they seek to develop products in and dominate. Coherence in the pipeline implies that the company aligns core competencies between projects in specific therapeutic areas with the biological innovations and applications made available by other companies in the network.

By contrast, for the licensors to do many deals it is important to have a general-purpose tool that allows it to map onto a variety of therapeutic sub-classes. For the product based biotech companies, it

<sup>8</sup> Johnson & Johnson acquired Centocor in 1999. American Home Products acquired a 60 percent stake in Genetics Institute in 1992 and took over the rest in 1996. Roche owns 59 percent of Genentech stock. Novartis owns 45 percent of Chiron shares.

is important for the seller to be specialised within a niche in which it is able to sell its unique, or almost unique, technology or knowledge to buyers that, on the contrary, are active in the big markets. Basically there is a separation between being specialised in a niche market upstream and being able to sell technology and products to firms that are able, downstream, to sell pharmaceuticals into health care systems.

At this point, the nationality of the partners should also be mentioned. In an analysis of inter-firm licensing done at different stages of the R&D process we find that in pre-clinical research the US firms – both originators and developers – are signing the highest percentage of licensing agreements. We observe a strong internal network within the US that is not found anywhere else. More than 80 percent of the agreements that are subscribed to by US firms and developers are made with US originators. By contrast, 50 percent of the licensing agreements signed by European firms are made with US firms.

To understand the potential importance of networks for the R&D process, we analyse the efficiency of the markets for promoting innovation. In particular, we consider the question of whether they promote higher productivity within the R&D pipelines (i.e. higher success rates) than in-house projects. See Table 4.2.

To evaluate licensing behaviour for the 1990s, we looked at the success and failure probabilities of licensed and in-house projects for the top 100 companies (in terms of sales on the worldwide pharmaceutical market) at different stages: pre-clinical research, all three phases of clinical trials and then marketing. To get a clearer picture, we also classified firms according to nationality (although only the total industry results are presented in Table 4.2). Success is defined as the probability of moving from one stage to the next, rather than about the success of eventually launching a product onto the market. Because of the short time span of our analysis relative to the length of the actual R&D process, we decided to focus on these intermediate indicators so as to capture what is happening as a consequence of the, relatively recent, division of labour phenomenon.

The first key finding is that the probability of success of licensed-in projects is higher than the probability of success of in-house projects.

Table 4.2 Probability of success of in-house versus collaborative research projects

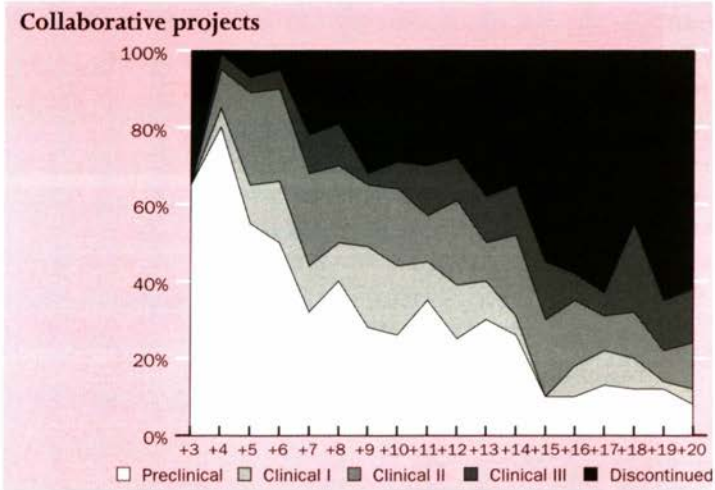
Transition to phase I			
	In-house	Licensed	Total
<b>Total (% of sample total)</b>	1,151 (79%)	311 (21%)	1,462 (100%)
<b>Failures (% of category total)</b>	698 (61%)	134 (43%)	832 (57%)
<b>Success (% of category total)</b>	453 (39%)	177 (57%)	630 (43%)
Transition to phase II			
	In-house	Licensed	Total
<b>Total (% of sample total)</b>	1,124 (78%)	310 (22%)	1,434 (100%)
<b>Failures (% of category total)</b>	763 (68%)	150 (48%)	913 (64%)
<b>Success (% of category total)</b>	361 (32%)	160 (52%)	521 (36%)
Transition to phase III			
	In-house	Licensed	Total
<b>Total (% of sample total)</b>	1,002 (78%)	281 (22%)	1,283 (100%)
<b>Failures (% of category total)</b>	840 (84%)	169 (60%)	1,009 (79%)
<b>Success (% of category total)</b>	162 (16%)	112 (40%)	274 (21%)

This result is robust across stages and types of firms and also across nationalities. For the transitions to Phase I and to Phase II clinical trials, the number of successful projects exceeds the number of failures for collaborative projects. This is not the case for in-house projects in either phase.

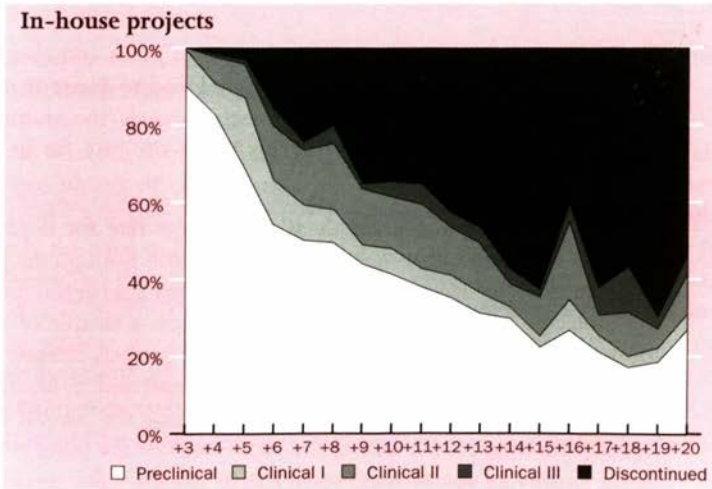
Second, we found that not only is the success rate for licensed-in products higher, but that these projects also move through the phases more quickly (see Figure 4.2). Once the contract has been signed and the molecule enters the pipeline, we find, from a sample of several thousands of projects, that the speed of the projects licensed-in is much higher than the speed of the projects generated in-house. The time and money spent by the buyer evaluating the project before signing the contract (as well as the capabilities of the seller reflected in the quality of the project) seem to pay off once the product has been internalised.



Figure 4.2 Moving through development stages: in-house versus collaborative projects



Note: Years since project inception is shown along the x-axis.



Note: Years since project inception is shown along the x-axis.

In a third result, we found that the US firms in the data set have a higher probability of success for their in-house projects than do the European companies. US companies also have a higher propensity to subscribe to licence agreements than Europeans, especially in the pre-clinical stage, and the propensity to succeed in licensing is also higher for US than for European companies, though the gap is smaller than for in-house projects (see Arora, Gambardella, Pammolli and Riccaboni, 2000).

So the market for technologies seems to present a potential tool that European companies could use to compete more effectively with their US rivals. Our data suggests that European companies are almost as likely to succeed in moving licensed-in projects forwards as US companies are. However, so far, the European companies do not seem to be maximizing their opportunity to use these markets for technologies.

If the story we have told about the functions of markets for technology and their potential contribution to economic performance, growth and innovation in the pharmaceutical industry is true, then intellectual property rights are key for two, perhaps conflicting, reasons. This dual role has been missed in the current debate about the public nature of knowledge. On the one hand, strictly defined property rights regimes can potentially restrict innovative activity by limiting public access to research results. On the other, the ability to write a contract, and thus enter into the specialised labour market of originators and developers, depends on companies' ability to patent their results. So intellectual property regimes also enable innovation. From this point of view, there is an important difference between pharmaceuticals and publishing (see Kay in Chapter 1).

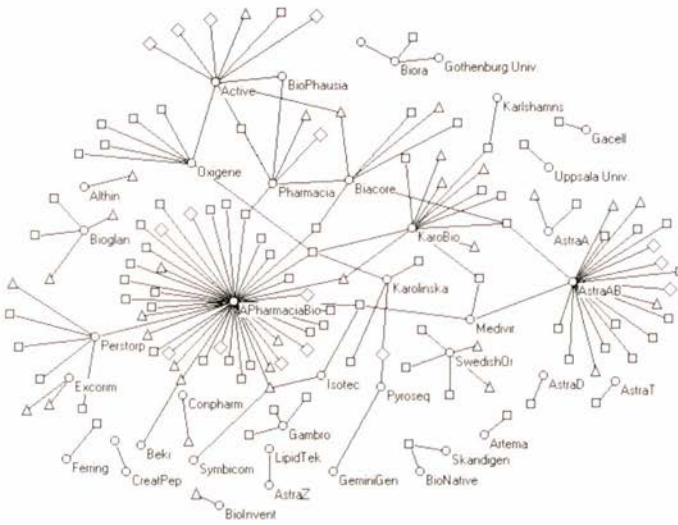
As latecomers to the market for technologies, European countries have to consider the importance of the intellectual property laws as they act to enhance the supportive infrastructure now in place with sector specific incentives for start-up companies. These new start-up firms have to enter the market of ideas, technologies and contracts, and in order to do that they need a strong infrastructure in terms of the legal and financial institutions that support this effort.

This point brings us back to one raised by Professor Galambos in Chapter 2. Specifically, seeking simply to imitate the existing institutions in the US could be counterproductive, given that the US is at a more mature phase in the industry's life cycle. For European countries to succeed, they must think about the policies and the solutions needed to support companies in a 'late but with opportunity to leap forward' position.

Finally, it's interesting to look at a picture of one particular network to see what types of players are involved, where they are located, and what role they are playing in the R&D process (see McKelvey, Alm and Riccaboni, 2001). Figure 4.3 shows the collaborations subscribed to by Swedish firms and organisations during the last 20 years. Many of the Swedish institutions and firms are geographically based around the Uppsala district, the Malmö district, and the Novum district around the Karolinska Institute. Figure 4.3 shows, however, that most of the 'Swedish network' is actually located outside Sweden. Only a handful of Swedish biotech firms succeed in structuring both a local and an international network (KaroBio, Active Biotech, Oxigene Europe, Biacore). After the Pharmacia-Upjohn and the Astra-Zeneca mergers, the two leading Swedish pharmaceutical firms (Astra, on the right of the chart, and Pharmacia, including the joint venture with Amersham, on the left) quickly shifted their research capabilities from Sweden toward the US and UK respectively. These post-merger shifts seem to be one of the causes of the fragmentation of the Swedish internal network. In general, the Swedish firms establish multiple links with foreign, especially US, originators and do not seem to have a strong internal network of formal collaborative agreements that connects them with local institutions. Sweden is not alone. Pictures of other European networks, perhaps with the exception of the UK, would also present fragmented networks with most of the links being between domestic and international partners.

This picture of the Swedish network can be used to emphasise two concluding points. First, there is an incredible amount of resources contained within this R&D network and companies use great effort to seek out the highest quality partners. Second, there is an unequal distribution in the type and profiles of companies between Europe

Figure 4.3 The Swedish network of R&D collaborations in biopharmaceuticals



Legend:  
 Circles = Swedish firms/organisations  
 Squares = US partners  
 Triangles = European partners  
 Diamonds = Other partners

and the US. As latecomers, European policy makers must therefore consider the risk of market saturation as they seek to boost national companies into the technologies market. Many new companies start up but never reach the necessary size and scope to link into the network core. This just leaves them small and isolated. Overcoming 'access to the network' obstacles is critical to creating competitive players in the dynamic network of biopharmaceutical technologies and R&D.



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## Chapter 5

# Pressures from the Demand Side: Changing Market Dynamics and Industrial Structures

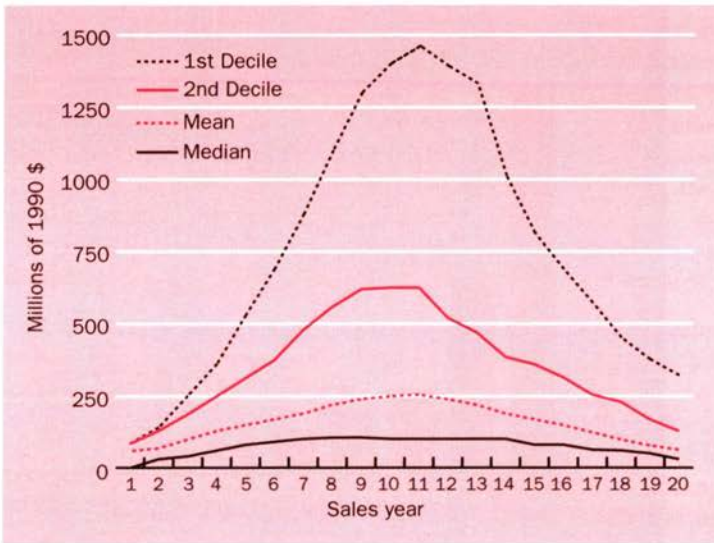
HENRY GRABOWSKI and JOHN VERNON

This paper has three parts. First it recaps the work from a 1994 study that looked at the overall profitability of a sample of products that came to the US and global market place in the early 1980s (Grabowski and Vernon, 1994a). Second, it presents research in progress on the next cohort of drugs which entered the US and global market place in the early 1990s. Finally, it draws out some implications for industry structure.

To give some context for the new study, we first consider some information and findings from our 1994 paper. It focused on a sample of 64 new chemical entities (NCEs) that were introduced between 1980 and 1984 in the US market place. It used sales data for each NCE (obtained from IMS) to estimate the sales profiles. In a second stage, we compared the present value of net revenues with the cost of bringing those products to market using R&D cost estimates from a study by DiMasi et al. (1991). Figure 5.1 shows the worldwide sales profiles for that cohort of 64 NCEs. These are the lifetime sales of products that were introduced in the US market place in the five-year period between 1980 and 1984, expressed in 1990 US dollars. The first decile, the top 10 percent of products ranked in terms of tenth-year sales, obtained at their peak about \$1.5 billion in annual sales. The second decile had peak sales of a little over \$600 million per annum. The mean peak was around \$200 million per annum sales, and the median peak for these products was somewhere below \$100 million.

The difference in overall economic performance of the 64 products is highlighted further in Figure 5.2, which compares the after-tax net present value (NPV) for each of the 10 deciles with average R&D costs per introduction. This after-tax NPV is calculated as sales revenue minus production and distribution costs, discounted to the point of launch. This is compared with average R&D costs per product, which are compounded to the year of launch. Average after-tax R&D cost per

Figure 5.1 Worldwide sales profiles of 1980-1984 NCEs



Source: Grabowski and Vernon (1994a).

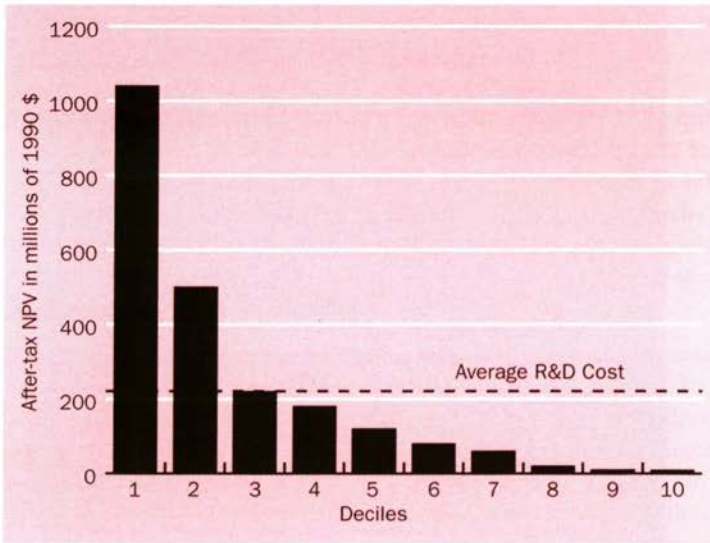
NCE launched for this period, derived from the DiMasi study, is just over \$200 million.

The distribution of NPVs is highly skewed. In this regard, the top decile accounts for 48 percent of the overall NPV generated by all of the products. That is, the top 10 percent account for nearly half of all the effective profit generated by these 64 products introduced in the US marketplace during the 1980-84 period.

Although it is not clear from Figure 5.2, the mean product does have a positive overall NPV. That is, its sales less production and distribution costs have a present value that exceeds average R&D costs (Grabowski and Vernon, 1994a). However, the median product does not. The median (32nd-ranked) product has a NPV that is roughly half the compounded value of average R&D costs for this period. The NCEs in deciles 4 to 10 have present values that are generally far less than average R&D costs.



Figure 5.2 Net present values by decile: 1980-1984 NCEs



Source: Grabowski and Vernon (1994a).

A key question is why did companies bring to market the 70 percent of products that have not covered average R&D costs? We considered two possibilities. One is that these products had lower than average R&D costs. One might expect the big products to be breakthrough products and, by definition, they may require greater research effort, have higher failure rates in development, and so on. In a separate piece of work, DiMasi et al. (1995b) examined differential R&D costs across therapy areas and by types of compound. This study of R&D costs found significant variability but nothing like the variability that is seen across the distribution of NPVs in Figure 5.2. In this respect, all US new product approvals share common discovery costs and have to satisfy similarly stringent FDA regulatory criteria.

We found, when we were looking at the effective patent life of this group of 64 products, that the most successful products tended to have a longer effective patent life (the time from market launch to the

point of patent expiration). This suggests that companies, to the extent they were able, were fast-tracking the products that they thought were most likely to be commercially successful. One of the ways in which they may fast-track is by spending more money through parallel R&D and related activities. It may be that the more lucrative products do cost more to bring to market. On the other hand, one of the most important elements of R&D costs is time cost. If companies are getting the product to market more quickly, then they are saving the opportunity costs of capital tied up in the innovation process. How these offsetting factors balance out is unclear. This is an issue that we plan to consider in future research.

The second explanation that we explored is that companies often cannot predict how successful a product is going to be until quite late in the process. This is due to unexpected clinical outcomes, regulatory lags, competitive developments of rival products, imperfect marketing forecasts and so forth. The R&D process in pharmaceuticals can be viewed as a sequential decision-making process under uncertainty. At each stage of the process, companies are in effect weighing the extra costs of going to the next stage against the expected revenues. The most likely explanation for bringing small revenue products to market is that, at the margin, by the time companies realize that these products are not going to be large sellers, the costs of carrying on and launching them are often relatively low compared to the money that has already been sunk.<sup>9</sup> Therefore it is worth getting those incremental revenues since they still make a positive contribution to the bottom line.

An interesting point of this NPV analysis is how the degree of skewness in rates of return to NCEs compares with what occurs in venture capital environments. To gain insights on this point, we compared the returns of the top 10 percent of pharmaceutical projects in this study with those from three venture capital studies analysed by Scherer et al. (2000). See Table 5.1.

<sup>9</sup> Firms are making stronger efforts to integrate economic modelling into the R&D process to avoid very expensive late-stage failures. See Grabowski (1997) on this issue.

**Table 5.1 Total value realized by the top 10% of innovations for select samples**

<b>Data set</b>	<b>Percent of value in top decile</b>
Venture Economics start-ups*	62
Horsley-Keough start-ups*	59
1980s IPOs – 1995 value*	62
1980-1984 NCEs**	48

Note: IPO = Initial public offering of shares.

Sources: \*Scherer et al. (2000).

\*\*Grabowski and Vernon (1994a).

The first two studies in the table looked at venture capital start-ups over a 20-year period. The first one, from Venture Economics, is based on 383 start-up projects commissioned by 13 venture capital companies. The top decile of products in this study account for 62 percent of the total value earned by all of the venture start-ups in the sample. The second study, the Horsley-Keough start-ups, involved an even larger group of 670 investments by 16 venture capital firms. Again looking at the returns, as measured by capital appreciation or loss at the point at which the venture capital exited, 59 percent of the overall returns from those projects came from the top decile.

The next study shown in Table 5.1 examined 131 high tech initial public offerings (IPOs) taking place in the mid-1980s and at their value 10 years later. In particular, it examined the returns after 10 years from a portfolio that involved an equal dollar investment in each of these IPOs. Scherer et al. found that 62 percent of the appreciation in the overall market value came from the most successful 10 percent of those high tech projects. The other 90 percent of these IPOs contributed only 38 percent of the overall increase in value. Furthermore, several of these IPOs dropped off the NASDAQ or exhibited long-term losses in market value.

Skewed outcome distributions imply high risks for both venture capital and pharmaceutical firm investments. In particular, as Scherer

(1999) and others have observed, the law of large numbers does not work very well in these circumstances. In other areas, if we invest in a large diversified portfolio of projects then, by and large, we expect that returns can be predicted with some confidence. When returns are highly skewed, considerable volatility in outcomes remains even if companies are investing in large numbers of projects as individual companies.

Overall a key implication of our 1994 work is that the returns of research-intensive firms are positive but are highly dependent on a few new blockbuster products. A related conclusion is that it is unwise to focus public policy attention simply on the products that were successful without a clear understanding that underneath there were many products that were making very poor returns or that never got to the market.

Given significant changes in the demand and supply sides of the pharmaceutical industry, we decided to repeat our original study with more up-to-date data. On the demand side, particularly in the US market place, we have seen a dramatic rise of managed care. One important effect has been a significant increase in the extent of insurance coverage for prescription drugs. This has been driven in part by a desire to substitute drugs for more costly medical interventions. Increased coverage for pharmaceuticals has been one of the main factors linked to the increased per capita expenditures on pharmaceuticals in the US in the 1990s (Berndt, 2000; Danzon and Pauly, 2000).

At the same time, the growth of managed care is still evolving and producing offsetting effects on pharmaceuticals. Health maintenance organizations (HMOs) and employers have widely subcontracted the management of their pharmacy benefit to management firms (PBMs). These specialty firms have instituted a variety of programs to reduce drug costs (Grabowski and Mullins, 1997; Schulman et al., 1998). In particular, where there were competing manufacturers in the same therapy area, PBMs have used formularies, multiple-tier co-payments and other mechanisms to try to obtain price discounts from drug companies. PBMs have also instituted strong incentives to encourage increased generic utilization. The degree of generic drug usage has grown significantly during the 1990s. This is a main factor



underlying faster sales erosion after patent expiration in the US market place.

Outside the US, cost containment measures have become more stringent over time (Danzon, 1997). Reference price reimbursement systems have evolved in Denmark, Germany, the Netherlands and New Zealand. In addition, controls on volumes and total expenditures have been superimposed on traditional price and reimbursement controls. In this regard, France has introduced manufacturer-specific budgets, while physician drug budgets have been utilized in Germany and the UK. Furthermore, patient co-payments have been on the rise in many leading European countries.

On the supply side, two critical things have happened. First, molecular biology and the emerging biotech industry have become an important source of new drug entities. By 1992, there were more than 200 biotechnology firms whose primary business involved the development of new pharmaceuticals. They had aggregate R&D expenditures in that year of over \$2 billion (Dibner, 1993). The vast majority of the biopharmaceuticals approved before 1993 originated in dedicated biotechnology firms, but many of these products were developed and marketed in collaboration with an established pharmaceutical firm (Grabowski and Vernon, 1994b). In an earlier chapter in this volume, Kettler documents the growing interdependencies that have occurred over time between the pharmaceutical and the biotech industries.

The second supply change in the US, that is also linked to the rise of the biotech industry in part, is the 1983 US Orphan Drug Act (Schulman et al., 1992). It was designed to give incentives to manufacturers to produce products for markets where the patient population is small, less than 200,000 in the case of the US policy. In normal circumstances, a company would not expect a commercial return from such a small patient group, and therefore might not develop the product. Under the Act, however, in exchange for bringing an orphan drug to market, companies earn tax credits and grants on R&D, a seven-year period of market exclusivity from the time of launch and, thirdly, expedited regulatory approval so that they can get an orphan drug to the market more quickly.

Our sample of products from the 1988-1992 period is much larger than the earlier one (110 versus 64), reflecting the increased number of products coming onto the US market in the 1980s and 1990s. This increase reflects in part the growth of biotech and impact of the orphan drug legislation. A quarter of the sample is products classified as orphan drugs for at least one indication.<sup>10</sup> There is also a close overall relationship between orphan drugs and biotech drugs during this period. This reflects the fact that many initial biotech drugs were recombinant versions of natural hormones that were already in the market place with approved indications for small patient populations. Orphan drugs status was also sought because there was uncertainty about patent rights in some areas of biotech and it was a way of obtaining market exclusivity for particular indications.

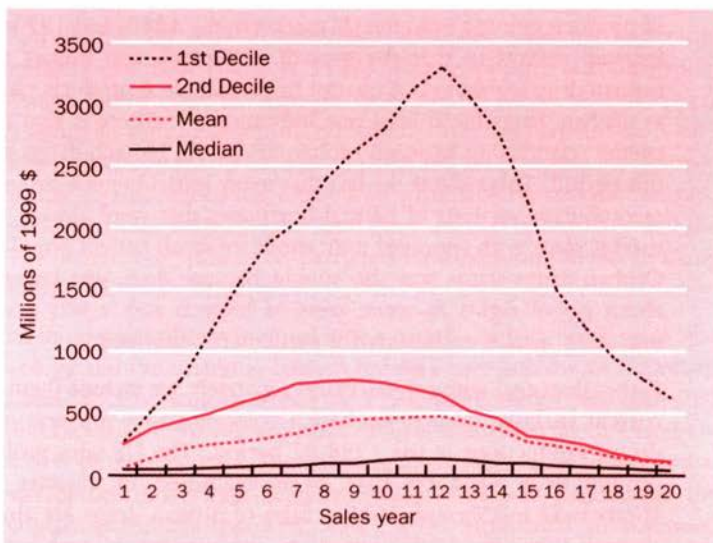
Rather than deal with orphan drugs separately, we include them in the current analysis. Hence, we have a comprehensive universe of new drug introductions in the 1988-92 period. The US sales profiles of orphan drug products have been examined in another paper (Grabowski and Vernon, 2000). Sales of orphan drugs are also very skewed. In the top decile of products, there are two biotech products, Epogen and Neupogen, that are among the top best-selling products in the overall sample, alongside several other products that were genuine orphan products with extremely small sales.

Figure 5.3 shows the worldwide sales profiles for the 110 NCEs launched between 1988 and 1992, based on IMS sales data extending through to 1999. There were up to 12 years of actual sales data for individual NCEs.<sup>11</sup> In most cases drugs' patents expire between 10 and 14 years after launch. Sales data were extrapolated to the point of patent expiration by a combination of two methods: first, by using

10 In some cases these products were very successful outside that indication and so were not orphans in the sense that they did not earn much money but were classified as orphan drugs under the terms of the Act. Neupogen is an example of this type of situation.

11 IMS data were obtained on US sales for all 110 NCEs and on worldwide sales for the 40 top-ranked drugs that accounted for over 90 percent of US sales from these NCEs. The latter sub-sample was utilized to construct foreign sales multipliers to estimate worldwide sales from US sales where worldwide sales data were unavailable.

Figure 5.3 Worldwide sales profiles of 1988–1992 NCEs



a reference life cycle sales curve based on new drug product introductions in the mid-1980s (the immediately prior drug cohort); second, by incorporating securities analysts' sales forecasts for leading compounds and therapeutic classes to take account of recent market developments. The post-patent expiry decline in sales was based primarily on an analysis of US products experiencing initial generic competition during the 1990s (Grabowski and Vernon, 1996; 2000).

Figure 5.3 confirms that blockbuster compounds remain critical to the success of research-intensive firms. The top decile of NCEs for the 1988–1992 period has a sales peak of \$3.2 billion (in 1999 dollars). This is roughly a doubling in real terms of the sales peak for 1980–1984 NCEs (Figure 5.1). Furthermore, the top decile has experienced a significantly higher growth rate over the earlier period than the second decile. Hence, it appears from Figure 5.3 that the distribution of sales has become more skewed over time. This issue is examined further below.

The top decile compounds are listed in Table 5.2. The group is

Table 5.2 Top decile compounds from the 1988-1992 sample

Prilosec	Zocor
Prozac	Pravachol
Zoloft	Zithromax
Epogen	Biaxin
Neupogen	Prinivil/Zestril
Norvasc	

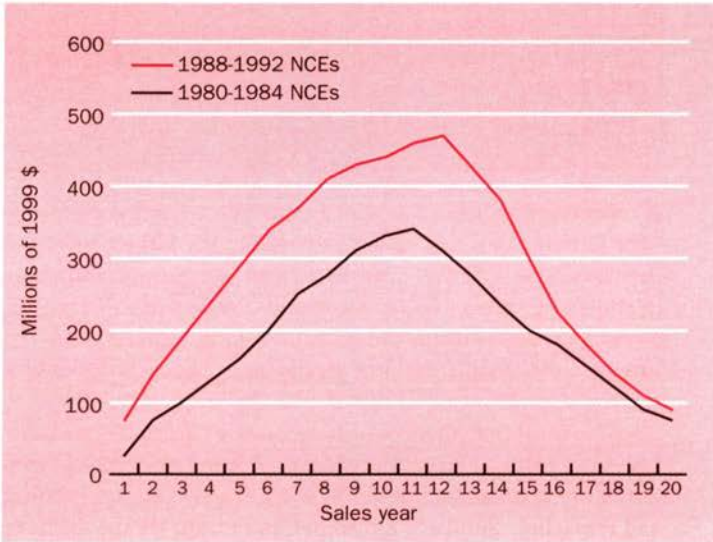
comprised primarily of new drug introductions that are pioneers or early entrants in a new therapeutic class. The largest-selling drug in the top decile, Prilosec, was the first proton pump inhibitor for the treatment of ulcers. It was the world's largest selling drug in 1999. Neupogen and Epogen, the two top-selling biotech products, from Amgen, also made the top decile and hence contribute to the skewness in the sub-analysis of biotech and orphan drug products. Also, interestingly, there are some cases of pairs of products being from the same therapeutic classes. Among the SSRIs, Prozac and Zoloft are both in the top decile as are the two leading statins, Zocor and Pravachol. Similarly, Zithromax and Biaxin are the initial entrants and leading products in the macrolide anti-infectives class. Other top-decile compounds include Prinivil/Zestril, the leading ACE-inhibitor for hypertension, and Norvasc, a new type of calcium antagonist for treating hypertension.

Figure 5.4 compares the mean worldwide sales curves for our current cohort of 1988-1992 NCEs with the earlier one for 1980-1984. The newer products produce the top, steeper curve. We can see that the more recent generation of products takes off more quickly and achieves higher peak sales. They are also projected to have a more rapid decline from this peak. This is associated primarily with increased price and generic competition after patent expiration compared to the earlier period.

The degree of skewness also has increased for the new cohort compared to the earlier one. In Figure 5.5, we compare worldwide sales by decile for the 1980-1984 and 1988-1992 cohorts. The sales data are based on the tenth year after launch. The biggest upward shift over time occurs in the top decile. In particular the top decile



Figure 5.4 Comparison of the mean worldwide sales for two NCE cohorts

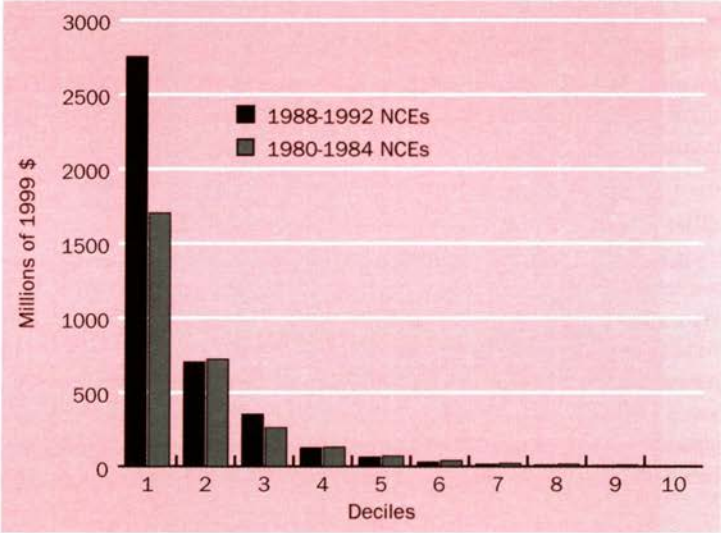


for the new cohort accounts for 64 percent of total worldwide sales versus 51 percent in the earlier sample.<sup>12</sup> If we omit the 28 orphan drugs, the top decile in 1988-92 accounts for 59 percent of worldwide tenth-year sales, so the orphan drug sample is even more skewed than the full sample of 110 drugs.

The overall conclusions from this stage of the analysis are that sales of the later cohort of 1988-1992 products, achieves higher peak sales, achieves greater sales overall, and exhibits more skewedness than the earlier sample. Given this high degree of skewedness, it is interesting to consider what relationship exists between how much a company spends on R&D and its subsequent sales from its new products. To gain insights

12. As pointed out in Table 5.1, the top decile for 1980-1984 NCEs accounted for 48 percent of the net present value (sales minus distribution and production costs) generated by the full sample. In future work, we plan to do a similar analysis of NPVs for the 1988-1992 cohort and compare the NPVs in each decile to R&D costs.

Figure 5.5 Comparison of worldwide sales for two cohorts of NCEs by decile



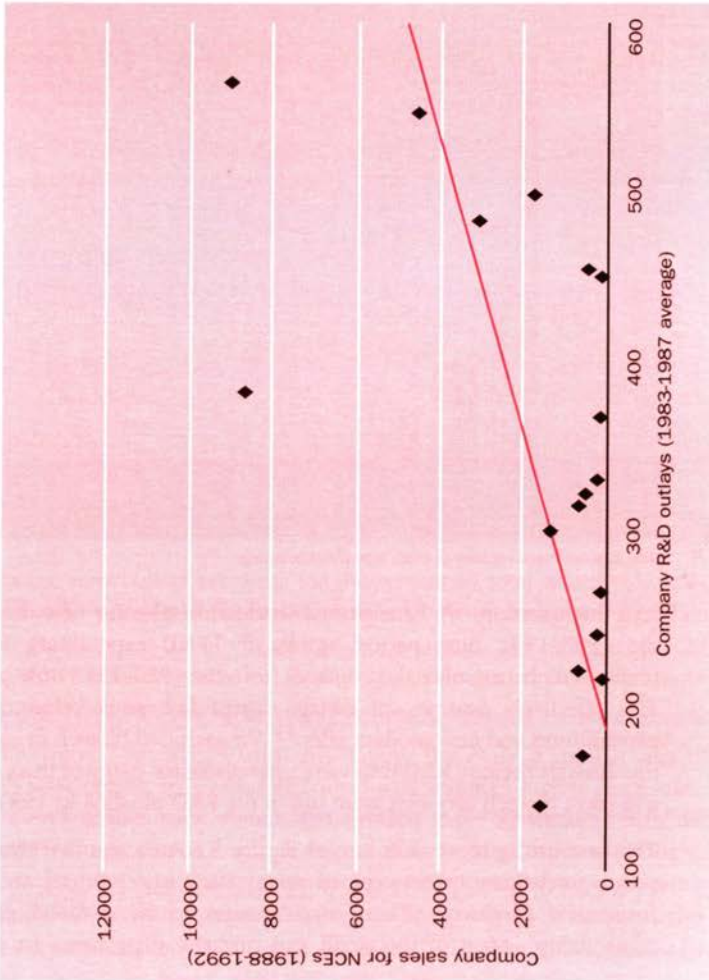
Note: Data are based on sales in tenth year after marketing.

into this question, we have plotted worldwide sales for new drugs for the 1988-1992 time period against the R&D expenditure for 18 traditional pharmaceutical companies from the 1983-1987 time period. This effectively assumes an average lag of five years between R&D expenditures and new product sales.<sup>13</sup> We excluded biotech firms from this analysis because R&D data were unavailable for many of these firms, and most biotech products were still in the R&D pipeline in 1992.

The best-fitting regression line in Figure 5.6 indicates that there is a positive relationship between company R&D expenditures and sales from new products. There also appears to be a threshold-type relationship. Most of the small and mid-tier drug firms have sales

<sup>13</sup> The full gestation period for a new drug introduction in this period is generally 10 years or more, so we took the midpoint of a 10-year stream of R&D expenditures, or five years, in the lagged relationship shown in Figure 5.6. The results are not sensitive to alternative lag structures around this value.

Figure 5.6 Worldwide sales plotted against R&D expenditures (in millions of 1992 dollars)



Notes: Company sales are for the tenth year of market life. They are the sum of all NCEs introduced by a firm in the 1988-1992 period. R&D outlays are lagged by five years, so that they correspond to products coming on to the market between 1988-1992.

well below the fitted curve. These firms have few blockbuster products. The larger R&D companies in the \$400 million to \$600 million range of R&D expenditure range during this period account for most of the blockbusters.<sup>14</sup> However, there is also a great deal of variation across these larger R&D firms. The tenth year's sales of their NCEs vary from practically zero to over \$9 billion. This reconfirms the point made earlier about the law of large numbers; even firms with large portfolios of R&D products are subject to substantial volatility in their new product sales.

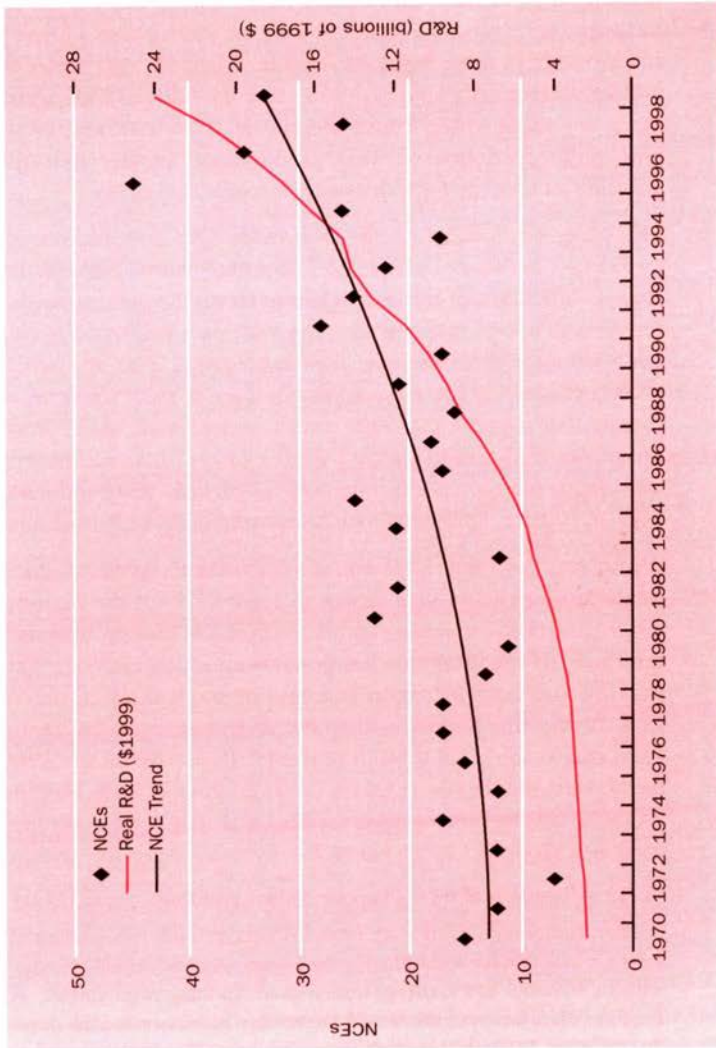
This paper has focused on the worldwide sales performance of NCEs introduced between 1988-1992. In future work, we will integrate analysis of R&D costs and compare them with the present values of net revenues as in our earlier work. The R&D data will come from a new R&D cost study by DiMasi et al. now in progress. While the new DiMasi R&D cost study is not yet completed, there is evidence from various sources that suggests that R&D costs have increased significantly since our earlier study. In this regard, Kettler (1999) has examined specific data trends for the various components of R&D costs and concluded that, on balance, R&D costs have increased significantly over time.

Rising real costs for R&D are consistent with some of the macro trends from industry data shown in Figure 5.7 for the period 1970-1999. Both R&D spending and NCE approvals have an upward trend, but the R&D spending line has been rising much more steeply. R&D expenditures have increased at a rate of more than 10 percent per annum over this period, while new drug introductions have grown from an average of 13.7 NCEs in the 1970s to 18.5 in the 1980s and to 27.4 in the 1990s (DiMasi, 2001). Hence, NCE outputs have doubled during this period while real R&D expenditures have increased six-fold (see Figure 5.7). Even allowing for qualifications

14 As discussed, Amgen introduced two of the blockbuster products in this period. The biotech firms were excluded because R&D expenditures generally were not available for 1983 to 1987, and many biotech firms were private firms without Securities and Exchange Commission reporting requirements. Had they been included, however, this would presumably have increased the dispersion in the less than \$300 million R&D segment, given the high degree of skewness exhibited for the biotech products in our sample.



Figure 5.7 Pharmaceutical industry inflation-adjusted R&D expenditures and NCE approvals, 1970-1999



Source: PhRMA; Tufts University CSDD.

such as lags and sample composition issues,<sup>15</sup> these industry trends suggest that the R&D costs of bringing an NCE to market have been rising significantly in real terms throughout this period. The forthcoming DiMasi study will provide a detailed microeconomic analysis of R&D costs encompassing the relevant period for our new sample of NCE introductions.

In conclusion, it is appropriate, given the objectives of this volume, for us to consider some implications for industry structure. Over the past two decades, the pharmaceutical industry has been characterized by contrasting structural changes. First, there have been many significant horizontal mergers and increased consolidation among established pharmaceutical firms (Grabowski and Vernon, 1994b). Second, there has been significant entry into the industry by hundreds of newly established biotech firms, especially at the research end of the spectrum. Third, there have been increasing collaborations and interdependencies between these emerging biotech firms and established big pharmaceutical firms.

The economic characteristics of the innovation process have been an important factor shaping these changes in drug industry structure. Our analysis indicates that R&D costs and revenues have increased significantly in real terms, while the distribution of sales revenues has remained highly skewed. We also found that the innovative output of the small- and middle-tier pharmaceutical firms was relatively weak for the NCEs analyzed in our sample, suggesting that many of these firms were either unable or unwilling to assume the increasing risks associated with the pharmaceutical innovation process.<sup>16</sup> Several of these mid-tier firms have now merged into larger entities. The R&D productivity of these firms in the post-merger period remains an interesting issue for further research.

15 For a discussion of these issues see Section 8 of DiMasi et al. (1991) which utilized aggregate data as a check on their micro analysis.

16 In a prior study that we performed with DiMasi, we also found lower R&D productivity for small- to mid-tier firms (DiMasi, Grabowski and Vernon, 1995). That study focused on NCE introductions in the 1980s by the group of 12 firms participating in the original R&D cost study. See also Henderson and Cockburn (1996) on this issue.

In the skewed outcome world, collaborations between big pharmaceutical companies and small biotech firms provide important potential benefits to both sides. They enable the big pharmaceutical companies to leverage their internal R&D and obtain more options for new products. At the same time, they enable the smaller biotech firms to get risk-sharing benefits and gain credibility for their technology. Thus the evidence of skewed returns reinforces points made by other contributors to this book about the nature and importance of the relationship between big pharma and the emerging new players in the biotech sector. Quantifying the economic benefits of these collaborations is another important topic for further research.

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## Chapter 6

# Investors' Views on Merger and Acquisition, Alliance and Licensing Activity in the Pharmaceutical Industry

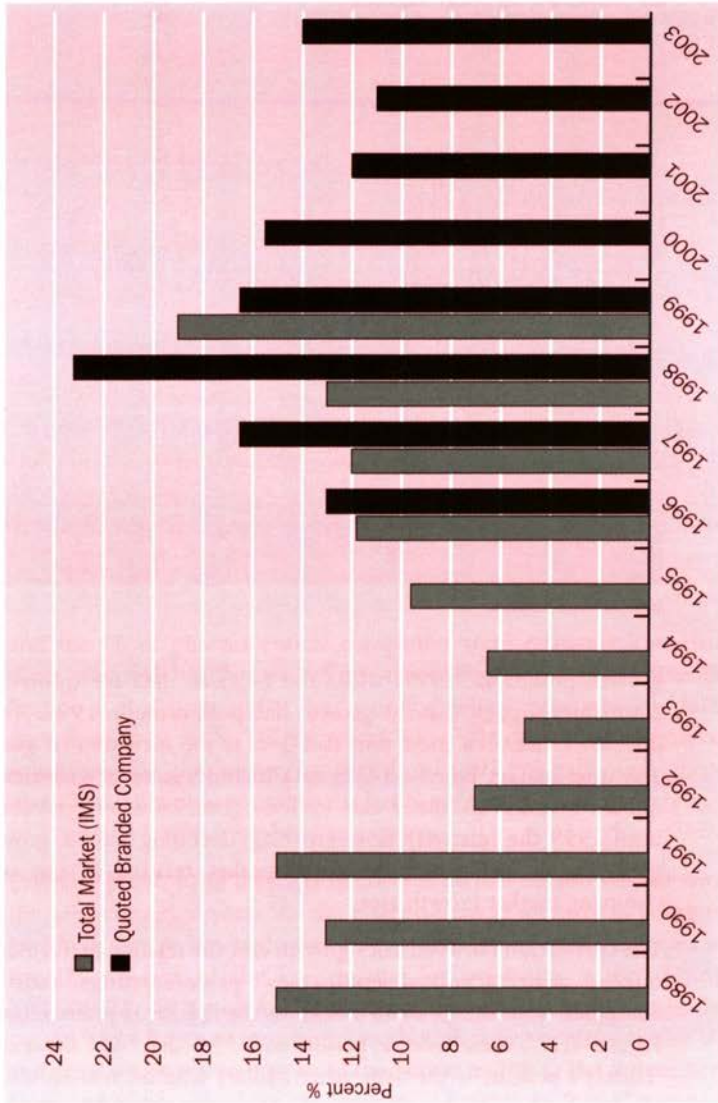
JO WALTON

Lehman Brothers' data and analysis presented in this paper highlight four key findings about the pharmaceutical industry:

1. Trends in market growth reveal a slow-down that seems to be one of the main drivers behind recent merger and acquisition activity. This is probably a more important driver than gaps in the pipeline of new molecular entities (NMEs).
2. There seems to be a growing divergence in performance between US and European players. US-domiciled pharmaceutical companies are showing stronger growth than either UK- or European-domiciled companies, and this has enormous implications for their ability to invest both in marketing and R&D.
3. Cost growth has been significant and also limits the number of companies that can afford to launch new products. There is an increasingly skewed pattern in the amounts companies invest in marketing and promoting products, where 'mega-brands' take precedence over others.
4. As far as scale is concerned, there seems to be a strong correlation between success and size of marketing effort, but less evidence of scale in R&D translating into success. Still, investors continue to pay premiums for large companies despite stagnating productivity.

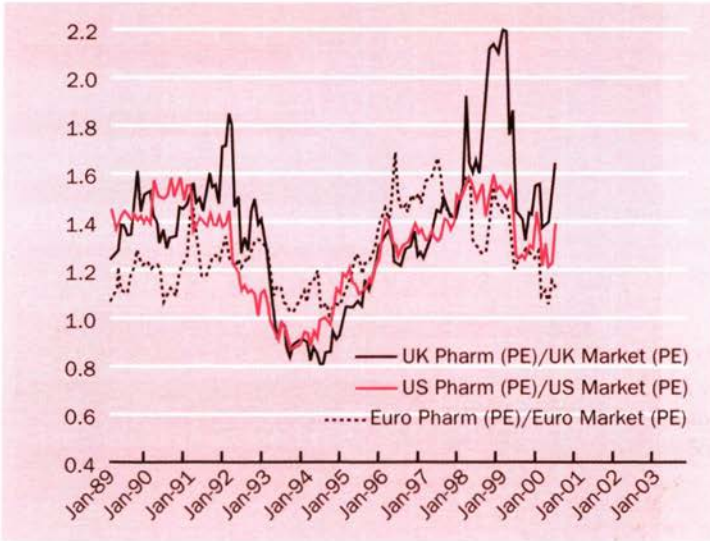
The key aspect of the industry looking forward is the growth of the largest pharmaceutical market in the world, the US. Figure 6.1 shows two sets of data. The lighter bars show the percentage growth in the US retail pharmaceutical market each year since 1989, using IMS audited data. On this measure the current US market is valued at around \$90 billion. The darker bars represent Lehman Brothers' universe of 32 quoted companies. The aggregate value of their global sales comes to around US\$102 billion. The IMS data imply that sales

Figure 6.1 US pharmaceutical market growth rates



Source: Lehman Brothers.

Figure 6.2 UK, US and European pharmaceuticals - PE relative to all stocks PE on local market

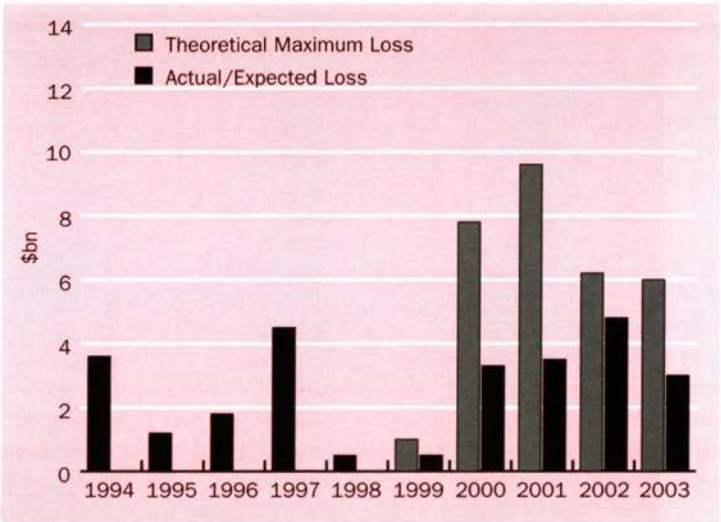


Source: Lehman Brothers.

growth peaked in 1999, while the Lehman data for quoted drug companies suggest that the growth rate peak came in 1998. The key difference between these two data sets is the inclusion of generics. The total market based on IMS data includes sales of generics. The quoted branded company data exclude generics where possible. So until 1999 the relatively slow growing/declining rate of growth of generics, slowed down the total market relative to the quoted company market growth rate.

The correlation between sales growth and the relative performance of quoted pharmaceutical companies' price/earnings ratio (PE) compared with the PE of all stocks on the market is pretty close. See Figure 6.2. There was a period in 1994 that was described as 'Hillary's bottom' – the time when Hillary Clinton was looking into the issue of health care reform in the US – when both US sales growth

Figure 6.3 Patent expiries in the US



Source: Lehman Brothers estimates.

and the PE of pharmaceutical companies were relatively low. But there was real health care reform throughout most of continental Europe at that time and it was a period when there was low sales growth not just in the US but world-wide. The peak of stock market valuations for the sector happened in 1998/99, although more recently the pharmaceutical sector has benefited from being perceived as a defensive, non-oil-related investment.

Evidence points to an inescapable conclusion that the growth rate over the next couple of years for the pharmaceutical industry is going to be lower than it has been over the last five years. Patent expiries in the US are one of the key reasons for predicting a dip during 2001/2002. In Figure 6.3 the dark bars show what happened in the period 1994-1998 in terms of the value of patent expiries in the US and what we expect to happen in the period to 2003. The lighter bars from 1999 onwards show the theoretical maximum loss of revenues



Figure 6.4 **Pharmaceutical company mergers**

<b>1970</b>	<b>1980</b>	<b>1990</b>	<b>2000 (proforma)</b>
Roche	<i>Hoechst</i>	Merck	<i>GlaxoSmithKline</i>
Merck	<i>Ciba</i>	<i>Bristol Myers Squibb</i>	<i>Pfizer Warner</i>
Hoechst	Merck	Glaxo	Merck
Ciba-Geigy	AHP	<i>SB</i>	<i>AstraZeneca</i>
AHP	Roche	Ciba	<i>Aventis</i>
Lilly	SmithKline	<i>AHP</i>	<i>Bristol Myers Squibb</i>
Sterling	Boehringer Ingelheim	Hoechst	<i>Novartis</i>
Pfizer	Sandoz	J&J	<i>J&amp;J</i>
Warner	Pfizer	Lilly	Lilly
Sandoz	Bristol Myers	Bayer	Roche
Upjohn	Lilly	Roche	<i>AHP</i>
Abbott	<i>Warner Lambert</i>	Sandoz	<i>Schering Plough</i>
Squibb	J&J	<i>RPR</i>	<i>Pharmacia Corp</i>
Bayer	Bayer	Pfizer	Bayer
Bristol Myers	Schering Group	<i>Schering Plough</i>	<i>Sanofi-Synthelabo</i>
<i>Results of previous acquisitions</i>			

Note: Companies ranked according to global prescription drug sales.

Source: Lehman Brothers.

from patent-expired products possible if the defence mechanisms in place against generic entry for the number of major drugs do not hold. Remember that this is a market currently worth about \$100 billion, so in 2000 patent expiries at their worst could result in an eight percent decline in the market and at best it will be something like a three percent decline. There seems to be an accelerating rate of decline going forward.

The rate of new drug development also affects the sales growth pattern. Lehman Brothers are perhaps more optimistic than many analysts about the size of new drugs' sales but are perhaps slightly more pessimistic regarding the rate of revenue loss following patent expiry.

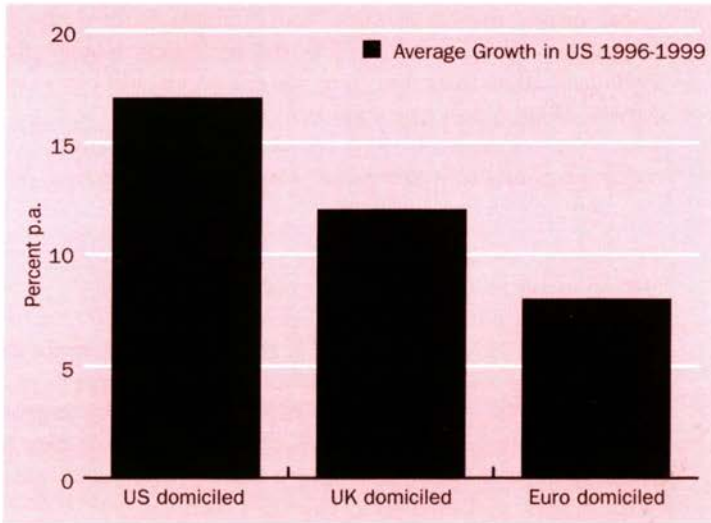
Figure 6.4 shows the accelerating trend of mergers in the pharmaceutical industry. It lists the top 15 companies, based on global prescription drug sales, and indicates those – the shaded companies – that have merged in the preceding decade. Between 1990 and 2000 there has been an enormous amount of merger activity. There is only one company that has been in the top three in every time period since 1970: Merck, which is also one of the few major companies not to have done a significant merger deal. Will this statement still be true in 2010?

To sum up the first part of the discussion, there has been an extraordinarily strong top-line growth and an earnings growth in general for the industry of about 15 percent per annum for the five-year period 1994-1999. The consensus of analysts' expectations for the next five years is for another 15 percent annual earnings growth. It seems extraordinary that the same degree of earnings growth going forwards is expected to be generated from a markedly lower rate of sales growth. The only way that can be done is by a skewed performance with some of the big US companies doing extremely well.

Jan Leschly<sup>17</sup>, the then Chief Executive of SmithKline Beecham (SB) made a presentation at the March 25th 1996 Financial Times World Pharmaceutical Conference in which, according to his data, the top 20 companies' R&D pipeline output was around half a new chemical entity (NCE) a year. For a company with around \$5 billion of sales in year 1, to achieve 10 percent annual growth for the next 10 years would require it to have about \$12 billion of sales at the end of that period. Assuming a 50 percent decline over 10 years in the existing portfolio, Leschly calculated that they would need to launch over \$9 billion worth of new products over the same period, or 2.2 new NCEs a year as compared with the expected 0.45. This calculation was the key driving force for SB moving more into over-the-counter (OTC) drugs and acquiring DPS, the US based pharmacy benefit manager. In retrospect, data presented in the next section suggest that Leschly would have been better off investing in more R&D or, more importantly, in marketing.

17 It is not fair to put this just at his door; an awful lot of executives would have given a very similar presentation at the same time.

Figure 6.5 Comparative sales growth rates



Source: Lehman Brothers.

So what happened in the industry between 1996 and 2000? Using SB as a proxy for the industry, it really has grown at 10 percent per annum but this growth has not been driven by a significant increase in the number of products launched per year. The most important driver of growth has been life cycle management. The key assumption that Leschly looks likely to have got wrong in 1996 was that there would be a 50 percent decline in sales for the existing portfolio over 10 years. Taking the industry average and looking at the total cohort of drugs that were around in 1990 and 1999, one finds that their sales value in 1999 was actually higher than in 1990.

SB itself holds an excellent example of that. Back in 1990 Augmentin was a \$670 million drug. Nobody expected it to keep growing through to 1999, but it did, reaching sales of about \$1.6 billion drug in that year. If Grabowski went back and reassessed the full life cycle experiences of some of the older drugs to check what the actual net

present value (NPV) had turned out to be, he would probably be surprised at the absolute longevity of some products.

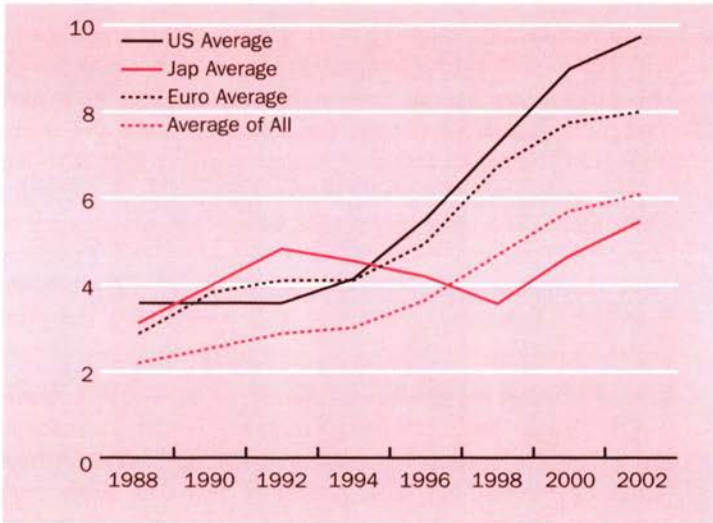
What permits this longevity is the growth of the largest market, the US. US-domiciled drug companies over the last five years have shown 15 percent per annum growth in sales in the US market; UK companies about 12 percent per annum growth; and continental European companies about eight percent. See Figure 6.5. Superior sales growth leads to superior marketing strength and superior R&D investment. That sales growth has been reinvested in a 15 percent annual increase in numbers of sales reps in the US. The companies with the higher top line growth have been growing their share of total R&D expenditures as well. This combination can produce a virtuous spiral going forwards.

Changes in cost must also be examined to understand the patterns of profit growth. For this we use data from AstraZeneca at the time of its creation by merger in 2000. Few analysts in 1995 would have correctly forecast the sales growth of this combined 'company', especially the extent of the success of Losec/Prilosec (omeprazole). The overall 'company' showed 15.5 percent compound annual sales growth globally and 24 percent compound annual sales growth in the US from 1995 to 2000. But even after allowing for royalty payments to Merck, these sales realised incremental profits at only a surprisingly low 20 percent rate. Costs in the pharmaceutical industry have been going up phenomenally, driven in particular by marketing costs, although some of these are well hidden in the R&D line. Sales rep numbers in the US provide supporting evidence of this: there has been a 15 percent rise in each of 1999 and 2000. The marketing burden increases as the number of launched products increases. Assuming that companies will market all products actively for six years following launch, though clearly not all at the same level, the number of drugs launched serves as a proxy for the marketing burden. See Figure 6.6. The marketing burden has been growing at a rate of eight percent per annum on average.

Advertising budgets are increasing and are focused on promoting new classes of compounds even when the older classes may effectively



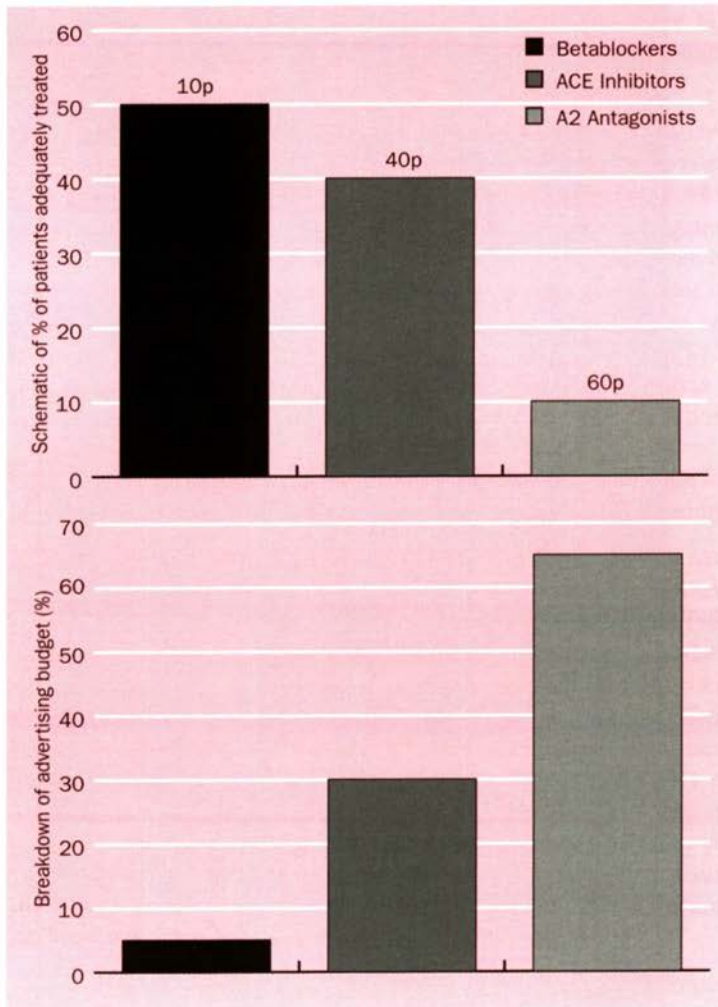
Figure 6.6 Marketing burden



Notes: Number of drugs within six years of launch used as a measure of marketing burden. Number of effective salesmen per drug has risen from 148 to 186 from 1996-1999, an 8 percent p.a. increase.  
Source: Lehman Brothers estimates.

treat a sizeable share of the targeted patient group. Figure 6.7 schematically illustrates what might happen. It shows that a lot of people will be very happy on a betablocker at 10 pence a day but that there is almost no promotion effort behind that. By contrast, there are relatively few people who absolutely require an angiotensin A2 antagonist for their health at 60 pence a day, but according to the skew of advertising dollars, these are the products that patients will hear about. From a health economics point of view, we need to have governments intervening to promote less commercially exciting, older classes of compound. Maybe there is a need for a 'step therapy' approach in government funded systems. But investing in marketing and advertising seems to pay off for companies and scale does seem to matter for this activity. 1999 data presented in Figure 6.8 show a

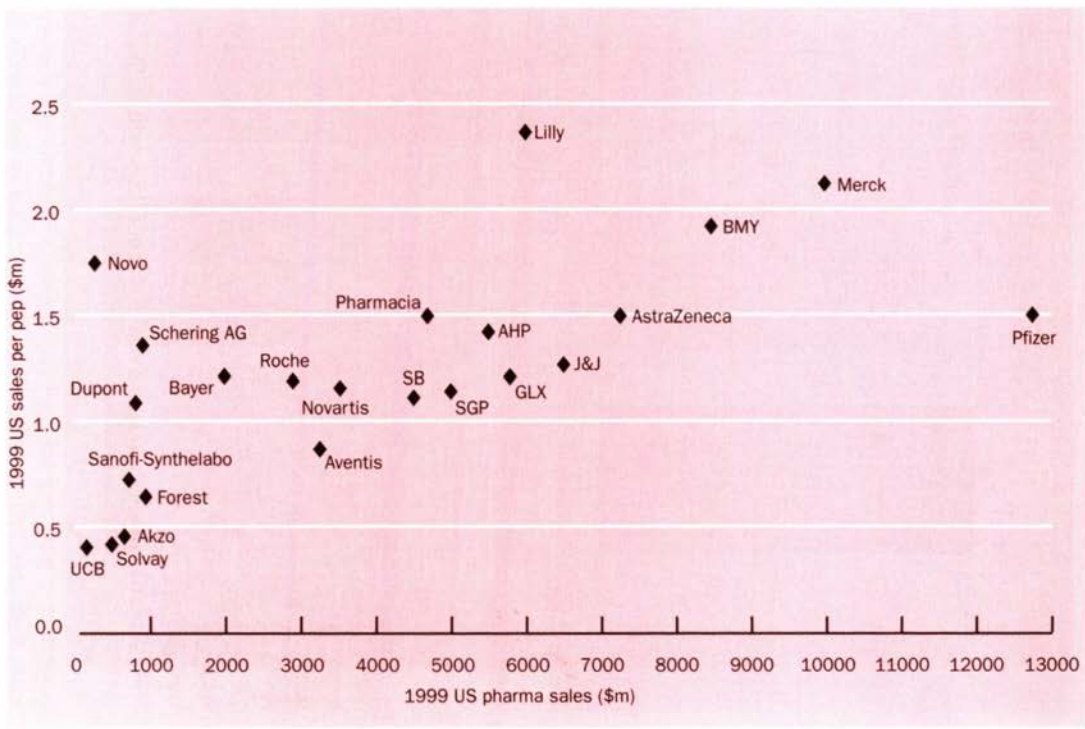
Figure 6.7 Step adoption of innovation



Note: Prices in the top half of diagram are therapy prices per day.

Source: Lehman Brothers estimates.

Figure 6.8 Scale counts for sales force productivity



Source: Lehman Brothers estimates

strong positive correlation between the level of US sales that a company reports and the sales per rep. There is a clear value from scale in terms of productivity. Pfizer appears to be an outlier here, but remember that Pfizer does not book the sales of a lot of compounds that it sells: Eisai, for example, books US Aricept revenues.

This correlation is the sort of thing that investors see and it is reflected in a premium to be paid for large companies (see below). There is no such support for economies of scale in R&D. Average annual R&D spending over the period 1992-1998 is plotted in Figure 6.9 against NCEs launched between 1996-1999, for Lehman Brothers' set of companies<sup>18</sup>. We assume that most companies thought at the time of launch that these NCEs would achieve significant sales. There are companies with R&D budgets ranging from \$1 billion a year to \$1.8 billion. It is interesting that no company has been able to sustain a launch rate of more than two NCEs per year over any reasonable time frame. An as yet unanswered question is whether this is the result of a block within the marketing department or whether this is an issue for the R&D department. Whatever the reason, it is worrying for investors.

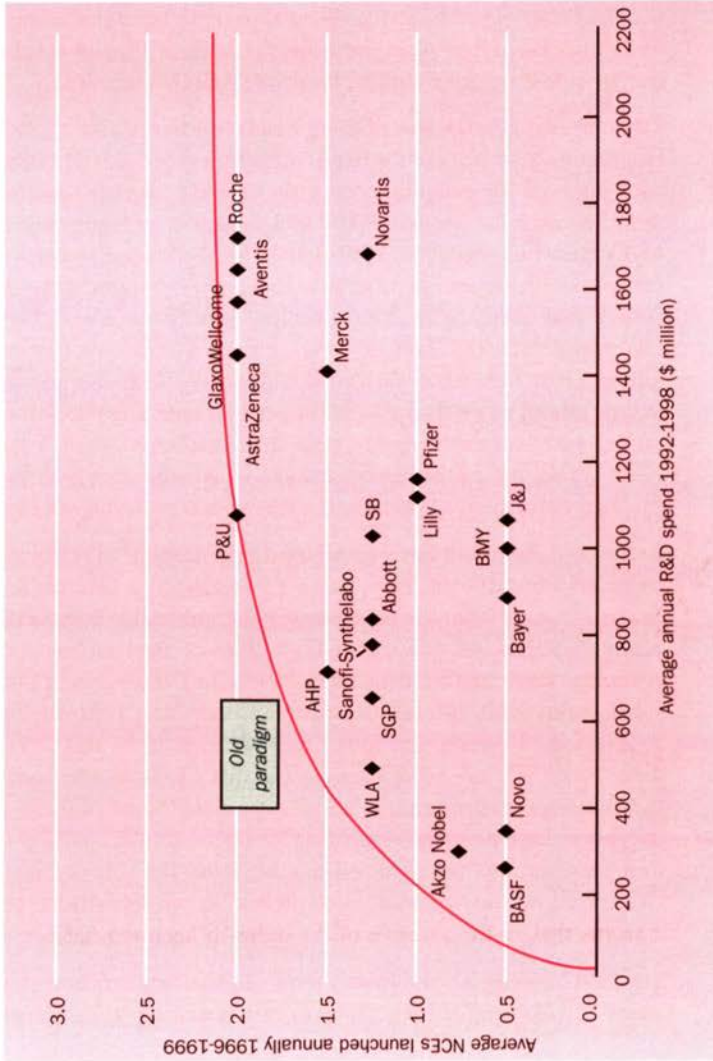
Kettler and Pammolli have both raised the question of when do new technologies start to deliver. Box 6.1 summarises a Lehman Brothers analysis from 1999 of the recent history of SmithKline Beecham's (SB) patents. SB moved towards a high level of new targets for their research work some time ago, including a highly publicised relationship with Human Genome Sciences Inc. Lehman Brothers looked at SB's patents and found that between 1994 and 1996 there were essentially no novel patents, but that by 1999 the number of novel patents was running at up to 250 a year. None of these patents appears to have provided drugs that have gone into drug discovery yet and there is also no correlation with leads that move into actual development, but there is nevertheless an evident move towards innovative research in terms of the patent filings within SB.

Figure 6.10 presents data from a joint Lehman Brothers and McKinsey study of R&D productivity. The cost of a 'ticket to play' is surprisingly

<sup>18</sup> This indicator captures the number of molecules but not their commercial values.



Figure 6.9 Scale is less significant for R&D productivity



Source: Lehman Brothers estimates.

**Box 6.1 Genomics starts to deliver: Case study of SmithKline Beecham**

- Lehman Brothers' analysis of SmithKline Beecham's patents over the last 6 years confirms that the number of patents referring to new targets has increased exponentially.
- Total number of patents filed per year has increased from 146 in 1994 to 472 in 1999.
- Genomics is the major driver for new target identification at SmithKline Beecham.
- However, very few of the drug discovery patents as yet reflect this genomics input.
- GlaxoSmithKline will almost certainly be the first pharmaceutical company to put new small molecules into clinical development, based on targets identified by genomics.

low. Interviews imply it might only be \$70-130 million. A lot of bigger companies are telling us that it is \$300 million plus. If our figures are reliable, and a 'rent' rather than a 'buy' strategy is a competitive alternative, this is good news for medium sized companies going forward and again supports the contention that success in R&D may not be dependent on large scale.

It is difficult to believe at the moment that greater scale leads to better R&D productivity but there is no conclusive evidence one way or the other. If we see a huge shift towards more use of novel targets, one might even predict that in the short term we would see an overall decrease in the output of R&D productivity because novel targets presumably have a higher failure rate through the system.

It seems that in the short term, in order to keep the balance of the output right, companies need to continue to pursue fast-follower approaches and to look at precedented as well as novel, unprecedented targets. There are an awful lot of precedented targets out there that are not fully 'fished-out'. Lipitor was a late entrant in the cholesterol-lowering market for example. The AstraZeneca/

Figure 6.10 Cost of ticket to invest in new technologies

There is a minimum \$70 million-130 million 'ticket to play' investment necessary to take advantage of new technologies

	<b>Informatics</b>	<b>Target validation</b>	<b>Lead optimisation</b>	<b>Exploratory development</b>
<b>Minimum approach</b>	Build or develop alliances to improve and integrate bioinformatics and cheminformatics platforms	Invest in functional genomics primarily through renting	Invest in toxicogenomics through alliances/internal investment	Invest in internal applications of existing technologies in exploratory development and experimental medicine
<b>Amount*</b>	\$20 million-40 million	\$20 million-40 million	\$10 million-20 million	\$20 million-30 million
<b>Rationale</b>	\$12-25 million to build 50-100 person informatics group Other costs in tight strategic alliances Bayer-LION deal valued at \$20 million per year over five years	\$5-10 million protein interaction database subscription/technology investment \$4 million protein structure database subscription \$3-5 million mRNA expression profiling investment \$4-8 million protein expression database subscription/technology investment \$2-3 million for model organism collaborations \$2-3 million technology investment	\$2-4 million database subscription for toxicology profiles \$3-5 million for ADME SNP database subscription \$1-2 million wet lab experiments/SNP profiling expenditure \$2-4 million library expansion and VLS development \$1-3 million for closed-loop chemistry tools \$1-3 million other technology investment	\$5-10 million for exploratory pharmacogenomics deals \$3-5 million for exploratory trial simulation deals \$5-10 million to build 20-40 person applications development group \$3-5 million other (e.g. <i>in vivo</i> imaging, novel animal models)

Note:\* Annual investment in 2005.

Source: Lehman Brothers and McKinsey analysis; industry interviews.

Shionogi product will be an even later entrant in the cholesterol-lowering market. Both of those promise to be exceptionally strong drugs. As another example, Pfizer was a late entry to the calcium channel market with the launch of Norvasc.

It is difficult to talk about an industry standard model. Figure 6.11 shows the product pipelines and R&D spends for 21 major pharmaceutical companies. There is a huge dispersion. Bayer has an annual spend of \$1.2 billion but only two drugs in Phase III while Sanofi-Synthelabo is trying to move forward seven products in Phase III and 19 products in Phase II with less than \$1 billion a year of annual R&D expenditure.

Coming back to a theme from earlier, Lehman Brothers' view of the net present value of the pipeline is that it has gone up. In 1995 there were 450 products in research included in our top 35 drug companies around the world. By the end of 1999, we were covering 617 products from the same cohort of companies. So there was more than a one-third increase in the number of products in the pipeline. But there was also a much bigger increase in the potential number of drugs with sales of over \$800 million, so that the net present value of later pipeline was clearly superior. See Figure 6.12.

An R&D spin-out is a restructuring tool that companies are considering in addition to mergers, acquisitions and alliances. Schering AG, for example, has published an intention to spin out its genomics operations. The pros and cons of this strategy are summarised in Box 6.2. In a separate organisation, managers should, in theory, have an easier time incentivising their staff; accessing world class technologies; and releasing capital to be invested elsewhere. That may in turn increase a company's earnings per share and it may provide an alternative acquisition currency. However, there are also problems such as: dual reporting; a limit to long-term growth driven by paying royalties; and the risk of a fragmentation of the company's culture. There is always an issue of minority shareholder rights too. On balance, the cons seem to outweigh the pros in our view but it is clearly something that companies are continuing to do whilst there is such a wide disparity in evaluation between biotech companies and pharmaceutical companies.



Figure 6.11 R&amp;D funding and pipelines

R&D funding for selected drug companies (US\$ million)									
Company	R&D 1999	Number of drugs by stage of development							Average funding per listed R&D project
		Pre-clin	P1	P2	P3	Filed	Intro	Mktd	
AHP	1400	0	1	7	9	5	7	19	48.3
Altana	136	1	3	1	2	0	1	2	17.0
Aventis	2492	10	0	13	13	3	8	40	53.0
Astra Zeneca	2769	14	7	18	10	2	0	33	54.3
BASF	369	2	5	6	5	3	5	12	14.2
Bayer	1221	12	5	6	2	1	3	11	42.1
BMY	1483	1	3	10	9	4	3	25	49.4
Glaxo									
Wellcome	2056	1	6	11	4	5	5	21	64.2
J&J	1663	0	1	5	9	2	5	20	75.6
E Lilly	1956	0	2	7	6	2	2	15	102.9
Merck	2040	1	5	7	8	2	4	24	75.5
Merck KGaA	397	5	4	10	3	2	3	11	14.7
Novartis	2377	1	6	8	8	5	8	22	66.0
Novo	391	0	5	4	2	1	2	5	27.9
Pfizer	3716	23	11	21	16	4	10	28	43.7
Pharmacia	1434	1	1	9	7	5	7	20	47.8
Roche	2020	0	3	7	6	2	6	35	84.2
Sanofi-Syn	961	17	7	19	7	2	2	20	17.8
SB	1649	8	7	13	8	1	0	18	44.6
Schering AG	715	1	1	5	4	3	4	28	39.7
Schering Plough	1128	1	1	4	6	3	3	18	62.7
<b>Total</b>	<b>32370</b>	<b>99</b>	<b>84</b>	<b>191</b>	<b>144</b>	<b>57</b>	<b>88</b>	<b>427</b>	<b>48.8</b>
Average	1541	5	4	9	7	3	4	20	

Source: Lehman Brothers.

Figure 6.12 Values of pipelines in 1995 and 1999

<b>Annual sales value (US\$ million)</b>	<b>800+</b>	<b>450-799</b>	<b>350-449</b>	<b>200-349</b>	<b>0-199</b>	<b>Total</b>
<b>1995 pipeline</b>						
Total number of drugs	15	27	106	138	164	450
Total NPV US\$ billion	12	16	42	34	13	117
<b>Average value per project (US\$ million)</b>						<b>260</b>
<b>1999 pipeline</b>						
Total number of drugs	94	156	31	142	194	617
Total NPV US\$ billion	208	97	13	40	22	380
<b>Average value per project (US\$ million)</b>						<b>616</b>

Source: Lehman Brothers.

Returning now to the issue of capital market valuations, large companies definitely earn a premium. Figure 6.13 shows the price/earnings ratio (PE) for a 30-company universe containing 15 large companies and 15 small companies, all in US health care to try and avoid any issues of currency distortion. From 1997 the average PE of the large companies has moved steadily up and away from that of the small companies. This is because there is a growing perception, rightly or wrongly, that there will be a move towards scale being important, not only in marketing, something that clearly is recognised, but also continuing in R&D.

The material presented so far as emphasised the importance of developing a marketing presence, especially in the US. Data here and in other chapters in this book have also raised questions about the effectiveness of external or networking strategies as competitive alternatives to in-house development. An important decision that companies must make, therefore, is how to pursue a marketing strategy: via co-marketing agreements or by developing their own infrastructure. It is interesting in this context to compare Lundbeck's strategy with its product Celexa, to Akzo-Nobel's strategy with Remeron. Lundbeck licensed Celexa to Forest Laboratories for

Box 6.2 Example of an R&D spin-out – the Schering AG genomics case

Pros	Cons
<ul style="list-style-type: none"> <li>● Incentivise staff more directly to their work/easier recruitment?</li> </ul>	<ul style="list-style-type: none"> <li>● Adds costs in dual reporting</li> </ul>
<ul style="list-style-type: none"> <li>● Ensure access to 'world class' technologies/staff</li> </ul>	<ul style="list-style-type: none"> <li>● May limit long term growth</li> </ul>
<ul style="list-style-type: none"> <li>● Enhance short term earnings/release of capital</li> </ul>	<ul style="list-style-type: none"> <li>● Fragmentation of culture</li> </ul>
<ul style="list-style-type: none"> <li>● Provide an alternative acquisition currency</li> </ul>	<ul style="list-style-type: none"> <li>● Issue of minority shareholder rights</li> </ul>
	<ul style="list-style-type: none"> <li>● Limited float paper may not be widely accepted</li> </ul>

marketing in the US. Forest Labs have done extraordinarily well, achieving much more rapid sales growth than Celexa achieved outside the US. Forest Labs initially co-marketed Celexa with Warner Lambert and when Warner Lambert pulled out following their merger with Pfizer, Forest Labs added another 700 or so sales reps themselves. Lundbeck gets a 15 percent royalty stream coming back from US sales of Celexa. However, Lundbeck does not end up with any infrastructure in the US which does not help Lundbeck's ability to develop into a long-term pharmaceutical company.

By contrast, Akzo-Nobel has tried a completely different approach. To market Remeron in the US, they have used limited promotion, only to psychiatrists, and this has earned them about an eight percent share of the market. However, despite the fact that their sales are much lower, Akzo Nobel may actually be making more profit than Lundbeck, with a much higher margin than 15 percent. In addition Akzo-Nobel are generating infrastructure for the future, because they have about 1,200 US sales reps, of whom a significant proportion are devoted to Remeron. Capital markets are not always very good at assessing, and appropriately valuing cases like this.

To finish with another note on how capital markets assessing companies' strategies, Figure 6.14 shows what they think of mergers and acquisitions. The lighter bars represent the share price change in

Figure 6.13 Capital markets place a premium on size – PE for large and small cap baskets of US health care companies



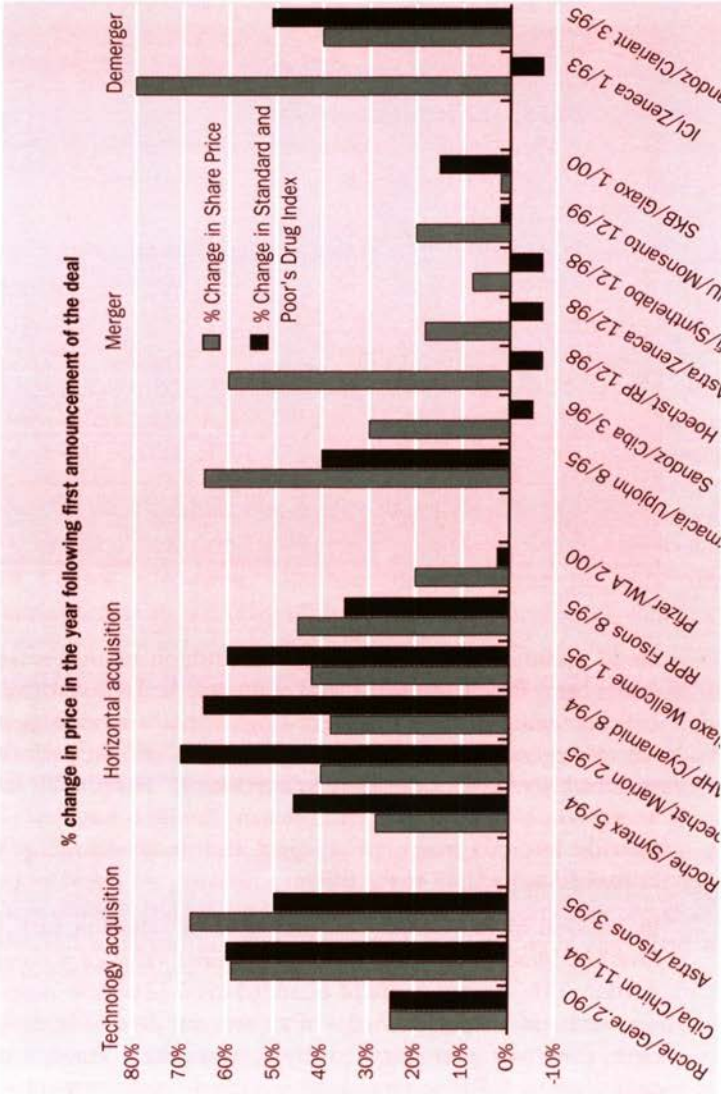
Source: Lehman Brothers.

the 12 months following the merger/acquisition announcement; the darker bar is the change in the level of the Standard & Poor drug index over the same period. So where the lighter bar is much higher than the darker bar, there has been a period of out-performance presumably related to the merger/acquisition. Historically mergers have been best accepted, but Lehman Brothers foresees a trend towards less acceptance of mergers and more favour given to horizontal acquisition in the future.

In addition to more traditional measures of valuation such as PE, investors increasingly look at the net present value of a company's portfolio. This approach can be extended to calculate how many more products – as yet unidentified – of a given size need to be developed over a certain period to justify a company's current market capitalisation. For a typical large capitalisation pure play drug



Figure 6.14 Share price responses to corporate strategies



company we can identify about 60 percent of the enterprise's value in terms of products that are on the market today, or from products that are still in development. This means that 40 percent of that enterprise's value must be attributable to products yet to be discovered and to other areas of infrastructure such as sales forces. Assuming, for simplicity, that all of this value can be attributed to new drugs and that as fully integrated companies they would expect to develop drugs with a 'normal' 35 percent pre-R&D but after-tax margin on them, we estimate that this group of companies will need to develop another 800 drugs by 2015 in order to justify their current aggregate valuation. If we look at the biotech-integrated companies, i.e. the likes of Amgen, they would need to generate about 107 drugs to justify their valuation.

Overall we need something like 2,000 new drugs by 2015, but we can see that the other biotechs and the platform companies such as Millennium and Incyte must generate a good half of the drugs that are going to be developed going forwards. Those in the pharmaceutical industry can decide whether that is right or not. If they believe that half of the new drugs will be originated from the likes of these biotech companies, then they should invest in them. If, however, they believe that more than half will come from the traditional pharmaceutical industry, then on balance they should invest in large capitalisation pharmaceutical companies.

## Chapter 7

# How to Regulate Pharmaceutical Companies: Ex Ante or Ex Post?

GEORGE YARROW

One of the unique features of the pharmaceutical industry is that it is subject not only to competition policy but also to additional regulatory supervision, both in terms of product safety and in respect of prices. In each member state of the EU there are different arrangements. In the UK, for example, the price regulation takes the form of the Pharmaceutical Price Regulation Scheme (PPRS).

The competition policy Articles 81 and 82 of the European Community Treaty is concerned with, and comments directly on, pricing. The Articles include lines such as: 'companies should not come together to fix prices'; 'if in a dominant position, the company should not charge excessive prices'; and indeed 'if the company is in a dominant position, it should not engage in undue price discrimination'. Yet, at the same time, we have additional regulatory instruments at the national level applied to the pharmaceutical sector.

The question of concern here is do we have, in current circumstances, a belt and braces policy where, in effect, we have got different instruments designed to do similar things, but which are not necessarily well harmonised with each other? This is a particularly important question at the moment in the EU. Take the UK as an example. Here the 1998 Competition Act<sup>19</sup> has been deemed a major development in competition policy. It is appropriate when a major reform like the Competition Act is introduced to look at the wider context. Do policies already in place mirror the provisions included in the Competition Act? If so, are they still needed?

This question is particularly important when dealing with areas such as price control. It is well known in the theoretical and empirical

<sup>19</sup> The Competition Act of 1998 came into effect March 1, 2000.

literature that one of the dangers of price controls is that they create distortions of markets and so they distort consumers' and producers' decisions. For pharmaceuticals perhaps the decision that is of greatest concern is the innovation decision. The 'wrong' price control policy, for example, could motivate companies to abandon investments in innovations in expectation that the additional costs and risks associated with innovation would not be reimbursed should they succeed in bringing that product to market.

It is always important to keep specific regulatory measures under review and to subject them to scrutiny as to their purposes and their effectiveness. In doing this it may be helpful to think of various policies as lying along a spectrum. At the one end lies ex ante regulation where, in effect, companies are given certain strict rules of behaviour. Price control in its strictest form can be regarded exactly as that: thou shalt price at this price and no other; or thou shall not price above this particular level.

At the other end of the spectrum are the kinds of competition policies that we find in Europe, which are largely ex post measures. These are policy interventions that occur after some event has happened that goes against the rules. The ex post approach does not set rules and prescriptions as much as set standards of behaviour. This is clearest in Article 82 of the European Community Treaty, or Chapter 2 of the UK Competition Act 1998, where, if a firm has a dominant position, it is prohibited from abusing that dominant position. The Article and Act say 'thou shalt not abuse a dominant position', which is a very general statement indeed. In effect this lays down a standard of behaviour, not a rule, which can only be defined after the event. The standard is largely defined through the case law that arises in response to the original prohibition. Cases occur and then the standard is given with greater precision and in greater detail through the individual cases. That is different from an approach that says we are going to take this sector and regulate it and there will be this and that rule from the outset.

Looking at different forms of price control, especially in the case of pharmaceuticals, one finds that in some jurisdictions the national



approach has already moved towards ex post regulation. The UK systems of price caps for utilities and the PPRS for pharmaceuticals, impose general overall constraints on revenues (in the former case) or profits (in the latter) that can be earned. But, from the beginning, these policies tend to be cast in fairly general form and apply a general constraint, leaving a considerable amount of discretion to companies subject to these kinds of arrangements to choose relative prices within them. Rather than fix each price, the company is told that a basket of products (in the case of utilities) or an overall level of profits (in the case of pharmaceuticals) should not go beyond certain bounds. (Although we should note that in pharmaceuticals, as in some of the utilities, there are restrictions on price increases for individual products). A question that then follows is how do you supervise the relative prices that emerge? Within any overall cap, relative prices could take various forms and some of these might be anti-competitive or abusive. In effect, there is a two-tier system. There is an overall cap but the supervision of detailed behaviour is the subject of another provision, maybe a no discrimination provision in the utility licence, or it may be the Competition Act or the EU Treaty and Articles. Any of these tools already sit quite a way along the spectrum towards ex post regulation.

What stops UK policy makers from opting for the full ex post approach? The pharmaceutical market is quite diverse. There are some groups of products where price competition is strong; others where price competition is weaker but still exists; and products where there is little or no price competition. Imposing an ex ante regulatory approach, which aims to restrict prices before anti-competitive behaviour actually occurs, constrains collectively this mix of different activities, all subject to different competitive conditions. That is the kind of circumstance where there is just concern that regulation may lead to distortions. In some cases, imposing a general type of cap gives companies an incentive to be predatory in certain areas where price competition is stronger.

Can competition policy in its current form cope with what are perceived to be the policy problems in the pharmaceutical sector? Are the instruments in the European legislature and at the member state

level sufficient to deal with policy makers' concerns? Are the competition policies adequate? One of the puzzles for pharmaceuticals is that the assumed inadequacies of general competition policy to retain sufficient competition in pricing have never been clearly demonstrated. People are justifiably worried about pharmaceutical prices, particularly for certain products, and the implications of them for health budgets. But the question as to whether the EU's Articles 81 and 82, the merger regulation and the new Competition Act in the UK are adequate for dealing with that particular set of problems has not been adequately studied. The presumption that sector specific regulation is also needed for pharmaceuticals remains untested.

## Chapter 8

# Competition Policy Issues for Regulators: a US Perspective on Pharmaceutical Industry Cases before the Federal Trade Commission

ROY LEVY and ABRAHAM WICKELGREN

### Introduction

It is hard to think of many industries that have contributed as much to human welfare as the pharmaceutical industry. The importance of the industry makes the job of the competition authorities that much more difficult and important. If Coca Cola and Pepsi Cola were allowed to merge then consumers would pay a higher price for soda pop and some would probably switch to other beverages, but many people would say that was a good thing. But having vigorous competition in pharmaceuticals is of crucial importance to consumers worldwide. That is why we must take care to allow pro-competitive, efficiency enhancing deals, while blocking transactions that are likely to harm consumers.

In recent years the pharmaceutical industry has changed at a rapid rate (Levy, 1999). Brand name and generic drug companies have consolidated. Some have entered into complicated agreements with suppliers and competitors. Large private buying organizations have developed. As new drugs have increased the size of the pharmaceutical industry the government has become more interested in prescription drug prices. The Federal Trade Commission (FTC) has had responsibility in the US for reviewing all types of transactions. The remarks here, which reflect the views of the authors and not those of the FTC or of any individual Commissioner, discuss some antitrust issues raised by three deals recently investigated by the FTC. The three cases demonstrate the breadth of issues involved in regulating the pharmaceutical industry, where competition via innovation and price both take place at different stages of the products' life cycles. The first two cases are examples of ex post intervention, to use the terminology of Yarrow. However, much of the FTC's work involves assessments of planned transactions where specific conduct has not yet taken place, such as planned mergers or planned product license deals. The third case is an example of the latter.

The first case involved efforts by Mylan Laboratories, a major generic drug company, to significantly raise the prices of two of its generic drugs - lorazepam and clorazepate – prescription drugs used for the treatment of anxiety and other related conditions. Mylan faced a lot of competition in these markets and had slim margins and profits. In the case of these two drugs, Mylan made deals to exclude its competitors from the market through the use of exclusive contracts with suppliers of active ingredients used to make these drugs. After striking these exclusive deals, Mylan eliminated competition both among its immediate competitors by forcing some of them out of the market and also among suppliers of active ingredients. Subsequently, Mylan raised the wholesale price of lorazepam from \$13.60 to \$378.40 for a bottle of 1,000 count 1 mg tablets, while in the case of clorazepate the wholesale price rose from \$22.72 to \$754.00 for a bottle of 1,000 count 7.5 mg tablets. Active ingredient prices rose initially from about \$775 to some \$150,000 per kg. The FTC found the deals underlying these price increases to be anti-competitive,<sup>20</sup> and authorized its staff to file a Federal District Court action against Mylan and its active ingredient suppliers. Recently, the FTC announced a suspension of trial preparations as Mylan offered to enter into a settlement agreement with the FTC.

Second, in one of a number of ongoing investigations of horizontal agreements between brand name and generic drug companies that arise in the context of the Waxman-Hatch Act of 1984, the FTC recently entered into a consent agreement with Abbott Laboratories and Geneva Pharmaceuticals. This was to resolve allegations that their agreement regarding the sale of terazosin tablets and capsules was anti-competitive<sup>21</sup>. Their sales agreement was an effort to extend patent-based market power through pay-offs and entry delays. Unlike a typical license agreement, it involved:

20 Federal Trade Commission v. Mylan Laboratories, Inc., et al., Complaint for Injunctive and Other Equitable Relief, (D.D.C. 12/22/98), 28.

21 In the Matter of Abbott Laboratories, Agreement Containing Consent Order, File No. 981-0395, and In the Matter of Geneva Pharmaceuticals, Agreement and Consent Order, File No. 981-0395.



1. provisions for payments flowing from the brand name to the generic drug company; and
2. provisions governing the timing of entry of generic versions of Hytrin, Abbott's brand name drug used to treat hypertension and other conditions.

Third, after an extensive investigation of Eli Lilly's acquisition of an exclusive license for R-Fluoxetine from Sepracor Inc.,<sup>22</sup> the FTC decided not to challenge this acquisition. However, the transaction raised some important antitrust issues. One centred on the question of whether R-Fluoxetine may become a close substitute for Lilly's Prozac, while another centred around a Lilly strategy to introduce R-Fluoxetine before the expiration of its Prozac patent in 2004 and before competition from generics. A third addressed Lilly's Prozac patent since only Lilly was able to market R-Fluoxetine before this patent expired. In other words, Lilly had a natural first-mover advantage it could exploit to the benefit of consumers.

### **Exclusive deals – the Mylan matter**

In its 1998 complaint in the Mylan matter, the FTC alleged that Mylan's exclusive licenses under Profarmaco's Drug Master Files (DMFs) for lorazepam and clorazepate represented an unfair method of competition in violation of Section 5 of the FTC Act<sup>23,24</sup>. Prior to

22 R-Fluoxetine is one of two molecules that make up Lilly's popular antidepressant drug Prozac. Sepracor separated these two molecules and obtained patent rights on R-Fluoxetine.

23 *Federal Trade Commission v. Mylan Laboratories, Inc., et al.*, Complaint for Injunctive and Other Equitable Relief, (D.D.C. 12/22/98), 18.

24 A DMF is a recipe for how the manufacturer makes the active ingredient. When a pharmaceutical manufacturer seeks approval to market a generic product in the US, it files an Abbreviated New Drug Application (ANDA) with the Food and Drug Administration. The ANDA must reference the DMF of the company supplying the active ingredient. The process of referencing a DMF can take up to a year or more. However, in this case, once Mylan secured exclusive licenses for Profarmaco's clorazepate and lorazepam DMFs, no other manufacturer could reference those DMFs.

the deals, Mylan engaged in significant price competition with rivals in both of these markets, and earned slim margins on both of these products. In the case of the generic market for lorazepam, an 18 million prescriptions market at the time, Mylan had over 50 percent of the market, and was vigorously competing with Purepac, Geneva and Watson/Royce.<sup>25</sup> In the case of the generic market for clorazepate, a smaller 3 million prescriptions market, Mylan sold to a majority of the buyers, but was rigorously competing with Watson. With regard to active ingredients for these generic drugs, two active pharmaceutical ingredient (API) suppliers – Profarmaco and FIS/SST – competed for sales of lorazepam and one active ingredient supplier – Profarmaco – provided API to Mylan and Watson. In the case of lorazepam, ANDAs of Mylan, Watson, and Purepac referenced Profarmaco's DMF, while ANDAs of Geneva and Royce referenced FIS's DMF. In the case of clorazepate, Mylan and Watson both referenced Profarmaco's DMF.

It was in this structural setting that Mylan management decided to raise generic drug prices by, in the cases of these two drugs, eliminating its competitors. This was part of a larger effort to change how generic prescription drug prices are set, moving markets from highly competitive positions to highly profitable ones. In the case of lorazepam and clorazepate, it took a number of important steps to do so. First, Mylan approached Profarmaco and agreed to an exclusive licence to Profarmaco's DMF for lorazepam and clorazepate. In exchange for the exclusive deals, Mylan paid Profarmaco sums of money and agreed to share its profits with Profarmaco. Mylan, through this agreement, immediately eliminated Watson and Purepac from the lorazepam market and Watson from the clorazepate market. Mylan, therefore, was the sole generic supplier of clorazepate and then sought to also eliminate Geneva and Royce, the two remaining rivals in the lorazepam market.

This leads to a second point. Mylan then approached FIS/SST and sought an exclusive licence under their lorazepam DMF. In exchange

25 It is noteworthy that, prior to the Mylan exclusives, Watson purchased Royce. At the time, Royce's ANDA for lorazepam referenced the DMF of FIS/SST.

for the licence, Mylan would share its profits with FIS/SST, but would not purchase any API from this supplier. This was clearly an effort by Mylan to secure the co-operation of FIS/SST in its efforts to become the sole generic supplier of lorazepam, a goal it intended to achieve by effectively paying off the active ingredient suppliers in both of these markets.

Third, although FIS/SST rejected Mylan's offer, this supplier did assist in Mylan's goal to monopolize the lorazepam market by significantly raising the price on its active ingredient sales. In fact, FIS/SST raised its API price to Geneva from \$775 to \$150,000 per kg. Watson/Royce decided not to purchase API at this higher price, meaning that Mylan, at least initially, faced only one generic competitor in the lorazepam market and was the sole supplier in the lorazepate market. The result was the higher prices mentioned earlier.

The FTC challenged Mylan and its API suppliers, but recently announced the suspension of its litigation against Mylan, pending the finalization of a settlement agreement with Mylan.

### **Horizontal agreements (Waxman-Hatch Act of 1984)**

To understand the Waxman-Hatch cases requires some background on the rules in the US for generic drug entry. When a generic drug firm wishes to sell a drug that is under patent, it submits an Abbreviated New Drug Application (ANDA). To secure regulatory approval, the ANDA must demonstrate that the drug is bio-equivalent to a pioneer drug. Under a provision of the 1984 Waxman-Hatch Act, the entrant must also certify that its drug does not infringe on an existing patent listed in the Orange Book (an FDA book that lists relevant patents) or that the patent is invalid. Once the pioneer is notified of such a certification, it has 45 days to sue the generic for patent infringement. If it sues within that time, the FDA cannot approve the ANDA for 30 months. This time limit would expire early if the generic drug firm won the court verdict in its patent litigation. Regardless of whether the pioneer files suit within the 45 days, it may later ask a judge for a preliminary injunction that would stay in place until the patent infringement suit is resolved.

To encourage generic manufacturers to challenge the validity of patents and enter the market, the first filer of an ANDA that certifies that the patent is invalid or does not block its product is given a 180 day period as the exclusive supplier in the market. The 180 day period begins either when the first filer enters the market or when a generic manufacturer wins a court verdict on the patent issues, whichever comes first. The FDA requires the generic manufacturer to withdraw its application if it loses on appeal.

In this environment, a generic drug manufacturer, Geneva Pharmaceuticals, filed for FDA approval of generic terazosin HCL in tablet form in January 1993. Geneva filed a similar application for a generic version of terazosin in capsule form in December 1995. In April 1996, Geneva filed a certification with the FDA that the listed Abbott patent was invalid. Within the 45-day period, Abbott sued Geneva for patent infringement on the terazosin HCL tablet product. However, Abbott inadvertently failed to file a similar lawsuit regarding Geneva's generic capsule version of the product, even though both tablets and capsules involved the same potential infringement issues. As a result, the FDA's review and approval process regarding the capsule form of generic Hytrin continued.

In late March 1998, when Geneva was about to receive FDA approval to market its unchallenged generic capsule, Geneva informed Abbott that it would launch its product unless Abbott paid it not to enter. Abbott estimated that the entry of a generic would cost it \$185 million in sales in the first six months (far more than Geneva hoped to earn by entering). Thus, Abbott and Geneva entered into a settlement agreement. Geneva agreed not to bring its generic product to market in either capsule or tablet form until the earlier of: 1) final resolution of the patent suit on the tablets, including appeal to the Supreme Court level, if necessary; or 2) entry into the market of another competing generic product. Geneva also agreed not to transfer, assign or relinquish its 180-day exclusivity right to market its generic product to another potential entrant.<sup>26</sup> In exchange, Abbott agreed to make

26 Ibid.



non-refundable payments to Geneva of \$4.5 million per month until the district court ruled. If the ruling was in Geneva's favour, Abbott agreed to put \$4.5 million monthly into an escrow account during the appeal process. The winner on appeal would receive the escrow funds. The trial court was not notified of the agreement.

Living up to its agreement, Geneva did not introduce its generic capsules after FDA approval in late March 1998 and in April 1998 it began collecting its \$4.5 million per month. The following September, the district court ruled in Geneva's favour, finding that Abbott's patent was invalid. Despite this victory, and the subsequent expiration of the Hatch-Waxman 30-month stay in December 1998, Geneva still did not enter the market with either its generic tablet or capsule. Instead, it continued to have Abbott make monthly \$4.5 million payments into the escrow account. On July 1, 1999, the Court of Appeals for the Federal Circuit affirmed the lower court's decision. Under the agreement, Geneva was to await Supreme Court consideration before entering. However, with the FTC's investigation pending, Abbott and Geneva ended the agreement, and Geneva finally entered the market in August 1999.

The FTC's complaint effectively alleged that Geneva, confident that it would win its patent infringement dispute with Abbott, planned to bring its generic terazosin HCL capsule to market as soon as possible after FDA approval, but its entry was delayed by an agreement with Abbott.<sup>27</sup>

This settlement between Abbott and Geneva is similar to others currently under investigation by the FTC. They all uniformly restrict the generic from entering for some period of time. In exchange, the potential generic entrant receives a payment from the pioneer until litigation is resolved, giving the generic an incentive to delay the resolution of litigation. Because subsequent generics cannot market their products (under Waxman-Hatch) until the first generic's 180-day exclusivity ends, any delay in entry by the first generic also delays subsequent entrants.

27 In the Matter of Abbott Laboratories, and Geneva Pharmaceuticals, Inc., Docket No. C-3945, Complaint, 21.

The basic motivation of these settlements is to preserve a monopoly for an extended period of time. Since the lost profits to the pioneer will greatly exceed the earnings of a generic entrant, an agreement that extends the life of an invalid or non-infringing patent causes consumers to face higher prices, but benefits both parties to the agreement. Arguably, in the case of dubious patent claims by the innovator drug company, such agreements should be per se illegal unless there is no compensation of any kind to the entrant; or unless there is immediate entry by the entrant in return for fixed lump sum payments. That is, settlements where the entrant pays for the right to enter immediately, or in which immediate entry is combined with an agreement about how much the entrant will have to pay the pioneer if it ultimately loses an infringement case, are unlikely to cause competitive harm.

Most of the settlements we have seen, however, do not have these characteristics. The parties to them often argue that agreements that involve payments to generic firms are necessary to reduce uncertainty associated with patent litigation. While this may sometimes be true, it may do so at the cost of the consumer. In other words, these agreements effectively give the pioneer firm the ability to protect its patent-granted monopoly without any court ruling that the patent is valid. Further, the disparity between the pioneer's monopoly profits and the generic producer's potential profits from entry give the generic firm an incentive to settle even the most meritorious case.

Generic firms sometimes claim that they would not enter in the face of such patent uncertainty. However, assume anti-trust authorities made an exception only for cases in which there was no chance that the generic would enter before the resolution of litigation. In such circumstances, pioneers would not offer pay-offs since they would know that the demand or acceptance of a payment by the entrant would imply that the pioneer was throwing away its money. Therefore, the appropriate policy may be to treat any such payments as per se anti-competitive.

The pioneer firm's best argument is that a generic manufacturer with very few assets has threatened entry. Thus, even if the pioneer ulti-

mately wins its case, it will not be able to recover all its lost profits from the generic entrant. The incumbent is effectively extorted. For example, assume that the pioneer's profits are \$20 million per week with no entry but only \$10 million per week with entry. The generic would earn \$1 million per week if it entered the market, all of which it would have to return to the incumbent if it lost the case. However, the generic has no other assets. Resolution of the case is years away, and both sides are certain that the patent is valid. There is no other entrant on the horizon. One might think that the incumbent could refuse to pay the entrant and that the entrant, facing certain legal defeat, would just fold. Yet the potential entrant could enter the market and challenge the incumbent to take its patent litigation to a verdict, lose an enormous amount of money, and potentially put it out of business should the pioneer firm prevail in the litigation. Alternatively, the pioneer firm can agree to settle with the potential generic entrant for a relatively small payment, say \$100 million. In the absence of an immediate deal, the potential entrant could come back a week later when the innovator is millions of dollars poorer and reinstate settlement discussions with the pioneer firm. Once a settlement is reached, the generic entrant would withdraw its product from the market and acknowledge the patent's validity. Under these circumstances, it is likely the incumbent will settle, and in fact will likely settle before the generic firm actually enters the market.

What is wrong with this argument as a justification for these settlement agreements? It would be supportable if it were impossible for an incumbent to get a preliminary injunction against entry. Yet, in addition to this legal approach, provisions of the Waxman-Hatch Act give pioneer firms 30 months, during which the FDA will not approve the first-filer's generic drug application, to get a preliminary or permanent injunction against any entry. These alternatives provide pioneer firms with more protection than firms in other industries receive. Further, the incumbent facing the threat outlined above is likely to have a persuasive argument to extend any preliminary injunction. In addition, by eliminating the ability of generic firms to receive payments, antitrust authorities would remove the incentive of an entrant to file an ANDA against a patent that was almost surely

valid, for the purpose of extorting a settlement payment. These considerations were incorporated into Abbott and Geneva's settlement agreements with the FTC.

### **The Lilly/Sepracor case**

In the Lilly-Sepracor case, Lilly proposed purchasing an exclusive licence for R-Fluoxetine (RF) from Sepracor. RF is closely related in chemical structure to Lilly's Prozac. Where Prozac contains both the R and the S isomers, RF is just the R isomer. Lilly purchased the intellectual property rights to RF from Sepracor as a potential replacement for and possible improvement over Prozac. While RF is very similar chemically to Prozac, the FDA will treat it as a new drug. At the time of the investigation, Prozac's patent was due to expire no later than July 2004 while RF will be protected until 2015.

Lilly's acquisition did raise some troubling competitive concerns because it could potentially limit competition between Prozac and generic drugs after the Prozac patent expires in 2004. To elaborate on this possibility, it is noteworthy that pharmaceutical firms compete in at least two distinct stages. At the first stage, a firm tries to persuade physicians to prescribe their drug over alternative drugs. Part of the physician's decision will depend on the relative prices of alternative drugs. Yet, because physicians are often not completely aware of relative drug prices and recognize that patients normally do not pay the full drug price, physicians' price sensitivity across drugs will likely be limited. The second stage arises when there is a generic equivalent available to the particular drug prescribed by the physician. In that case, when filling their prescription at the pharmacy, a patient can choose between the prescribed branded drug and its generic equivalent. Competition from generic entry typically causes branded drugs to lose 70 percent of their market within one to two years.<sup>28</sup>

By acquiring the rights to RF, Lilly may be able to bring RF to market before the Prozac patent expires. If Lilly's sales force could convince

28. Levy, *op cit*, 1999 pp.14-15.



physicians to prescribe RF over Prozac now, then after 2004 those patients using RF will pay more than they would if they were purchasing a generic version of Prozac. Because physicians are not completely price sensitive, they may prescribe RF without giving due consideration to the fact that after 2004 it will cost the patient much more than would generic Prozac. Of course, even without the acquisition, Sepracor could try to convince doctors to prescribe RF over Prozac. Indeed, because Sepracor earns no profits from Prozac sales, it has an even greater incentive to convince physicians to prescribe RF over Prozac. Yet, Lilly may have a greater ability to shift patients from Prozac to RF both because it controls the price and marketing effort of Prozac and because the Prozac patent blocks the introduction of RF until 2004.

It is important to recognize that the magnitude of the potential competitive harm from any such switching strategy is limited by the degree to which physicians and their patients will make a myopic decision to switch to RF when the added therapeutic benefit is not worth the added expense they will incur after 2004. Also, it is worth noting that there is little danger that this deal will cause patients to purchase either a less effective treatment or no treatment at all because of a price increase. After patent expiration, they can still purchase generic Prozac; before expiration, there is no cheaper alternative with or without the transaction.

Against these limited potential anti-competitive effects from the transaction, the FTC had to weigh the benefits from the early introduction of a potentially superior treatment. Blocking the acquisition could either preclude or at least delay the introduction of RF to the market, assuming it proves to be a safe and effective drug. Clearly, if the drug really is superior for even a small percentage of the market, any anti-trust challenge to the deal would create a real social cost. While RF could have still gone to market if the firms worked out a licensing agreement, Lilly would have little incentive to invest in developing and marketing RF without at least some prospect for long-term rewards. If physicians' decisions are in fact heavily influenced by marketing, as the most likely anti-competitive argument requires, then a lack of such incentives could severely impair patient access to

an improved treatment. On the whole, this argument is much more compelling than the danger of price increases that might potentially increase insurance costs.

This case also raised issues relating to innovation incentives. It could be argued that allowing Lilly to buy the intellectual property rights to RF reduces its incentive to produce its own successor for Prozac. However, small companies like Sepracor will have a much greater incentive to develop innovative new drugs if they can profit from these innovations earlier rather than later.<sup>29</sup> In addition, Lilly's original incentive to develop drugs like Prozac is enhanced by allowing it to take advantage of complementary innovations by companies like Sepracor. As a result, innovation market considerations did not justify blocking this acquisition either.

As the structure of pharmaceutical R&D changes and major companies conduct more of their innovations in collaboration with external actors, anti-trust analyses of both structural changes and pharmaceutical conduct will likely have to change as well. If more is done via the external network with value added by external companies, does the size of the major company well represent their dominance in a therapeutic category? Changes in who conducts sales may also have an impact on the question of dominance. For example, if contract sales lead to price interdependencies across therapeutic groups, then it may no longer be appropriate to narrow the focus of analysis to particular therapeutic categories or segments.

## REFERENCE

Levy, R. (1999) *The Pharmaceutical Industry: a Discussion of Competitive and Antitrust Issues in an Environment of Change*, Bureau of Economics Staff Report.

<sup>29</sup> In fact, Sepracor's ability to transfer its intellectual property rights to an existing patent holder is what allowed Allegra to come to market to replace Seldane, providing for the same or better allergy relief with much less severe side-effects.

## Chapter 9

# Competition Policy Issues for Regulators: a European Perspective

BERND LANGEHEINE

The European Commission has been actively involved with the consolidation process in the pharmaceutical industry as some major European companies were involved in important mergers and joint ventures. The Commission has also been following the co-operation agreements between pharmaceutical companies, in particular in the field of R&D. This chapter looks at how those mergers, joint ventures and co-operation agreements are viewed by European regulators in Brussels.

EU member states' price systems are not dealt with in this paper although cases involving prices are an area of concern for the European Commission. A judgement by the European Court on the Adalat case is pending, for example, and could affect the outcomes of other cases, such as the Glaxo Wellcome dual pricing case in Spain. The choice between ex ante and ex post control here is different from other sectors, in that the regulators and the regulators' intentions differ. What we are concerned with in applying rules on anti-trust or on merger control is the behaviour of companies or the structure of the market in order to ensure that we have sufficient effective competition. The price control systems that have been introduced in several member states are part of national social policy. This is something which the European Commission has been told time and again to keep out of. Hence, there is very little scope for the Commission to become involved, against the will of member states, in the social policy considerations that lie behind some of the price control systems.

What we are concerned with, and this will also be a point that will probably be discussed in the Glaxo decision, is whether agreements would be exemptable from the prohibition of Article 81. In other words, whether there would be pro-competitive effects that would outweigh the anti-competitive effects.

Turning to the question of competition and merger control, it is the task of the EU Commission to scrutinise all mergers that have a so-called 'Community dimension'. This basically means a global turnover of the companies concerned of over €5 billion and this includes most pharmaceutical mergers. The European Commission also looks at mergers occurring between non-European firms, provided that at least two of them have a turnover of at least €2.5 billion in the EU. Some lower thresholds apply in specific cases. If there are multiple notification requirements in at least three member states, then the total turnover threshold is brought down to €2.5 billion. The merger evaluation procedure is rapid. Clearance is normally given after one month, unless the European Commission discovers that there are competition problems, in which case a period of four months is added to the process.

Instead of merging, companies often engage in joint ventures, especially if they only want to carry out certain of their activities jointly. Under EU competition rules, joint ventures are undertakings that are jointly controlled by two or more undertakings. There are two types of joint ventures. The first is full function joint venture, which refers to a case where the new entity operates on the market, performing the functions normally carried out by other companies participating in that market. A full function joint venture must have its own management and access to sufficient resources to conduct its business activities on a lasting basis. The second type are joint ventures that take over only specific functions within the parents' business activities and do not have access to markets. R&D and production joint ventures often fall into this second category.

These distinctions are important because the two types of joint ventures are judged according to different criteria. Full function joint ventures fall under the merger control rules; the others fall under the rules for restrictive agreements. In the first type of legislation, a dominance test is conducted; in the second, the key question is whether there is an appreciable restriction of competition.

To understand the European Commission's merger decisions, its definition of a market and its methods for assessing dominance are



important. Remedies to remove competition concerns are often introduced in merger decisions. As far as market definition is concerned, basically the European Commission distinguishes between product markets and geographical markets. In product markets the Commission has grouped products into three categories: pharmaceutical specialities; active substances; and future products.

For 'pharmaceutical specialities', the European Commission considered it appropriate in most cases to base the product market definition on the third level of the anatomical therapeutic classification, ATC, though there have been a few exceptions. This allows medicines to be grouped together by reference to their composition and their therapeutic use. It is assumed that these groups of products generally have the same indication and cannot be substituted by products of other ATC III classes.

'Active substances' are treated as separate and specific markets, which are upstream of the market for pharmaceutical specialities. They may be manufactured for in-house purposes or they may be traded. Where active substances are almost exclusively manufactured for the party's own production, this will not normally raise competition issues.

In the pharmaceutical industry a full assessment of the competitive situation also requires an examination of the products which are not yet on the market but which are at an advanced stage of development, so-called 'future products'. The European Commission looks at R&D potential in terms of its importance to existing markets but also for future market situations. For future scenarios, the market definition can be based either on the existing ATC classes, or it can be guided by the characteristics of future products or the indications to which they will be applied.

The geographic component is important because a company operating in narrow geographic markets may have higher market shares than one with Europe-wide or world-wide markets. For pharmaceutical specialities the European Commission has assumed that markets are national. This is justified because national health authorities design purchasing policies for the sale of medicines and the resulting prices may vary considerably across member states.

There are differences in reimbursement levels and in the definitions of package size and brands. For active substances the Commission has established that the upstream markets are at least EU-wide, if not world-wide. For future products national restrictions again do not play an important role and markets are either EU-wide, or even world-wide.

Decisions have been slightly different with regard to pharmaceutical wholesaling, where the European Commission has found that the markets are essentially regional or local in nature. In one case, the alliance between UniChem and Unipharma, we referred the merger to the Italian competition authorities, who were better placed to decide on the operation.

Having defined the scope of markets, we turn to the assessment of dominance. The basic question is: above what threshold does market share become a problem? As a rule, the European Commission only analyses markets in which the parties have a combined share of 15 percent or more. Normally a detailed assessment is only necessary for the market segments in which the parties' activities overlap and result in a combined market share of more than 25 percent.

There are no fixed rules for how cases with a market share of 30 percent or more are decided. It depends on the circumstances of the case. Factors taken into account include the number and strength of competitors, barriers to entry, status of pipeline products, and various other factors.

If the market share is in the 30-35 percent range and the addition of market share through merger is smaller than five percent, then the European Commission has in the past considered it as little threat to competition. Even if the market share addition is more than five percent, the Commission has found that a combined market share of 30 percent is generally not a problem, provided that there are several other competitors in the 5-15 percent range, as well as other major pharmaceutical companies that might enter the market.

In general, a number of key issues factor into the decision. One is the difference of the parties in terms of size relative to the next largest

competitor. Another is whether the parties have recently increased their market shares or whether competitors have recently lost market shares. We would also look at the position of generic products, (whether they are strong or weak) and at the extent of new competition to be expected from pipeline products. Pipeline products are considered less relevant where the producer is not yet present on the relevant market.

The influence of rival companies on competition rarely depends on their numbers alone. Much more important are their relative strengths, their cost structures, their innovative capacities and their competitive strategies. Equally important is the structure and dynamic of the market concerned, for example: a level of transparency concerning price and quantity, the state of the product cycle (mature or new), excess capacity, and the structure and evolution of demand. All of these are factors that the European Commission would take into consideration. Member state regulations concerning registration criteria, procedures or reimbursement schemes are also important.

The threat of entry often affects our competition analysis, because it creates a disciplinary effect upon actual market participants. Whether the credibility of this threat is real, i.e. the contestability of the market, depends in turn on the importance of barriers to entry. The main barriers to entry in the pharmaceutical sector are the amount of time and expenditure needed for R&D, registration and marketing of products. The patent situation is another crucial factor for market entry. Entry barriers are particularly high as long as the active substance in question is covered by patent protection. If a merger creates a combination of overlapping patents, market foreclosure can result and market access may only be possible by imposing on the merging companies certain remedies, either to divest areas of R&D and production or to grant licences to viable and independent third parties.

In the pharmaceutical industry, a full assessment of the competitive situation requires the examination of products that are at an advanced stage of development but not yet on the market. But the market

strength of the undertakings in R&D is difficult to estimate, since success in R&D can normally be assessed only after it has been completed.

As a general rule, the European Commission takes a positive approach towards R&D co-operation between competitors, provided that they do not have significant market power in existing markets and there are no significant reductions in innovation. Nevertheless, licensing arrangements or mergers involving overlapping pipeline products can often only be cleared once appropriate divestitures or out-licensing to an independent third party take place.

The recent consolidation trend in the pharmaceutical sector provides some examples. In May 2000 the proposed Glaxo Wellcome/SmithKline Beecham merger gave rise to competition concerns in asthma treatment products. To resolve these concerns, the parties agreed to license out one of SmithKline's pipeline compounds but only in the event that competitors' pipeline products fail to reach the market.

Also in May 2000, the Pfizer/Warner Lambert merger raised competition concerns in the market for anti-Alzheimer products, where the parties combined would have captured high market shares in many member states, ranging from 60 percent to almost 100 percent in some cases. Pfizer's product is currently regarded as the premium standard in this category. Although investigations suggest that Alzheimer's disease represents an attractive market for future R&D, the European Commission could not determine whether the pipeline products currently under development would become viable competitors in the future. To ensure competition, the parties therefore divested all assets relating to Warner Lambert's Alzheimer product.

In many of these merger cases, in particular where US and European companies are involved, the EU Commission co-operates closely with the US anti-trust authorities. The co-operation focuses in particular on discussions about market definitions and remedies. Confidential information cannot be exchanged, however, unless the parties expressly grant permission.



Finally, a few words about R&D co-operation agreements. These involve the pooling of fewer resources than a full merger. By the end of the year, the EU Commission hopes to have in place a new R&D block exemption regulation and guidelines on R&D co-operation agreements. There are no guarantees that the Commission will actually adopt the text in its present form but some of the key points under discussion are as follows.

EU rules on R&D apply to all sectors, but they contain some elements, that are particularly relevant for the pharmaceutical industry. The new regulation includes a so-called block exemption, a legal text which exempts certain categories of agreements that do not exceed a certain market share (in this case 25 percent) from the prohibition of Article 81.

The guidelines distinguish between product markets, technology markets and competition in innovation. 'Competition in innovation' refers to R&D efforts. This more or less corresponds to the 'future markets' category in merger analysis. The challenge is to measure competition in innovation. There is a specific reference to the pharmaceutical industry in the guidelines where they assume that for this industry the process of innovation is structured in such a way that it is possible to identify so-called research poles. This would refer to Phase III trials and is similar to the approach recently adopted in the US guidelines about the collaboration of competitors through R&D agreements. The EU guidelines do not specify explicitly how many research poles must be left for an agreement to be exempted from the prohibition, but examples suggest that three research poles will be considered sufficient. It is clear that a co-operation agreement cannot be exempted and will not be exempted by the European Commission in cases where it is being proposed that the only two existing research poles be combined.

The European Commission normally views R&D agreements favourably. In fact, so far, there are no prohibition decisions in the books. This supportive stance is not well publicised as often cases are closed by administrative letters.

Pure R&D agreements only become a problem if competition through

innovation is significantly reduced. Even R&D agreements which include joint exploitation are generally acceptable assuming that the parties involved are not competitors, i.e. where they could not have undertaken the R&D on their own. Also, in cases where there is only a marginal overlap, the European Commission generally does not consider the co-operation restrictive of competition. That was the position, for example, in the 1997 Sanofi/Bristol-Myers Squibb case.

It is necessary to distinguish between R&D directed at the improvement of existing products and R&D directed at entirely new products. Competition problems are more likely to arise when existing products are to be refined or improved. If the R&D involves new products, then the analysis will focus on possible restrictions of innovation, such as the quality and variety of future products or the speed of innovation. If two firms which are engaged in the development of a new product start to co-operate at a stage where they are independently rather near the launch of the product, restrictive effects may arise if there is not sufficient competition in innovation left.

Industry argues that the old block exemption in the existing text is insufficient, that it is hardly ever used in practice, is much too narrow and too demanding for qualification. Under the new text, co-operation agreements would be exempted up to a market share of 25 percent, where the parties are competitors for existing products that are being improved. Of course, in the case where the parties are not competitors, this market share threshold is not relevant.

Joint exploitation will probably be covered for up to seven years. The time limit is five years at the moment. The separate 10 percent threshold for joint exploitation in the present regulation will be eliminated. The exemption continues to apply even after seven years where the combined market share of the parties does not exceed 25 percent. If that share goes beyond 25 percent, it does not necessarily mean that the agreement will have to end. The guidelines indicate that joint exploitation is individually 'exemptable' for a longer period where the parties can show that this longer period is necessary to perform the R&D and earn an adequate return on investment. In

particular, the pharmaceutical industry argues that the current five-year, and possibly even the new seven-year, period is too short. Companies will be responsible for providing evidence to support this claim on a case by case basis.

Another novelty of the new block exemption will be that there will no longer be a 'white list' of clauses that must figure in the agreement. There will only be a black list of clauses that are absolutely prohibited, such as price fixing (unless joint distribution is agreed), market-sharing, prohibition of passive sales and some other less important things. If one of these black-listed clauses is present, the whole agreement fails to qualify for the block exemption.

Some conditions must be fulfilled for the block exemption to apply. All parties must have access to the results of the R&D. There is only one exception and that relates to research institutes or companies that provide R&D as a commercial service and are not normally involved in its exploitation.

The prohibition of field of use restrictions remains in place, unless the parties are not competitors. In the latter case field of use restrictions will be possible. Joint exploitation must continue to relate to results of R&D that are protected by intellectual property rights.

In conclusion, there are two concerns at the centre of the EU's regulatory activity. One is the reduction of competition with regard to existing products, in particular where there are overlapping activities among the parties. This is critical in the range above 35-40 percent market share, unless there are very strong competitors or pipeline products and the barriers to entry are low. The reduction of competition with regard to innovation is also a concern and is measured for the pharmaceutical industry by reference to so-called research poles. At least three research poles will usually be required in order for a co-operation agreement to be approved.

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