EUROPEAN INNOVATION MONITORING SYSTEM (EIMS)

EIMS PUBLICATION N° 32

EUROPE'S PHARMACEUTICAL INDUSTRY:

AN INNOVATION PROFILE

BY

SPRU,
University of Sussex, UK

EUROPEAN COMMISSION

DIRECTORATE GENERAL XIII

The Innovation Programme

EIMS Project N° 94/114

THIS STUDY WAS COMMISSIONED BY THE

EUROPEAN COMMISSION,

DIRECTORATE-GENERAL "TELECOMMUNICATIONS,

INFORMATION MARKET AND EXPLOITATION OF RESEARCH",

UNDER THE INNOVATION PROGRAMME

STUDY FINISHED ON: AUGUST 96

Contents

		Page
1	Introduction	1
2	Current Developments in the Pharmaceutical Industry	2
3	Major Market and Technology Trends	12
4	Firm Level Analysis	24
5	Biotechnology - A New Route to Drug Discovery	40
6	Alliances, Linkages and Technology Transfer	49
7	Conclusions	56
REFERENCES		**61**

Tables:

1:	Trends in R&D Intensity of the Pharmaceuticals Sector	4
2:	Major Take-overs 1990-1996	8
3:	Top Twelve World Market Share with Newly Merged Companies	9
4:	Health Expenditure and Pharmaceutical Consumption in Developed Countries	13
5:	Pharmaceutical Production in Major World Markets	15
6:	R&D Intensity by Industry	18
7:	Trends in the Distribution of Pharmaceutical R&D	19
8:	Trends in the Distribution of US Patenting in Pharmaceuticals	21
9:	Top 50 Branded Products by Country of Origin	23
10:	Company Rankings by sales 1993	26
11:	Changing Places - the world's top 20 pharmaceutical corporations 1976-94	27
12:	Seller Concentration Ratios in the Pharmaceutical Industry	30
13:	Top 20 companies in terms of Pharmaceutical R&D expenditures	31
14:	Company market share in Europe, United States and Japan	34
15:	Geographic Location of Pharmaceutical Firms' US Patenting Activities	37
16:	Top Non-national firms patenting in Europe	38
17:	Top Ten Biotechnology drugs on the Market in 1993	48
18:	Alliances and Joint Ventures between US DBFs and leading European multinationals	50
19a:	US-DBFs involved in biotechnology alliances 1982-91	
19b:	Biotechnology Alliances 1992-94	
20:	Linkages between US-based facilities of European and Japanese companies	54
21:	Collaboration through publication - company profiles	55

EIMS 94/114

EUROPE'S PHARMACEUTICAL INDUSTRY: AN INNOVATION PROFILE

Margaret Sharp, Pari Patel and Keith Pavitt

August 1996

Final Report prepared for DG XIII - D-4
Contract: EIMS 94/114

Margaret Sharp/Pari Patel
Senior Fellow/Research Fellow
Science Policy Research Unit
Mantell Building
University of Sussex
Falmer
BRIGHTON
BN1 9RF
Tel: +44 1273 678169
Fax: +44 1273 685865
e-mail: m.l.sharp@sussex.ac.uk
p.r.patel@sussex.ac.uk

1 INTRODUCTION

1.1 The main objective of the study is to describe and explain intra-industry differences of innovative performance in the pharmaceutical industry (NACE 2423) across European countries.

1.2 One of the reasons for focusing on the pharmaceutical industry is that in sectoral comparisons of innovative performance between Europe, Japan and the USA, it emerges as one of the main areas of strength for Europe. It is a science-based industry with high levels of R&D intensity. Europe's capabilities date back to the late nineteenth century when the German chemical company, Bayer became the first major company to develop in-house R&D facilities which in turn became an internal 'engine' for innovation. Since then, German and Swiss companies have continued to be major players in the pharmaceutical industry, challenged in the post-war period by their US counterparts and more recently by the sharp rise of UK-based companies such as Glaxo. Cut backs in health care budgets combined with new routes to drug discovery being introduced as a result of new biotechnology-driven methodologies are currently stimulating major changes in both structure and strategy, with external sub-contracting of R&D and new product development becoming a more usual phenomenon than in the past.

1.3 This report uses publicly available qualitative and quantitative information to map a number of key trends in the industry since the 1980s:

- Rising health care costs
- Rising R&D intensity
- Increasing globalisation of R&D
- Increasing use of external sources of knowledge: alliances, mergers and acquisitions
- The rise of biotechnology

1.4 Its main aim is to examine how the innovative performance and strategies of European firms have been affected by these trends with the focus being a comparison between the leading European firms and their American and Japanese counterparts.

1.5 The report begins by identifying the main current developments in the pharmaceutical industry world-wide (in section 2) which have led to a squeeze on profits. In Section 3 the main consumption and production trends at the national level are identified. Section 4 uses publicly available data to make comparisons of technology and market trends at the firm level. The strategies of European companies on how to cope with the rise of biotechnology is focus of sections 5 and 6. Section 7 contains some conclusions and policy recommendations.

2 CURRENT DEVELOPMENTS IN THE PHARMACEUTICAL INDUSTRY WORLD-WIDE

2.1 The pharmaceutical industry is one of Europe's success stories. Emerging in the late nineteenth century as an adjunct to the chemical industry, it was for many years dominated by German and Swiss firms. After World War II the American industry emerged as a strong player, taking advantage of the incapacity of the German industry in the aftermath of the war and establishing itself, via subsidiaries, in many European markets. By the 1960s German companies had re-established themselves but failed to regain their pre-war market share. Since the 1960s it has been the British firms that have seen the strongest gains and this has helped to restore the European position. In 1995, of the 20 top ranking companies in terms of sales, 10, including the top two slots, were European firms, seven American and three Japanese.

2.2 In spite of its record of success, the European pharmaceutical industry is highly pessimistic about its future. Briefly, the main reason for this is that costs, especially R&D, are rising, and revenues are falling, resulting in a squeeze on profits. For an industry which

has enjoyed above average profits for a considerable period of time, this is an uncomfortable situation. It is worth exploring the developments which lie behind these trends.

High and rising levels of R&D intensity

2.3 Table 1 gives details of R&D intensity in the industry since the early 1970s. While there are significant differences between countries (which can to some extent be explained, as we shall see, by the degree to which the industry in that country is dominated by the leading firms in the industry) the other notable feature of the table is the rise in R&D intensity over time. Whereas in the 1970s, R&D intensity averaged 7-8 per cent in the leading drug producing countries (USA, Germany, Switzerland, UK and France) by the 1990s it averaged 10-12 per cent. There are two main explanations for these trends:

1 *Increased regulatory requirements* - over time safety checks on drugs have become more and more rigorous and time consuming. In the 1960s many compounds being tested were anti-infectives whose efficacy was readily apparent within a short time frame. Drugs now being developed increasingly target the chronic long term diseases such as cancer, heart disease and ageing, where efficacy takes time to judge and, more importantly, where side effects sometimes take years to become apparent. Regulatory authorities are becoming tougher; tests are more complicated and the time required to bring the drug to market is longer;

2 *Diminishing returns to drug discovery* - in the 1950s and 1960s, the so-called 'golden age' of drug discovery, new compounds for testing suggested themselves fairly readily and a number of major breakthroughs emerged from the exploitation of the properties of families of compounds such as the histamines, steroids, penicillin and the cephalosporins. As time went by all the ready targets had been investigated and the search had to be extended over a wider field and was therefore necessarily more expensive. The more targeted approaches to drug discovery, pioneered by Sir James Black with beta-blockers and cimetadine, helped to stave off diminishing returns, but

Table 1 Trends in R&D Intensity of the Pharmaceuticals Sector in selected OECD Countries: 1973 to 1992

	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992
Sweden	18.6	15.2	14.6	17.4	20.0	19.1	19.7	18.7	18.1	17.1	17.7	23.5	27.8	28.4	24.3	23.2	27.1	27.2	28.8	30.4
Denmark	12.2	10.6	9.4	9.3	9.1	9.7	9.9	8.9	8.7	9.4	9.5	9.7	9.1	10.0	10.2	12.2	14.3	16.4	18.3	18.0
UK	7.8	7.2	7.5	8.3	8.0	8.5	10.3	10.6	11.2	11.2	11.5	11.6	11.6	11.8	13.3	14.4	14.5	16.8	14.9	16.3
USA	7.9	8.0	8.8	8.4	7.8	8.0	8.9	9.1	9.5	10.2	10.6	11.4	11.0	10.4	10.6	13.1	12.8	12.7	11.5	14.3
Finland	9.7	9.5	10.0	7.8	8.0	7.7	8.4	9.3	10.2	12.3	12.8	10.7	11.3	14.4	13.5	13.3	13.0	13.6	12.3	12.1
Netherlands	9.0	8.7	9.9	10.7	10.5	10.5	10.1	9.8	9.3	9.7	9.3	9.3	9.3	10.5	10.7	12.7	12.1	12.2	10.1	10.5
Japan	4.0	4.3	4.7	5.0	4.9	4.8	6.1	5.6	5.7	5.8	6.7	6.9	7.8	7.3	7.5	7.7	7.9	8.6	9.8	9.8
Germany	7.6	7.8	8.1	8.3	7.7	9.7	9.9	8.7	7.5	8.5	8.4	7.4	7.4	7.9	9.6	9.6	9.5	9.2	9.1	9.2
France	5.2	5.1	5.3	5.5	5.6	5.6	6.2	6.3	6.6	7.0	7.1	7.6	8.1	7.9	8.4	7.9	8.3	8.8	9.0	8.7
Italy	4.0	5.1	5.1	4.7	4.9	5.2	5.7	5.4	7.2	6.8	7.6	6.5	6.3	6.5	6.3	6.3	6.3	6.3	6.3	8.1
Canada	3.2	3.1	3.1	3.1	3.0	2.7	2.9	3.5	3.6	3.7	3.7	3.2	3.3	3.9	3.3	3.9	4.9	6.4	6.4	6.4
Australia	4.1	3.7	3.2	2.9	3.0	2.8	2.3	2.0	2.0	2.1	2.3	3.4	4.0	4.6	6.0	6.5	6.0	6.0	5.3	5.2

Total R&D as a proportion of gross output

Source: OECD

the hope that biotechnology would short circuit the process and open up a whole new range of cheap and easy targets proved ill-founded. On the contrary, biotechnology has to date proved an even more expensive route to drug discovery.

2.4 A recent report from Lehmann Brothers[1] suggests that R&D costs have now become untenable. They calculate that it now costs $187 million ($120m grossed up over the 8-10 years taken) on average to launch a successful new drug. If allowance is made for R&D which goes into drugs which fail to make the grade, then the cost goes up to $359 million.[2] Even to break even requires profitable sales for 10 years with peak sales of at least $260 million. Lehmann Bros calculate that to obtain a 15 per cent rate of return on the $22.7 billion spent by the pharmaceutical industry on R&D in 1993 requires growth of 13 per cent per annum. As such growth rates are not feasible in the current market conditions, the conclusion has to be that current levels of R&D are untenable and that some way has to be found to cut the costs of new drug development.

Pressures to cut health care costs

2.5 Company profits have come under pressure from another source in recent years. With the exception of the US, the main funder of health services in developed countries is the public sector (see below Table 4). A combination of slow growth, rising unemployment and an ageing population has put intense pressure on welfare budgets at a time when the buoyancy of tax and social security revenues has disappeared. Governments have sought to make savings and the high prices (and high profits) of the pharmaceutical companies provided an obvious target. In Germany, for many years one of the few countries in Europe where there were no controls over drug prices, stringent controls were introduced and doctors have been enjoined (as they had earlier in the UK) to limit prescribing to a 'limited list' of

[1]PharmaPipelines: Implications of Structural Change for returns in the pharmaceutical industry Lehmann Bros Pharmaceutical Research London. June 1995

[2]This was the figure quoted by the Office of Technology Assessment in their recent survey of innovation in the pharmaceutical industry.

branded pharmaceuticals and to use generics where possible. Even in the US, where health care is largely privately funded, the costs of supporting the publicly funded Medicaid (for low income families) and Medicare (for the elderly) have become insupportable, and the soaring costs of private health insurance led to health care reform being one of the main issues in the 1992 Presidential election. As might be expected, the pharmaceutical industry in America was amongst the most vociferous opponents of Mrs Clinton's reform proposals.

The search for savings - mergers, acquisitions and managed care organisations

2.6 The response of the pharmaceutical industry to these pressures has been to look on the one hand for savings, particularly in R&D expenditures, and on the other for unexploited areas of profitability. The first has led in a number of different directions:

1 *Extending patent life* - as regulatory procedures lengthened the time needed for clinical trials so the effective life of patents had been eroded. In the 1960s when a 5-7 year period of discovery/development was common, a 20 year patent enabled the company introducing a new drug to reap 'premium' profits for 13 years provided no major competitors emerged. Development times of 10-12 years cut 'effective patent life' back to 10 or 8 years. A concerted campaign by American companies in the 1980s secured an extension of patent life by 5 years for products affected by such delays, and this was followed by similar moves in Europe. The recent GATT round harmonized US patent laws with those of other countries and makes the patent start from the time when the patent is *filed* (previously in the US it had been from the time it was granted). However, the provision for the five year extension remains where there are undue delays in the patenting process.

2 *Parallel trials and simulations* - in seeking savings in the R&D process, many drug companies have experimented with ways of short circuiting the lengthy development period. Increasing use is being made of molecular modelling techniques which enable companies to simulate the effects of drugs. Such developments have been particularly

useful in the early phase of development but (rightly) cannot substitute for clinical trials at later stages. It has, however, provided for effective screening and companies making extensive use of the process (eg Glaxo, Zeneca) claim that it is highly cost effective in helping to slim the number of drugs under development. At the same time, companies moving into clinical trials, which have normally been undertaken on a sequential basis, are 'doubling up' and running two trials in parallel. This, too, seems to have been effective and companies are reporting a time saving of up to three years on development times.[3]

3 *Collaborations* - an increasing number of products are being licensed-in by pharmaceutical companies as a response to the emergence of biotechnology and the need to cut costs. Where two companies cooperate in the development of a new drug, development costs are shared. Traditionally pharmaceutical companies have not liked such collaborations. In the last few years, 'vertical collaborations' between large companies and small specialist firms (eg biotech companies) have become common. At the same time cost pressures are now making 'horizontal' collaborations between large companies at the R&D stage of development much more routine.[4]

4 *Mergers* - the logic that underlies collaborations leads inevitably to mergers. Given the relatively small (world) market share enjoyed by even the largest companies, pressure on profit margins has been the underlying factor in the large number of mergers in the sector in recent years. In 1989 the first of the 'mega-mergers' involved mainly US companies: Bristol Myers with Squibb, Smith Kline with the UK's Beecham, and Dow with the mid-size US company Marion Merrell, and in 1990 Rhône Poulenc acquired Rorer. The recession brought a lull, but 1994 and 1995 have seen a renewal of merger activity, the largest being Glaxo's take-over in early 1995 of their fellow UK company, Wellcome for $14.5bn and the agreed merger of Sandoz with Ciba Geigy to form the new Swiss company, Novartis (see Table 2). Although

---

[3]See David Bloom: 'Mergers and the Future of R&D - big is not always beautiful', *Scrip Magazine*, July/August 1994, pp 20-21 and Roger Longman: 'Pharmatactics in an age of strategic diversity', *Scrip Magazine*, October 1995, pp 30-34.

[4]See Roger Longman, *op cit.*

Table 2 Major Take-overs 1990-1996

Year	Target	Buyer	Price
1990	Rorer	Rhône Poulenc	$3bn
1994	Sterling Health[1]	Elf Sanofi	$1.8bn
1994	Syntex	Hoffmann LaRoche	$5.1bn
1994	American Cynamid	American Home Prod	$9.7bn
1994	Sterling Health[2]	SmithKline Beecham	$2.9bn
1995	Wellcome	Glaxo	£8.9bn (c $14bn)
1995	Marion Merrell Dow	Hoechst	$7.1bn
1995	Boots	BASF	$1.3bn
1995	Fisons	Rhône Poulenc Rorer	$2.7bn
1995	Pharmacia	Upjohn	Agreed merger
1966	Sandoz	Ciba Geigy	Agreed merger
Mergers involving biotechnology companies			
1990	Genentech (60%)	Roche	$2.1bn
1991	Cetus	Chiron	$650m[3]
1993	Synergen	Amgen	$260m[3]
1994	Chiron (49.9%)	Ciba Geigy	$2.1bn
1995	Affymax	Glaxo	$0.5bn

1 This consists of just the prescription drug division of Sterling Health.
2 SKB acquired the OTC division of Sterling Health. It subsequently sold the N American part of the operation (including Bayer's aspirin) to Bayer for $1 billion.
3 These two cases were of one biotechnology firm acquiring another one.

American Cyanamid's take-over by American Home Products was a US:US merger, Glaxo:Wellcome a UK:UK affair and Sandoz:Ciba Geigy and all Swiss merger, the remaining seven mergers recorded in Table 2 have been cross-Atlantic, with the European firm the more pro-active partner. The overall result of all this merger activity has been a considerable increase in concentration. The top ten companies now control 33 per cent of the world market (Table 3). They enjoyed an average profit margin of 18 per cent and an R&D investment totalling $9.8 billion. (*Scrip Magazine,* May 1995, p 25). Nevertheless, there is considerable scepticism as to how far mergers will lead to cost savings. Many commentators point to the relatively higher profit record of the non-merged companies, the disruption and extra administration costs caused by merger and conclude that there may be few if any

Table 3 Top Twelve World Market Share with Newly Merged Companies

	Company	% Market Share 1995/6
1	Glaxo Wellcome	4.7
2	Novartis (Sandoz + Ciba Geigy)	4.5
3=	Merck	3.5
3=	Hoechst/MMD	3.5
5	Bristol Myers Squibb	3.1
6	Am Home Products	3.0
7=	Pfizer	2.9
7=	Johnson & Johnson	2.9
9	Roche	2.6
10	SmithKline Beecham	2.5
Total Top 10		**33.2**
11	Rhône Poulenc	2.2
12	Bayer	2.1

Source: IMS AG Pharmaceutical Review 1995 edition. Quoted in FT Survey. 25 March 1996.

gains from merger. In particular, there are doubts as to how far merger can lead to real savings in R&D.[5]

2.7 The other strategy to counter pressure on profit margins has been for the companies to diversify into new areas of potential profit. Two routes have been particularly popular:

1 *Over-the-counter and generic sales* - for a long time the 'ethical' drug manufacturers scorned the over-the-counter (OTC) market as 'patent medicines' of the old wives' variety. The introduction of government approved limited lists combined with the increasing number of mainstream remedies whose patents were expiring (and which would therefore become prey to generic imitations) has led many companies to

[5]See in particular Robin Davison: The future for R&D investment - the law of diminishing returns *Scrip Magazine* July/August 1994; and Moira Dower: To merge or not to merge Scrip Magazine May 1995. The big savings from merger in fact come in administration and sales. Many companies have large staffs dedicated to sales in one country (because health systems vary from country to country). Merger enables considerable rationalisation amongst such staff.

reconsider their positions. Far from being pressured to keep drugs on prescription, governments were confronted by requests to allow low dosage non-prescription formulations for drugs such as Tagamet and Zantac. With patents expiring the companies have been anxious to keep as much of the branded market as possible; equally, where price discrimination is possible (and regulation fragments markets) they have been more than willing to play this game (which helps to explain the very considerable price variations across Europe). So far the UK and German governments have been more inclined to accede to the companies requests than the US authorities. Simultaneously there has been revived interest in the OTC operations, the biggest deal being in 1994 when SmithKline Beecham bought Sterling 's substantial ($2.9bn) OTC business from Kodak, only to sell off the North American side to Bayer (which thereby regained its name and trademark in N America for the first time since 1939).

2 *Pharmacy Benefit Management and Managed Care* - with reforms in the US health care system encouraging the development of health maintenance organisations (HMOs),[6] a number of pharmaceutical companies sought to pre-empt the system by allying themselves with the suppliers of care. Merck was the first big company to move in this direction by means of a $6.6 billion deal in 1993 with Medco, one of the largest suppliers of drugs to the HMOs. This was followed in 1994 by further deals involving SmithKline Beecham, Pfizer, Bristol Myers Squibb and Lilly. With 115 million people in the US in HMO plans in 1994, the implications of their being tied into purchasing from specific pharmaceutical companies caused interest from the US anti-trust authorities, who rapidly indicated that they would not look favourably upon any purchasing restrictions imposed on HMOs and demanded that their consent was obtained to any further mergers.[7] This rapidly put a damper on what had seemed, briefly, to be a strategy about to transform the whole of the pharmaceutical industry.

---

[6]Integrated health care organisations where physicians are linked into hospital groups to offer the individual a 'managed care' package for an annual per capita payment - given the high costs of health insurance, many individuals and companies found such packages to be preferable.

[7]See G Tobias and N Faigan: 'US reform is dead - long live reform', *Scrip Magazine*, January 1995, pp 16-18.

3 *Pharma-economics* - links between the pharmaceutical companies and the HMOs has led to the development of another new promotional idea - pharma-economics. Given an organisation such as an HMO (or the NHS in Britain - which has been for a long time the equivalent of a national HMO) with a relatively stable population of patients, it is possible to track the long term response to different types of care and medication. By using patient records in this way, the companies hope (a) to show that drug therapy can be just as cost effective, if not more cost effective, than other forms of intervention; and (b) to identify which types of drug therapy are the most cost-effective.

The pharmaceutical industry in the 1990s

2.8 The upshot of these trends has been to create turmoil in an industry which for years has been remarkable for its stability. As we shall see when we discuss firm level data, some thirty firms have dominated the 'ethical' or prescription drug industry for the last fifty years. While some have changed places within this cohort, the group as a whole have remained surprisingly constant. Now these old certainties are breaking. The search for cost savings is driving trends towards merger. Changes in technology, particularly the advent of biotechnology and new routes to drug discovery, have destroyed the unique advantage of the former R&D departments - mastery of synthetic organic chemistry; created a new cultural divide *within* companies (between chemistry and biology) and caused many, for the first time, to look beyond their own internal resources for new ideas and new competencies. The following sections explore these developments in more detail focusing in particular on the European industry and its innovative record.

3 MAJOR MARKET AND TECHNOLOGY TRENDS

Consumption

3.1 The European Union (EU) grouping of 15 countries now constitutes the world's largest market for pharmaceuticals. Table 4 shows that total consumption for the EU 15 using 1989 figures totalled over 57 BECUs, compared to 50 BECUs for the United States and 36 BECUs for Japan. Within the EU, the largest markets are Germany (14.7 BECUs) and France (13 BECUs) , followed by Italy (10.9 BECUs) with the UK (5.9 BECUs).

3.2 In terms of per capita consumption, the United States at 200 ECUs per head is relatively modest compared to Japan at 295, Germany 240 and France at 233 ECUs per head. As might be expected the poorest countries of the EU, Greece, Portugal and Ireland have the lowest per capita expenditure (59, 54, and 68 ECUs per head respectively). However, Norway (105), the UK (104) and the Netherlands (111) all record well under half German per capita expenditures and illustrate that it is not always the poorest who spend least. Indeed, expenditures per capita depend to a considerable degree upon the type of health delivery system and, in particular, the price regimes within such systems. The British National Health Service (NHS), for example, not only regulates the prices that may be charged for pharmaceuticals through the Pharmaceutical Price Regulation Scheme (PPRS) but also limits the range of products that may be prescribed, encouraging the use of generics wherever possible. By contrast, in Japan most doctors still dispense their own prescription drugs, on which they take a percentage mark-up, and therefore have a built-in incentive to prescribe the most expensive. The variations in terms of ex-factory prices (Column 3 of Table 4) are even greater, again reflecting the different regimes operating in the different countries,[8] and illustrating how far the EU has to go to achieve a single market in pharmaceuticals (and why manufacturers are so worried about parallel importing).

[8]The British NHS, for example, has always had considerable clout in its negotiations because it was the main purchasing authority for the whole of Britain

Table 4 Health Expenditure and Pharmaceutical Consumption in Developed Countries

	ECUm* 1989	ECU per head 1989	ECU per head (1) 1989	Total health expenditure as % of GDP 1970	1980	1985	1990	Pharma Consumption as % of GDP 1989	As % health care spend 1989	% funded by public source 1989
Austria	1,069	141	62	5.4	7.9	7.6	8.4	0.87	10.9	68
Belgium	1,763	179	74	4.1	6.7	7.4	7.4	1.36	19.0	58
Denmark	627	122	54	6.1	6.8	6.3	6.2	0.71	11.3	61
Finland	760	155	77	5.7	6.5	7.2	7.4	0.79	10.7	50
France	13,066	233	99	5.8	7.6	8.5	8.9	1.60	18.8	64
Germany	14,754	240	95	5.9	8.4	8.7	8.1	1.46	17.9	73
Greece	585	59	27	4.0	4.3	4.9	5.3	1.51	29.7	70
Ireland	267	54	34	5.6	9.0	8.3	7.1	0.82	11.1	68
Italy	10,986	190	88	5.2	6.8	7.0	7.6	1.51	20.0	70
Netherlands	1,654	111	45	6.0	8.0	8.0	8.1	0.89	10.7	68
Portugal	685	68	39	3.1	5.9	7.0	6.7	2.17	31.0	57
Spain	4,085	104	52	3.6	5.6	5.7	6.6	1.28	20.4	71
UK	5,865	103	54	4.5	5.6	5.8	6.1	0.85	14.3	78
Sweden	1,387	164	73	7.2	9.4	8.8	8.7	1.01	11.7	75
Total EU	57,553	165						1.32	16.7	67
Norway	443	105	46	5.0	6.6	6.4	7.2	0.58	8.0	76
Switzerland	1,395	179	89	5.2	7.3	7.6	7.4	0.92	12.8	64
Total EFTA	5,054	170	84					0.90	10.7	65
USA	49,708	200	110	7.4	9.3	10.7	12.4	1.15	9.8	10
Japan	36,316	295	198	4.4	6.4	6.5	6.5	1.53	29.5	85

Note: * Conversion to ECU according to end-of-year parity.
1 At ex-factory prices

Source: MEFA, 1992: Remit Consultants. Quoted in Mossialos, E; Kanavos, F and Abel Smith, B (1993), Table 2.3

3.3 The remaining columns in Table 4 go further to illustrate the variations in health regime between countries. The United States now spends 12.4 per cent of GDP on health expenditures, compared to the EU's lowest, Greece, at 5.3 per cent but with the UK (6.1 per cent) and Denmark (6.2) the next lowest spenders. Every country, except Denmark, has seen a considerable rise in health care expenditures as a per cent of GDP over the course of the last two decades, but there is some evidence that the rise has been slower in the last decade (almost certainly reflecting the tightness of public sector budgets). There are interesting variations in the proportion of the health budget devoted to pharmaceuticals. In the EU, Greece and Portugal top the list with 29.7 and 31 per cent respectively, a figure matched by Japan at 29.5 per cent, whereas the US records a figure of 10.7 per cent. Within the EU, the Scandinavian countries and Austria show the lowest percentages at approximately the 10 per cent mark, with Britain somewhat higher at 14.3 per cent. Britain has the highest share of pharmaceutical expenditures funded by the public sector (78 per cent) and Finland has the lowest at 50 per cent. The EU 15 average was 66 per cent as of 1989.

Production

3.4 Table 5 shows the production of pharmaceuticals within the EU, compared to the US and Japan. The EU15, as a whole, top the world production league, with 58 BECUs in 1990 compared to 42 BECUs in the United States and 30 BECUs in Japan.[9] These figures include the production of foreign multinationals within the respective countries so that, for example, the British figure includes the of production of companies such as Merck or Pfizer in Britain. The figures indicate that the EU15, as a whole, is a marginal net importer from the rest of the world.[10]

---

[9]1990 figure which gives a better idea of relativities than 1989 figure. See footnote to Table 5 about yen/ECUs values.

[10]In 1989 production in the EU 15 was 54.5 BECUs and consumption was 57.1 BECUs. Including Switzerland, Europe as a whole becomes a net exporter. Switzerland however publishes remarkably few statistics which make it very difficult to make precise comparisons.

Table 5 Pharmaceutical Production in major World markets (in ECUs)

	1981	1986	Market share (%)	1989	1990	Market share (%)	1991	Market share (%)	Growth rate 90/86 ('%)
Germany	6,327	9,573	24.4	11,745	12,512	21.5	15,085	24.1	40
UK	4,661	6,606	16.8	9,418	9,433	16.2	10,780	17.2	44
France	5,513	8,834	22.5	11,325	12,446	21.4	13,343	21.3	54
Italy	4,540	6,523	16.6	8,993	10,271	17.7	11,111	17.7	47
Spain	na	2,611	6.6	4,416	4,881	8.4	5,560	8.9	171
Netherlands	906	943	2.4	1,402	1,455	2.5	1,568	2.5	42
Belgium	na	1,077	2.7	1,450	1,589	2.7	1,718	2.7	na
Sweden	na	613	1.6	1,196	1,505	2.6	na	na	145
Ireland	na	300	0.8	662	792	1.4	na	na	164
Denmark	na	724	1.8	950	1,053	1.8	1,086	1.7	45
Austria	na	535	1.4	666	719	1.2	812	1.3	34
Greece	na	296	0.8	356	404	0.7	456	0.7	36
Portugal	na	288	0.7	502	581	1.0	686	1.1	102
Finland	na	358	0.9	432	482	0.8	489	0.8	35
EU Total	na	39,281	100.0	53,513	58,123	100.0	62,694	100.0	45
Switzerland	na	na		na	3,378		na		na
Norway	na	44		347	352		na		700
USA	20,673	35353*		41,031	42,113		na		19
Japan									
(ECUm)**	15,629	16,911*		41,987	30,544		33,935		148*
(Ybn)	3,679	4,281		5,502	5,595		5,697		31*

Notes: * Data available for 1985. Accordingly, growth rates have been estimated with respect to 1985, where applicable.

** The ECU valuation has affected positively the performance of Japan. For this reason, we include output figures in yen denomination and measure the output growth rate, which, in terms of yens, is substantially lower than the one in ECU terms.

Source: Mossialos, Kanavos and Abel Smith, 1993, Table 2.6, p 12.

3.5 Within the EU, Germany, France, the UK and Italy emerge as the major producers, although Spain, with a production of over 5 BECUs and recording a growth rate of 174 per cent over the period 1986-1990, is rapidly gaining ground. Germany and France are both net importers of pharmaceuticals, whereas the UK is a substantial net exporter. Switzerland, with a population of less than one tenth that of France, Italy or the UK, records a production of 3.3 BECUs to consumption of 1.3 BECUs and should also be considered a major European producer. It is also worth noting the rapid expansion of production of Ireland which has attracted substantial investment from US multinationals within the last decade.

R&D, patents and new chemical entities

3.6 The modern pharmaceutical industry came into being in the post-1945 period based on the development of a new range of chemically-based therapeutic drugs, the first of which , the sulphonimides, emerged in the 1930s. The 1950s and 60s, often now referred to as the 'golden age' of the pharmaceutical industry, saw a multiplication of such products through the exploitation of families such as the anti-histamines and the emergence of a whole range of new anti-bacterial drugs based on the development of the penicillins and cortisone. Innovation was the key to success and a high-profile innovative drug yielded high profits which could be ploughed into R&D to produce yet more new drugs. The key was to discover new chemical entities (NCEs) of potential therapeutic value, patent them and bring them to market. There were, of course, uncertainties - not every new drug was a winner - indeed the process has been described as molecular roulette - and after the thalidomide scare of the early-1960s the authorities demanded increasingly stringent testing procedures before authorising use. Such regulation, however, played into the hands of the existing companies by requiring substantial up-front R&D expenditures and delaying profitability. This effectively blocked entry since only well established companies could afford such outlays.

3.7 Pharmaceutical companies thus invest in R&D:

(i) in order to discover/invent innovative new drugs which will give 'first mover' advantages and bring appropriate monopoly profits;
(ii) in order to prevent competitors from enjoying too great a profit from such first mover advantage;
(iii) in order to meet the stringent regulatory requirements in relation to the toxicological and clinical testing of any drug and to prepare the drug in other ways for market - eg in terms of formulation and dosage requirements;

Items (i) and (ii) might properly be described as 'research' whereas (iii) comes closer to development. The whole process seldom lasts less than eight years and more frequently lasts 10 to 12 years. Estimates of the cost vary, but allowing for failures, the OTA (1993) put the cost higher at $359m.[11]

3.8 Given these costs it is hardly surprising to find that the pharmaceutical industry is characterised as highly R&D intensive, or that the proportion of sales devoted to R&D has been increasing over time (as the regulatory hurdles have increased). Table 6 (together with the earlier Table 1) shows that pharmaceuticals, together with electronics and aerospace, tops the R&D league tables among industries.

3.9 Table 7 examines the trends in the distribution of R&D expenditures among seven European countries for which time series R&D data are available and compares European performance with that of the US, Japan, Canada and Australia. The total expenditures (in current prices) of these countries have risen from $1.7 billion[12] in 1973, to $5.1 billion in 1981, and to $18.7 in 1992. Until the early 1980s the EU accounted for roughly the same proportion of this total as the US (around 40%), but this has declined in the last 15 years,

[11]It is estimated that for every 100, 000 compounds screened as possible new therapeutic agents, only 100 make to further investigation, only 10 to clinical trials and only one to be launched as a drug. The figure quoted takes account of the costs associated with the screening and testing of the 99,999 other molecules! Dimasi *et al* (1991) put the cost somewhat lower than the FDA - at $250m.

[12]All national currency data converted to US dollars using Purchasing Power Parities

Table 6 R&D Intensity by Industry 1992 (BERD/production in percentages)

Sector	USA	Japan	France	Germany	Italy	UK	Netherlands	OECD-12
Total Manufacturing	3.2	2.5	2.5	2.3	1.1	2.2	1.5	2.5
Food, beverages, tobacco	0.3	0.6	0.3	0.1	0.1	0.3	0.3	0.3
Textiles, footwear, leather	0.2	0.8	0.2	0.2	0.0	0.1	0.2	0.3
Wood and wood products	0.2	0.3	0.1	0.2	0.0	0.0	0.0	0.2
Paper, printing	0.5	0.3	0.1	0.1	0.0	0.1	0.0	0.3
Chemicals	3.7	3.5	3.0	2.7	1.9	3.5	2.6	3.2
Industrial chemicals	3.3	4.5	3.4	3.9	1.3	2.6	3.6	3.3
Pharmaceuticals	14.3	9.8	8.7	9.2	8.1	16.3	10.5	11.9
Petroleum refining	1.5	0.9	0.7	0.2	0.6	0.8	0.6	1.0
Rubber and Plastics	1.4	1.5	1.5	0.8	0.5	0.2	0.5	1.2
Non-metal mineral products	0.9	2.5	1.0	0.6	0.1	0.3	0.2	1.0
Basic metals	0.4	1.4	1.0	0.4	0.3	0.4	0.7	0.8
Ferrous metals	0.3	1.2	1.0	0.4	0.3	0.4	0.8	0.7
Non-ferrous metals	0.6	2.1	0.8	0.4	0.2	0.4	0.4	0.9
Fabr metals and machinery	6.1	3.7	4.6	3.6	2.4	3.7	2.5	4.4
Fabricated metals	0.7	0.7	0.5	1.1	0.3	0.3	0.4	0.7
Non-electrical machinery exc comp	2.0	2.6	2.0	2.0	0.7	1.2	0.9	2.0
Computers, office machinery	20.2	7.1	4.6	6.0	7.4	5.8	6.7	11.0
Electrical machinery exc comm	1.3	4.0	2.6	2.6	1.6	1.7	..	2.7
Communication equip and semic	10.9	5.8	12.4	9.4	8.9	12.8	2.8	9.0
Shipbuilding	..	0.8	0.6	0.8	1.9	0.0	0.2	..
Motor vehicles	4.7	2.9	3.2	3.5	3.6	2.5	3.3	3.4
Aerospace	12.5	8.3	14.3	20.8	14.1	8.2	1.9	12.4
Other transportation	6.4	1.7	1.0	0.9	2.1	0.0	0.0	2.5
Scientific instruments	7.7	6.8	2.2	3.0	0.8	1.6	1.5	6.4

Source: OECD, STAN/ANBERD databases (DSTI, EAS Division), March 1995

Table 7 Trends in the Distribution of Pharmaceutical R&D in selected OECD countries

	1973-74	1975-79	1980-84	1985-89	1990-92
UK	10.4	10.8	10.8	11.4	11.5
Germany	13.4	14.3	10.3	9.0	7.7
France	7.4	7.2	7.6	7.3	6.9
Italy	6.2	5.7	5.9	6.1	5.7
The Netherlands	2.1	2.1	1.5	1.5	1.2
Denmark	0.9	0.7	0.7	0.8	0.9
Sweden	1.5	1.5	1.6	2.1	2.2
Finland	0.3	0.3	0.4	0.3	0.3
EU[1]	42.1	42.5	38.9	38.5	36.4
USA	42.0	41.1	42.3	42.4	44.2
Japan	14.2	15.2	17.7	17.6	17.6
Other[2]	1.6	1.2	1.1	1.5	1.8
Total OECD	100.0	100.0	100.0	100.0	100.0

Notes: 1 EU for these purposes consists of eight countries listed above.
2 No data available for Switzerland

Source: OECD

while the US has increased its share from 41% in 1981 to 47% in 1992. Japan increased its share steadily up to 1981 but has also declined slightly since then. Table 7 also shows the distribution of pharmaceuticals R&D within the seven EU countries. The UK accounted for a quarter of the EU total in 1973 and has increased that to one third in 1992. Over the same period Germany has declined from 31% to 20%, while Sweden has more than doubled its share (from 3.7% to 6.1%).

3.10 Patent statistics have long been used as indicators of technological activities by both academics and policy makers. Like other technology indicators (such as R&D expenditures) they have their own advantages and disadvantages and these have been discussed in detail elsewhere (see Pavitt (1988); Griliches (1990); Patel and Pavitt (1995)). Their main advantage for the current study is that they are available over long periods of time and can be

broken down by detailed technical fields and by named institutions such as companies. Moreover surveys (such as the Yale survey and the more recent PACE survey of European firms) which assess patents versus other means of protecting technological leads show that in the pharmaceutical industry patents are an extremely important means of protection.

3.11 Table 8 shows the distribution of US patents granted to inventors from different European countries compared to Japan and the US.[13] Here again it is clear that Germany, the UK, France and Switzerland are the major European players, with the Swiss steadily declining throughout the period. Both Germany and the UK show a substantial rise in patenting activity during the late 70s and early 1980s, while both, but particular Germany, have seen falls since the mid-1980s. The EU as a whole peaked in patenting activity in the late 1970s but has recently been losing share. The US lost share as Europe gained in the late 1970s and early 1980s, but since that time has been steadily regaining share. Japan has been steadily gaining patent share.

3.12 Such tables have to be treated with care. While patenting is of vital importance to this industry, practice varies considerably from company to company and country to country. All companies indulge in what is called 'defensive patenting' - that is not only taking out a patent on NCE which constitutes the new discovery, but patenting widely around the NCE to pre-empt imitators. Japanese companies are well known for the systematic approach they adopt to such defensive patenting and this may partially explain their relatively high patenting share. Different traditions can also account for different practice even between EU countries. For example, in Germany it is required that researchers in a corporate laboratory who have been involved in discovering new chemical entities are not only identified on the patent but also rewarded for their efforts. This leads to relatively narrow patents whereas in the UK, where no such requirement exists, composite patents are often lodged in order to save costs.

---

[13]The figures in this table record the number of patents with inventor addresses in the different countries. It does not take account of patenting by companies whose HQ is in one country but which have substantial patenting outside that country.

Table 8 Trends in the Distribution of US Patenting in Pharmaceuticals: 1969 to 1994

	69-74	75-79	80-84	85-89	90-94
Germany	7.0	11.1	10.4	9.7	7.8
UK	4.1	7.3	7.5	6.2	5.3
France	4.5	5.9	5.1	4.8	4.7
Italy	1.4	1.8	2.8	2.6	2.2
Netherlands	1.0	0.7	0.8	0.6	0.8
Denmark	0.3	0.5	0.4	0.6	0.8
Sweden	1.2	1.4	0.8	0.8	0.7
Belgium	0.3	0.6	0.8	0.6	0.6
Austria	0.2	0.3	0.3	0.4	0.4
Spain	0.2	0.3	0.1	0.3	0.3
Finland	0.0	0.1	0.1	0.3	0.2
Ireland	0.0	0.0	0.0	0.1	0.1
Greece	0.0	0.0	0.0	0.0	0.0
Portugal	0.0	0.0	0.0	0.0	0.0
EU	20.5	29.8	29.3	27.1	24.0
Switzerland	4.7	3.6	3.3	2.3	1.9
USA	60.8	52.9	49.8	51.9	54.6
Japan	10.9	9.6	13.3	14.2	14.7
Other	3.1	4.0	4.3	4.5	4.8
Total	100.0	100.0	100.0	100.0	100.0

Source: Data supplied to SPRU by the US Department of Commerce, Patent and Trademark Office

3.13 Small biotechnology firms are particularly prone to be frequent patenters because they are anxious not only to protect their main capital assets but also to advertise to potential partners where their expertise lies. By contrast, the uncertainties of biotechnology patents have lead many larger companies to keep developments in-house until a fairly late stage because they have arguably lost nothing and avoided revealing to competitors their area of interest. Thus, assuming the mix of companies within any one country remains approximately stable, the time trend of patenting in any one country for any one company is a good measure of innovative activity, but cross-section comparisons between

countries/companies should be treated with some caution. In particular, in pharmaceuticals, patents (or any other single measure) should never be taken as the sole indicator of successful innovation. In all cases they need to be backed up by other indicators.

Other measures of innovativeness

3.14 An important measure of innovativeness in the pharmaceutical industry is the number of NCEs launched by any one country/company over a given period of time and (given that so many drugs that are introduced are 'me too' products possessing little novelty) also the number of products amongst the top selling prescription drugs. Table 9 gives both these measures for the main European drug producing countries, the US and the Japan. It shows a number of interesting trends:

(i) while Germany and France have both been fairly prolific producers and launchers of new drugs, neither has been very successful in marketing the high selling drugs, with the French record in particular looking undistinguished;

(ii) within Europe, the UK and Switzerland are the most successful drug producers in terms of numbers of products in the top 50, with the UK being particularly successful in spite of the fact that its record of new introductions is well down on its competitors;

(iii) worldwide, the US tops the bill on both scores with approximately 50 per cent of the top selling brands, and more new introductions (but fewer new launches) than any other country. However, given that the UK population is only 25 per cent of that of the US, the UK record on top selling drugs is actually better than that of the US, as is that of Switzerland;

(iv) in spite of fears in the early 1980s that Japan was set to break into the pharmaceutical industry as it had in electronics, the Japanese record does not match that of these other three countries;

(v) the poor record of new launches in the US is explained by differences in regulatory procedures. Until recently, the backlog of cases with the US authorities (the Food and Drug Administration - FDA) led to lengthy delays in drug approvals which in turn encouraged US drug firms to launch new drugs in European markets rather than in the US. Recent reforms to FDA procedures may well change this in future.

Table 9 Top 50 Branded Products by Country of Origin and Worldwide New Chemical Introductions by country of origin and by country of first launch

Country	Number of products in top 50				← NCE introductions[1] →							
	1985	1987	1989	1990	1961-70		1971-80		1981-90		1990		1991		1992	
Germany	5	4	5	5	112	(140)	91	(77)	67	(660)	3	(1)	3	(2)	2	(1)
UK	9	10	12	12[4]	45	(83)	29	(66)	28	(41)	5	(7)	4	(4)	5	(3)
France	1	1	2	0	171	(194)	98	(113)	37	(46)	1	(1)	2	(2)	1	(3)
Italy	0	1	1	0	49	(52)	70	(72)	37	(53)	3	(2)	1	(2)	4	(5)
Spain	0	0	0	0	6	(13)	15	(33)	13	(21)	4	(4)	0	(0)	3	(2)
Be/Ne/Lux	0	0	0	0	24	(28)	14	(31)	7	(27)	0	(6)	0	(5)	1	(2)
Total EEC[2]	15	16	20	17	407	(510)	317	(392)	189	(255)	16	(21)	10	(15)	16	(16)
Switzerland	6	5	4	6	66	(43)	48	(36)	48	(27)	4	(1)	4	(0)	2	(2)
USA	23	23	18	27[4]	202	(79)	154	(36)	142	(39)	10	(7)	13	(11)	10	(7)
Japan	5	5	6	2	80	(83)	74	(76)	129	(145)	7	(12)	12	(13)	14	(11)
Scandinavia	0	0	0	1	29	(18)	21	(13)	21	(22)	2	(0)	3	(0)	0	(0)
Other[3]	0	0	0	0	70	(111)	62	(117)	31	(83)	0	(0)	1	(0)	1	(0)

Notes: 1 By country of origin and by country of first launch in brackets.
2 Excluding Denmark which is incorporated under "Scandinavia".
3 NCEs firstly introduced in Ireland, Portugal & Greece are included under "Other countries". This figure also includes former centrally planned economies.
4 The three best-selling drugs of Smith Kline Beecham are credited to both countries, since the company is of joint US and UK ownership.

Sources: Mossialos, Kavanos and Abel Smith, Table 3.8, p 34. They quoted the sources as being *Pharmazeutische Industrie*, 55, 1, 1993; Scrip Review of 1990, 1991, 1992; Scrip Yearbook 1991.

Trends in innovation between countries

3.15 Summing up the data on country level performance presented in this section, it is clear that looking at it from a global perspective, the US remains the strongest player. It has the largest home market of any industry, but remains a significant exporter and products from its companies dominate the top 50 drugs league tables. Whereas many countries have experienced declines in their shares of patenting and R&D, the US has held its own. Europe, by contrast, has seen its share of both patenting and R&D fall, and variations in costs/prices from market to market indicate that although potentially a larger market than the US, it is still highly fragmented. The one success story among European countries is the UK which has seen a relative increase in its R&D expenditures in this sector and has been especially successful in developing products amongst the top selling drugs. This, as we shall see, helps to create a virtuous cycle of R&D and innovation which is so important in this industry. By contrast, Germany and Switzerland, the former dominant players in this sector, record a relatively disappointing performance. France and Italy have both recorded a strong R&D performance, but still fail to develop drugs of top class potential.

4 FIRM LEVEL ANALYSIS

A tight-knit international oligopoly

4.1 One of the notable features of the pharmaceutical industry is that it is a highly regulated but intensely competitive international oligopoly dominated by a relatively small number (30-40) of large companies. World-wide there are many thousands of companies but many of these are small companies producing traditional remedies sold over-the-counter in chemists shops and with very limited markets. Others are companies producing off-patent *generic* brands of medicine, often also for a local market. Because entry to such markets is easy, competition is keen, mark-ups low and turnover among firms considerable. The larger

companies tend to concentrate on what are called the 'ethical' prescription drugs[14] most of which are still covered by patents which limit entry and enable companies to reap as high a profit as they can.

4.2 Table 10 lists the top 30 companies in 1993 by sales, market share and ranking in 1991, 1992 and 1993. Because of the intense merger activity (see Tables 2 and 3 in Section 2) there has been a number of changing of place at the top of the table in the last two years and a considerable increase in concentration. There is considerable variation in the percentage of total sales devoted to pharmaceuticals, ranging from 100 per cent for Glaxo to 16 per cent for Bayer. Many of the companies listed have interests in other parts of the chemicals industry (eg, Zeneca with pesticides and agro-chemicals) or in over-the-counter health and beauty products (eg, Johnson & Johnson with baby products, soaps, shampoos, etc). It is also worth noting the relatively low levels of concentration for the industry as a whole: while Merck and Glaxo each had more than 4 per cent of the world market in 1993, half the firms on the list have less than 2 per cent.

4.3 Altogether these 30 companies contribute 60 per cent of world market sales, but over 75% of total R&D expenditures. Those that remain are to all intents and purposes, small players in this industry. Some of those small players are, like the new biotechnology companies we shall discuss in Section 5 below, highly creative, innovative companies, challenging these industry giants at the core of their capabilities, namely in novel drug design. But many, as already indicated, form a long tail of not very creative, imitative companies which for many years have been 'living off' the innovative activities of the top 30. In terms of innovation, these are the companies that count.

4.4 Table 11 shows the rankings of the top 20 firms for the last 20 years. While positions within the league table may change, there has been surprisingly little change

[14]As we shall see, quite a number of the larger companies have recently been expanding their activities from the production of on-patent prescription drugs into the generics and over-the-counter markets.

Table 10 Company Rankings by sales 1993

Rank by Year 1993	1992	1991	Company	Nationality	Sales Group	Pharm	%	World Market Share[1] (%)
1	1	1	Merck	US	10633	8921	84	4.50
2	2	2	Glaxo[4]	UK	8157	8157	100	4.10
3	3	3	Bristol Myers Squibb	US	11413	6524	57	3.30
4	4	4	Hoechst[5]	Germany	27890	6019	22	3.00
5	5	5	SmithKline Beecham	UK	9072	5240	58	2.60
6	8	11	Pfizer	US	7478	5129	69	2.60
7	6	9	America Howe Products[6]	US	8305	4775	57	2.40
8	9	7	Eli Lilly	US	6452	4759	74	2.40
9	12	13	Roche	Switz	9696	4554	47	2.30
10	10	8	Sandoz	Switz	10217	4543	44	2.30
11	11	10	Johnson & Johnson	US	14138	4490	32	2.30
12	7	6	Ciba Geigy	Switz	15323	4465	29	2.20
13	13	14	Takeda	Japan	6557	4325	66	2.20
14	14	12	Bayer	Germany	24838	3910	16	2.00
15	15	15	Rhône Poulenc Rorer	US[2]	4019	3492	87	1.70
16	18	22	Sankyo	Japan	4655	3445	74	1.70
17	17	20	Schering-Plough	US	4341	3375	78	1.70
18	19	18	Upjohn[3]	US	3611	3007	83	1.50
19	24	23	Shiniogi	Japan	3104	2938	95	1.50
20	20	19	Cyanamid	US	4278	2866	67	1.40
21	25	26	Astra	Sweden	2902	2848	98	1.40
22	16	17	Marion Merrell Dow[5]	US	2818	2818	100	1.40
23	22	16	Zeneca	UK	6669	2810	42	1.40
24	21	24	Wellcome[4]	UK	3150	2720	86	1.40
25	28	33	Pharmacia[3]	Sweden	3176	2693	85	1.30
26	23	21	Boeringer I	Germany	3375	2650	79	1.30
27	27	27	Yamanouchi	Japan	3322	2555	77	1.30
28	26	25	Schering	Germany	3250	2508	77	1.30
29	29	28	Fujisawa	Japan	2450	2180	89	1.10
30	30	29	Warner-Lambert	US	5794	2114	34	1.10

Pharmaceutical sales levels do not include OTC medicines which are included in the group sales. The low percentage figures for such firms as Johnson & Johnson and Warner-Lambert reflect this.

1 Assuming worldwide ethical sales of $200bn in 1993.

2 The American subsidiary Rhône Poulenc-Rorer is 100% owned by Rhône Poulenc which is French.

3 Upjohn and Pharmacia announced they were merging on 21/8/95

4 Glaxo acquired Wellcome in 1995

5 Hoechst acquired MMD in 1995

Source: James Capel: *global Pharmaceutical Review,* October 1994, p 11.

Table 11 Changing Places- the world's top 20 pharmaceutical corporations 1976-1994

	1976	1980	1985	1989	1991	1994
1	Hoechst (WG)	H la R	Merck	BMS	Merck	Glaxo(UK)
2	Merck (US)	Merck	Hoechst	AHP	Glaxo	Merck(US)
3	AHP (US)	Hoechst	Ciba Geigy	Merck	BMS	BMS(US)
4	H la R (Sw)	Ciba Geigy	Bayer	Glaxo	Hoechst	AHP(US)
5	Ciba-Geigy (Sw)	Bayer	AHP	SmithKline B	SKB	Pfizer(US)
6	Bristol Myers (US)	AHP	Pfizer	Ciba Geigy	Ciba Geigy	SKB(UK/US)
7	Pfizer (US)	Sandoz	Sandoz	H la R	Eli Lilly	J&J(US)
8	Warren Lambert (US)	Bristol Myers	Glaxo	J&J	Sandoz	Roche(Sw)
9	Bayer (WG)	Warren Lambert	Eli Lilly	Hoechst	AHP	Ciba G(Sw)
10	Sandoz (Sw)	Pfizer	H la R	Eli Lilly	J&J	Hoechst(G)
11	Eli Lilly (US)	Boehringer I.	Abbott(US)	Sandoz	Pfizer	Lilly(US)
12	Boehringer I (WG)	Eli Lilly	Warren Lambert	Bayer	Bayer	Bayer(G)
13	Upjohn (US)	Upjohn	Bristol Myers	Pfizer	H la R	Schering Plough(US)
14	Rhône Poulenc (Fr)	Rhone Poulenc	SmithKline	MMD	Takeda	Sandoz(Sw)
15	Takeda (Japan)	Takeda	Upjohn	RPR	RPR (Fr/US)	RPR(Fr/US)
16	Schering Plough (US)	Glaxo	J&J	Takeda	Zeneca	Abbott(US)
17	Squibb (US)	Smith Kline(US)	Takeda	BI	MMD (US)	Takeda(Jap)
18	J&J (US)	Squibb	Wellcome(UK)	Warren Lambert	Upjohn	Wellcome(UK)
19	Sterling Winthorp (US)	Schering Plough	Boehringer I	Sanofi	Cyanamid	MMD(US)
20	Glaxo (UK)	Beecham(UK)	Schering Plough	Zeneca	Schering Plough	Sankyo(Jap)

Key:

H la R	Hoffman la Roche	**BMS**	Bristol Myers Squibb (Merger 1989)
SKB	Smith Kline Beecham (Merger 1989)	**MMD**	Marion Merrell Dow (Merger 1985)
J&J	Johnson & Johnson	**AHP**	American Home Products
BI	Boehringer Ingelheim		

Source: For early years; Burstall, M L and Senior, I (1984): The Community's Pharmaceutical Industry Economists Advisory Group for the Commission of European Communities
For 1985: Andrew Chetley (1990): *A Health Business*, Zed Publications.
Since 1985: *Scrip Magazine*

amongst the overall cohort. As already noted the Germans (and Swiss) dominated the early development of the industry, but with the war and the demand for antibiotics to treat the wounded, the American industry emerged as a major player. As Table 11 shows, American, German and Swiss companies, and names such as Bayer, Hoechst, Ciba Geigy, Merck, and Johnson & Johnson still dominate the league tables. The most notable change of the last two decades has been the emergence of the UK industry as a significant player.[15] Firms such as Glaxo, Wellcome and (SmithKline) Beecham, who were minor companies in the 1950s, have joined the top 20.[16] They are now joined by Zeneca, the pharmaceutical/agro-chemicals arm of ICI which demerged in 1993. Nevertheless, with 9 out of the top 20 firms, the American presence in the league tables is still impressive. The Japanese have yet to make much impact. Amongst European firms, the British and Swiss have been in the ascendant; the Germans on the wane. The biggest shake-up in the industry has in fact come from the international mergers of the last few years, which are not reflected in Tables 10 and 11: although Bristol Myers Squibb and SmithKline Beecham appear as joint companies, Glaxo/Wellcome, Hoechst/Marion Merrell Dow and Upjohn/Pharmacia mergers are not recorded. These international mergers and alliances increasingly make national demarcation irrelevant. Firms which for some time have been international in operation are now also becoming international in ownership. It is noteworthy, for example, that Upjohn Pharmacia, respectively American and Swedish firms, have chosen to locate their headquarters in London which, they describe as becoming "a global pharmaceuticals' centre".[17] We return to this theme below when considering the increasing internationalisation of R&D.

---

[15]The French firm Rhône Poulenc has also advanced rapidly up the league tables, but largely as a result of merger with the US pharmaceutical company Rorer (to form Rhône Poulenc Rorer - RPR). As we shall see later, although the French companies feature as fairly substantial producers of drugs, their innovative record is not strong and there has been a tendency for the industry to rely on too many 'me too' products. The restructuring of RPR and the re-organisation of RP's vaccine interests around Merieux has strengthened RP's innovative capabilities, particularly in biopharmaceutical products. It still has to be seen whether the company is able to profit from this potential.

[16]L G Thomas suggests that the rise of the British companies was helped by the existence of a price control regime which favoured the innovative drug companies, British or foreign, over me-too companies. See L G Thomas III, 1994.

[17]*The Times*, 6 February 1996.

Low levels of concentration

4.5 Another significant feature of the international pharmaceutical industry - its low levels of concentration - has been noted. Until the recent spate of takeovers the top three firms in the industry commanded less than 12 per cent of total world markets.[18] Even within national markets, where it might well be thought concentration ratios would be higher, concentration ratios are low as Table 12 demonstrates. The reason for this is the degree to which companies concentrate on particular product areas - for example, cardiovascular, central nervous system, antiviral, etc. Typically a company will concentrate its product range in two or three areas and will find itself competing in these areas with, say, half a dozen of the other major companies. Within product areas, therefore, concentration is likely to be much higher than for the industry as a whole. Nevertheless, the introduction of a successful drug in one area always attracts imitators. Tagamet, for example, SmithKline's extremely successful anti-ulcer drug which was launched in the late 1970s, was challenged within five years by Glaxo's Zantac, which in turn has been challenged by Merck's Pepcid and Astra's Losec. In other words, concentration in specific product areas may lead to temporary excess profits but also helps to promote the innovative dynamic of the industry. Firms are constantly jockeying with each other to introduce new, high selling pharmaceuticals.

Technological performance of large firms: R&D, patenting and new chemical entities

4.6 The discussion above has already made clear the degree to which the pharmaceutical industry is dominated by large multinational companies and the intense product competition between these companies, with R&D and innovation the key issues. Table 13 lists the top 20 firms in the industry ranked by their R&D spending in 1993, together with their US patenting activities, and the number of new drugs in R&D and their number of top selling drugs. The most important message from this table is the lack of correlation between most of these variables: the only significant correlation is between R&D intensity and number of new

[18]Recent takeovers have increased this to 16 per cent - see Table 3 above.

Table 12 Seller Concentration Ratios in the Pharmaceutical Industry in Selected European countries, the USA and Japan

	Germany	France	UK	Italy	Spain	Netherlands	Belgium	Greece	USA	Japan	Japan
Top 1											
1988	2.5	3.5	6.5	4.1	4.0	7.9	5.5	0.0	6.7	5.3	5.3
1990	2.4	4.1	7.0	4.2	3.5	8.4	5.0	10.2	7.0	4.9	4.9
Top 5											
1988	10.9	14.4	22.3	17.7	16.3	21.3	19.4	*27.7	20.8	21.9	21.9
1990	11.4	15.4	22.8	17.4	14.9	26.7	20.0	28.3	22.5	21.4	21.4
Top 10											
1988	19.5	23.9	33.7	28.9	26.2	34.3	33.0	*41.7	33.8	36.2	36.2
1990	20.2	26.2	33.0	29.3	24.7	38.8	32.6	0.0	33.5	35.4	35.4

Note: *Year of reference is 1987

Sources: LSE, European Institute based on Farmindustria, 1990, 1992; Pharmetrica, 1992; Menarini Group, 1992, quoted in Table 2.8 in Mossialos, Kanavos and Abel Smith.

Table 13 Top 20 companies in terms of Pharmaceutical R&D expenditures

	R&D (1993)		US Patents (1990-94)		No of drugs in R&D 1993/4			No of products in Top 50
	$m	% Sales	Number	per mil sales	Total	Own	Under Licence	Selling brands 1993
1 Glaxo (GB)	1288.7	15.17	151	1.78	80	51	29	6
2 Roche (CH)	1226.3	23.20	358	6.77	115	72	43	1
3 Merck & Co (US)	980.2	11.17	728	8.30	113	94	19	6
4 Hoechst (DE)	966.6	16.08	649	10.80	79	52	27	0
5 Sandoz (CH)	900.8	18.11	117	2.35	85	57	28	1
6 SmithKline Beecham (GB)	743.5	14.21	264	5.05	101	61	40	4
7 Eli Lilly (US)	690.5	14.69	248	5.28	93	67	26	3
8 Johnson & Johnson (US)	683.0	15.21	177	3.94	79	48	31	1
9 Pfizer (US)	668.3	13.03	245	4.78	57	43	14	3
10 Ciba-Geigy (CH)	649.0	12.72	356	6.98	102	71	31	1
11 Bristol-Myers Squibb (US)	644.8	9.88	413	6.33	94	76	18	2
12 Rhône-Poulenc Rorer (FR)	561.2	13.96	176	4.38	64	40	24	0
13 Schering Plough (US)	549.7	15.10	145	3.98	52	27	25	1
14 Upjohn (US)	534.6	17.78	66	2.19	69	50	19	1
15 Boehringer Ingelheim (DE)	531.1	19.21	93	3.36	69	51	18	0
16 Wellcome (GB)	489.6	15.97	115	3.75	38	46	12	1
17 Schering AG (DE)	473.6	18.92	147	5.87	49	35	14	1
18 Abbott (US)	459.9	10.48	235	5.35	51	27	24	0
19 Marion Merrell Dow (US)	451.0	16.00	294	10.43	57	33	24	3
20 Zeneca (GB)	434.1	15.45	326	11.60	49	44	5	3

Sources: SPRU/OTAF Patent Database; SPRU Large Firm Database; *Scrip Magazine*, January 1995, p 45 for Drugs under Development; James Capel, *Global Pharmaceutical Review,* October 1994, p III for 1993 Drug Ranking for Top 50 products.

drugs as a percentage of sales. Thus although Glaxo's R&D spending in 1993 was high (inflated by the large expenditures incurred on building its new R&D facilities) and, together with Merck, it topped the league in terms of top selling drugs, its patenting activities and the number of new products under development were relatively poor compared to companies with much lower R&D expenditures. In contrast, Hoechst has the highest patent intensity, is roughly equal to Glaxo in new drug development activity but has no drugs in the top 50 best sellers. At the same time Roche, which currently tops the league in terms of the percentage of sales devoted to R&D at 23 per cent, and is amongst the top group in patenting activity and new drug development, has only one of the top selling drugs. Zeneca, at the bottom of the table in terms of overall R&D spend (although higher up in terms of R&D as a percentage of sales), has a much better patenting record than Glaxo, and has three drugs in the top 50. Zeneca also has a very slim development portfolio with nearly all the new drugs derived from its own R&D rather than being developed under license.

4.7 As Table 13 indicates, there are important factors specific to each company and it is these, more than general factors, which determine R&D and innovation strategy. For example, Rhône Poulenc Rorer, the major French pharmaceutical/chemical company, has been advancing up the pharmaceutical company league tables by a process of aggressive acquisition, the most important of which was the take-over of the US middle size pharmaceutical company Rorer in 1989. Hoffmann La Roche aims to increase the company's presence amongst top selling drugs and hence has maintained a high R&D investment rate for some years. This has helped to put it at the top of the league in terms of drugs under development (115 compared to Merck's 113) but it has still to turn these into best sellers. Upjohn, which recently merged with Pharmacia of Sweden, is another company whose sales ranking was disappointing and whose spending on R&D could be seen as a defensive attempt to revitalise sales. Indeed, it is notable that those companies with the highest R&D to sales ratios (Roche, Boehringer Ingelheim, Schering, Sandoz and Upjohn) all have on only one or no drugs among the top 50 best sellers. By contrast, Merck, which has for the last decade been considered the most innovative drug company in the world and

matches Glaxo's record of 6 out of 50 top selling drugs, has relatively low R&D intensity but shows high numbers of patents and products under development.

4.8 It is also worth noting in Table 13 the number of drugs under development which have been licensed-in from other companies. This has long been a feature of pharmaceutical companies who both license-in and sell drugs discovered by fellow pharmaceutical companies. Development here may mean taking the drug through the later stages of clinical trials in order to satisfy the indigenous regulatory authorities (the US FDA, for example, insists that any drug launched on the US market goes through clinical trials in the US), or it may mean taking the drug from Phase I clinical trials onwards, a process which can last anything from upwards of 5 or 6 years. The development of biotechnology and the increasing tendency for the large pharmaceutical companies to ally themselves with the small dedicated biotechnology companies who do not have the knowledge or facilities to take drugs through clinical trials has resulted in all pharmaceutical companies licensing-in more drugs than they used. A high level of licensing-in should not therefore be seen as a sign of weakness in innovation. On the contrary, there are an increasing number of companies who now recognise that they cannot maintain in-house the wide range of expertise and speciality required for modern drug development (eg combinatorial chemistry and genomics) and who deliberately seek to license-in such expertise arguing that the task of the large firm is increasingly to act as co-ordinator in the drug discovery process. That said, there have also been quite a number of pharmaceutical companies caught short by the rapid advance of biotechnology and the bio-pharmaceutical drugs and obliged to reinforce their product portfolios by buying-in products from the small biotechnology companies. (See Section 5 below for more discussion of this point.)

The role of multinationals and the internationalisation of R&D activities

4.9 The pharmaceutical industry is characterised by an increasing number of truly multi-national firms. Table 14 illustrates the degree to which different markets within some of the

Table 14 Company market share in Europe, United States and Japan by company nationality in 1991
(percentage of the pharmaceuticals market in each country)

	Company Country of Origin[1]											
Market	BEL	GER	SPA	FRA	ITA	NET	POR	UK	SWE	SWI	USA	JAP
Belgium	10.7	13.7	0.0	9.8	2.1	1.5	0.0	16.9	3.0	10.2	29.5	0.7
Germany	1.7	51.9	0.3	5.1	0.9	1.5	0.0	6.2	3.3	8.1	18.6	1.1
Spain	1.7	14	31.0	4.5	5.9	0.9	0.0	9.3	2.1	11.7	17.0	0.1
France	2.1	12.3	0.0	46.0	0.6	1.0	0.0	8.1	1.6	6.7	20.5	0.4
Italy	0.5	13.8	0.0	5.3	38.3	0.3	0.0	9.6	0.8	11.6	18.9	0.3
Netherlands	2.4	14.5	0.0	4.1	1.3	11.6	0.0	18.4	7.0	10.1	23.6	1.9
Portugal	3.2	12.5	3.3	8.6	3.7	0.7	14.7	11.2	0.9	13.5	25.3	0.6
United Kingdom[2]	1.1	10.4	0.0	4.7	0.4	1.0	0.0	35.0[2]	3.6	7.1	25.8	0.3
United States	0.4	4.6	0.0	1.2	0.1	0.0	0.0	14.6	0.1	8.0	70.2	0.3
Japan	0.0	4.8	0.0	0.2	0.0	0.2	0.0	2.9	0.3	3.1	5.9	82.1

1 Market share calculated from direct sales by companies or their majority-owned subsidiaries. Product sales under licence are credited to the company marketing them and not to the original patent-holder.

2 8.4% of the British market is occupied by generics for which the country of origin of the group marketing them is not specified. British companies are estimated to manufacture half the generics. This would add 4% to the market share of British companies in the UK.

Source: 'The Realities of the Pharmaceutical Industry in France', SNIP, February 1993, quoted as Table 3.2 in Mossialos, Kanavos and Abel Smith (1993).

OECD countries are controlled by national and foreign firms. Thus while the diagonal illustrates the degree of self-sufficiency (with Japan the highest at 82 per cent, the US 70 per cent, Germany 52 per cent, France 46 per cent) the vertical columns show who is supplying whom. Table 14 also illustrates how important American companies are in all European markets (the column under USA showing the proportion of each market supplied by US companies). Two features are worth highlighting. First, that German, British and Swiss companies are the major European suppliers to European markets; France, although second in terms of production in Europe, is less important as a supplier to Europe.[19] Secondly, only three European countries have companies making a noticeable impact on the US market - the UK, which in 1991 enjoyed a market share of almost 15 per cent, Switzerland with an 8 per cent share and Germany with a 4.6 per cent share. Given the importance of the US market as the most open and competitive market for pharmaceuticals in the world and the very strong showing of US pharmaceutical companies in other markets, US market share is a reasonable indicator of competitiveness. It suggests again that in spite of their smaller productive size, the UK and Swiss industries are amongst front runners in Europe.

4.10 The UK has in fact attracted a good deal of investment from foreign, and particularly American, pharmaceutical companies. Initially they came in the 1950s when the dollar-strapped UK authorities demanded local drug formulation and provided subsidies for location in the less favoured regions. As they matured they shifted from formulation to manufacture and R&D and the availability of high quality scientific manpower proved a major attraction. (Lake, 1976). In turn the UK authorities sought to attract them by offering favourable treatment under the price regulation system to companies setting up R&D departments. Most of these subsidiaries and R&D laboratories were staffed and run by UK nationals and over time provided a training ground for many who went on to work for the successful UK companies. In other words, the presence of successful multinational pharmaceutical companies in the UK in the 1950s and 1960s provided a role model and a training ground which subsequently helped the UK's indigenous companies to success. It took, however, a

[19]France is however a major exporter, particularly to Third World countries.

generation (25 years) for the effects to work their way through the system (Brech and Sharp, 1985).

4.11 Within Europe, the UK is still a favoured location for many multinational companies as the recent decision by Upjohn Pharmacia signified. Like the UK, France and Italy both at one time demanded local formulation and manufacture, and offered favourable treatment for the location of R&D laboratories, but were less successful in attracting such facilities. Patenting activity provides an another way of measuring how far the increasing internationalisation of the industry is resulting in a shift of innovative activity. Table 15 shows the geographic distribution of US patenting activities[20] for the 115 largest pharmaceutical companies worldwide. This shows that, for example, 89 per cent of patents granted to US firms in 1990-94 were derived from activity within the US. At the same time for German firms, 29 per cent of their innovative activity was located abroad, predominately in the US; for British companies 35 per cent was abroad, again mainly in the US; and for Swiss companies 58 per cent was abroad, 44 per cent of this being in the US. Within Europe, the UK is the most important location of innovative activity, followed by France, Germany and Italy.

4.12 Table 16 supplements the data in Table 15 by listing the foreign firms engaged in patenting in Europe as a whole and in the UK, France, Germany and Italy. In Europe as a whole, as might be expected, the top foreign patenters are the US pharmaceutical firms with Johnson & Johnson, Pfizer and Dow Chemical topping the list. In each individual country, other European companies are often major players. Hoechst, for example, owns France's second largest pharmaceutical company (Roussel) and thus tops the foreign companies patenting in France. Rhône Poulenc Rorer own May and Baker, one of Britain's oldest pharmaceutical companies, which helps explain their place on the British list. Taking patenting as a measure for innovative activity, once again Britain stands out as the most innovative environment for pharmaceuticals in Europe. It hosts a large number of the leading

20These figures come from analysis of inventor addresses of patents granted to these firms in the US.

Table 15 Geographic Location of Pharmaceutical Firms' US Patenting Activities, according to nationality: 1990-94
(percentage shares)

Firm's Nationality	Home	Abroad	Of Which US	Japan	Europe	Ger	UK	Fr	NL	Swe	Bel	It	Den	Fin
USA (25)	89.2	10.8		2.2	8.4	0.8	4.6	0.6	0.0	0.0	1.5	0.6	0.0	0.0
Japan (36)	94.9	5.1	4.4		0.5	0.3	0.0	0.0	0.0	0.1	0.1	0.0	0.0	0.0
Europe	81.5	18.5	17.2	5.3										
Germany (13)	71.0	29.0	16.8	1.7	10.2		1.6	5.3	0.3	0.0	0.0	2.3	0.0	0.0
UK (10)	64.9	35.1	24.8	0.1	9.9	1.6		4.2	1.0	0.1	0.2	2.8	0.0	0.0
France (7)	80.1	19.9	10.9	0.3	8.4	1.1	3.4		0.0	0.0	2.1	1.7	0.0	0.0
Netherlands (3)	56.8	43.2	18.0	0.0	23.7	3.6	12.9	4.3		0.0	1.4	0.0	1.4	0.0
Sweden (2)	69.7	30.3	10.1	1.1	15.7	1.1	1.1	0.0	1.1		0.0	9.0	1.1	2.2
Belgium (2)	16.7	83.3	11.5	0.0	71.8	24.4	0.0	6.4	41.0	0.0		0.0	0.0	0.0
Italy (5)	88.8	11.2	7.9	0.0	2.6	1.3	0.0	1.3	0.0	0.0	0.0		0.0	0.0
Denmark (2)	75.8	24.2	20.3	0.5	3.3	1.6	1.1	0.0	0.0	0.0	0.0	0.0		0.0
Finland (1)	88.0	12.0	4.0	0.0	8.0	0.0	0.0	0.0	0.0	0.0	8.0	0.0	0.0	0.0
Spain (1)	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Norway (1)	34.3	65.7	31.4	0.0	34.3	2.9	0.0	0.0	0.0	11.4	0.0	0.0	5.7	0.0
Switzerland (7)	41.9	58.1	43.5	2.0	12.5	4.8	2.7	3.4	0.0	0.0	0.0	0.4	0.0	0.0
All Firms (115)	79.2	20.9	10.7	1.4	8.5	1.2	2.7	1.9	0.4	0.1	0.8	1.1	0.1	0.0

Source: SPRU Large Firms Database

Table 16 Top Non-national firms patenting in Europe: 1990-94

Numbers of US Patents granted

Top 10 non-European firms patenting in Europe	
Johnson & Johnson	70
Pfizer	52
Dow Chemical	47
Merck Inc	45
Monsanto	36
American Home Products	36
Warner-Lambert	29
American Cyanamid	19
Eli Lilly	18
Bristol-Myers Squibb	15
Top 5 non-national firms patenting in UK	
Pfizer	49
Merck US	36
American Home Products	34
Rhône-Poulenc Rorer	21
Monsanto	19
Top 5 non-national firms patenting in France	
Hoechst	104
Zeneca	39
Dow Chemical	13
Hoffmann-La Roche	12
Merck EAG	5
Top 5 non-national firms patenting in Germany	
Ciba-Geigy	24
Solvay	19
Hoffmann-La Roche	15
Monsanto	11
Warner-Lambert	10
Top 5 non-national firms patenting in Italy	
Dow Chemical	24
Hoechst	19
Boehringer Mannheim	18
SmithKline Beecham	15
Sanofi	12

Source: SPRU Large Firms Database

US pharmaceutical companies, who in their turn contribute substantially to overall innovative activity. Pfizer's 49 patents, for example, equal Zeneca's total and exceed Wellcome's 38 over the same period (Table 13). In looking at Europe's overall innovative potential in this area, these multinational companies should not be forgotten.

Innovative Traditions and Innovative Companies

4.13 In concluding this section it is worth emphasising again the importance of *companies* to innovation in the pharmaceutical industry. It is in fact meaningless to talk, as we did in Section 3, about a country's record in innovation, for it is the companies operating within that country that create the innovation. The infrastructure and environment in a country may be conducive to innovation - as seems to be the case with Britain - but each company is different and has its own innovative profile. Merck, for example, is widely regarded today as the most innovative pharmaceutical company in the world and certainly scores well on all the various indicators presented in Table 13.

4.14 What makes for an innovative company such as Merck? Archilladelis *et al* (1990) suggest that in the chemical and allied industries the concept of a 'technological tradition' is of vital importance. The success of an innovation is, they found, linked to previous success which itself provides both experience and/or knowledge of research at the forefront of the relevant science. Success in pharmaceuticals, measured in terms of top selling drugs, is, as noted previously, a key factor in funding R&D which in turn is a necessary (but not sufficient - note Hoffman La Roche's heavy R&D expenditures in Table 13) condition of further success. This view is echoed by Gambardella (1995). In his concluding chapter he writes:

> "The case studies also suggested that competitive advantages based on science and innovation exhibit self-reinforcing properties. Leading innovators produce new drugs, which generate profits that can be reinvested in research, thereby strengthening innovative capabilities. Firms lacking strong research capabilities have had great difficulties in breaking into this virtuous spiral. Hence many of them, even though

> they did attempt to become research intensive producers, had to merge with other firms to join complementary resources in marketing and research, and to withstand the enormous competitive pressures of the 1990s."
>
> (Gambardella, 1995, p 163)

4.15 Gambardella warns, however, that scale is not everything. "The biological approach implies that scientific creativity and highly qualified human capital, rather than scale, have become the critical resources for drug discovery." (Gambardella, 1995, p 163). It is important, therefore, to consider the impact of biotechnology and its effect on the European pharmaceutical industry. This we do in the next two sections.

5 BIOTECHNOLOGY - A NEW ROUTE TO DRUG DISCOVERY

The emergence of the new biotechnology

5.1 Biotechnology as a new route to drug discovery dates from the early 1970s when two breakthroughs in molecular biology - the discovery of a mechanism by which part of a foreign gene could be inserted into another and thereby change its characteristics (recombinant DNA) and techniques for fusing and multiplying cells (hybridomas) - heralded the coming of genetic engineering. The applications of these radical new techniques were rapidly appreciated. They have led to the emergence of a whole new generation of protein drugs which are currently being launched on world markets. In the pipeline are further 'generations' of these products based on more sophisticated technology and beyond this developments in gene therapy and genome mapping open the way a wholesale revolution in medical technology. (See OTA (1991) for a detailed discussion of these developments.)

5.2 The leading edge of this new technology rapidly emerged in the United States, where the combination of a ready venture capital market, more lenient stock exchange rules and, above all, leading edge research in the life-sciences generously funded from the federal

purse,[21] led to the serendipitous burgeoning of a large number of small entrepreneurial firms to exploit that research. Companies such as Genentech, Cetus and Biogen were established in the 1970s but were followed by many others at the turn of the decade with the total population of small dedicated biotechnology firms (DBFs) growing from 50 in 1978 to approximately 500 by 1984 and 700 by 1987 after which the population has remained relatively stable.[22] Many were spin-offs from academic laboratories, offering researchers both first class facilities in which to pursue their scientific interests and a chance, through stock options, to make themselves considerable wealth when the firm went public and launched its shares on the stock exchange.

5.3 The DBFs were, however, more than just a convenient route to research. If they were to flourish they needed markets for their research and it was the large companies which provided the market. Companies such as Dow, Du Pont, Shell, Eli Lilley and Hoffman LaRoche were amongst the earliest to place contracts with these small firms, many for as little as $1m or $2m which was but a small amount for the large companies but vital for the finances and credibility of the small. In this essentially contract research role the DBFs performed two very useful functions. Firstly, they acted as intermediaries between the large companies and the academic base. Because of close academic links they were able quickly to put together the cross-disciplinary teams required to develop new products in this new technology, whereas the big firms, with their traditional contacts in chemistry not biology departments, found it difficult to find the right people (Kenney, 1986). Secondly, they helped the large companies to hedge their bets. Research contracts for $1m, $2m even $5m were limited commitments which might yield substantial prizes but, at a minimum, would provide the contractor (ie, the large company) with useful research results and avoid long term and

[21] Spending on the life sciences in the US in 1987 amounted to 48 per cent of all publicly funded expenditures on academic and academically related research. This compares with proportions ranging from 30 to 35 per cent in Europe and Japan. See Irvine, Martin and Isard. (1991). This reflected the war against cancer launched originally by President Nixon in the 1970s. When private charitable funds are added, the total weight of funding going towards the life sciences in the US is generally perceived to have been one of the main reasons why that country has maintained an intellectual lead in biotechnology.

[22] Dibner (1991) lists 742 DBFs as existing in 1991. Within this stable population there are many births and deaths. What is interesting is that, for the population to remain stable, there have to be as many births as deaths. The earlier figures in the text are derived from OTA (1988).

expensive employment commitments at a time when it was still uncertain where biotechnology was going.

5.4 In Europe the DBF has not flourished in the same way, partly because the institutional framework (high funding/leading edge research in the life sciences, active venture capital market) did not exist, partly because the academic entrepreneur was alien to much of the European academic tradition. Earlier studies (Coleman 1987; Clark and Walton 1992) suggest that the total population of small firms in Europe was small and grew only slowly. However, recent research suggests that the early 1990s was a period of rapid change for this sector in Europe and there is now a core of some 300 DBFs (Rizzoni 1995 unpublished research). Most of them, however, are much smaller than their US counterparts and to date relatively few are working at the leading edge of research. (See Martin and Thomas (1996) in relation to developments in gene therapy.)

The first decade - establishing a window on the technology[23]

5.5 None of Europe's large traditional chemical/pharmaceutical companies played much part in the first decade of 'the new biotechnology'. Most of the companies were uncertain what to make of the new technology and especially of the hype surrounding its development that grew with the small firm sector in the US. Some had experience of fermentation technology through the production of biological pharmaceuticals such as penicillin, or with the use of enzymes and the techniques associated with immobilisation of enzymes that had been developed during the 1960s. The latter, however, had tended to be the preserve of medium-sized specialist companies such as Gist Brocades (Netherlands now owned by Shell) or Novo (Denmark) rather than the large firms. A number of the larger companies had also dabbled in single cell protein, including Shell, BP, Hoechst and ICI, but only ICI had pursued

[23]The information in this section is culled from an earlier study by one of the authors on the development of biotechnology in Europe up to 1985. See Sharp (1985a). It is supplemented by case studies of how five of Europe's large integrated chemical/pharmaceutical - ICI, Bayer, Ciba Geigy, Montedison - have accommodated to the emergence of biotechnology in the last 15 years. See Sharp and Galimberti (1993).

its interests through to the market place with its ill-fated animal feed supplement, Pruteen. While the experience had been valuable in giving ICI hands-on experience of large scale continuous fermentation technology, its main legacy was in fact to make the company extremely cautious about further commitments to biotechnology.

5.6 This combination of uncertainty, scepticism and inexperience led to what might be called a minimalist strategy on the part of most large firms. While avoiding large investments most of the companies built up teams of researchers large enough to keep abreast of the science and to monitor developments and competitors.[24] Thus Bayer, ICI and Ciba Geigy all established small research teams in their corporate R&D laboratories with a fairly free rein to explore ideas as they wished.(Sharp and Galimberti 1993) Other companies, for example BASF, left even these moves until the early 1980s, having only minor interest in pharmaceuticals and being very uncertain whether biotechnology would have any relevance to their main interests in areas such as plastics and fibres. (Sharp 1985a)

5.7 One consequence of this strategy of 'watching and waiting' (Sharp 1985b). Was that it conceded leadership in the development of the new technology to the American DBFs which were so closely linked into the academic base. In this phase of development relatively few of the major European chemical firms were to be found as partners to the DBFs, although some, such as Ciba Geigy and Hoffman LaRoche, acknowledging that the US science base in this area was much stronger than that available in Germany or Switzerland, threw tradition to the winds and placed research contracts with a number of DBFs.[25] Hoechst, in placing a $67m, 10 year contract in 1981 with the Massachusetts General Hospital (MGH), also linked itself directly to the US academic base and made arrangements for its researchers to be trained at the MGH, thereby implicitly acknowledging the limitations of its indigenous science base. Other companies, among them Glaxo, Wellcome and Bayer, chose instead to expand their

[24]The exception was the US company Monsanto which in 1978 had appointed a biochemist as research director who championed early and major investments in biotechnology. (See Joly, 1992.)

[25]American and Japanese chemical and pharmaceutical companies were more prominent as partners in the early part of the 1980s. See OTA (1984) which (wrongly) predicted that the main competitive challenge to the US in biotechnology would come from Japan.

own research base into the US, setting up laboratories which were able to link directly into the US research base.[26]

The mid 1980s - major investments

5.8 By the mid-1980s the period of watching and waiting was over. Most companies recognised that, whatever their original reservations, biotechnology had established itself as an important *enabling* technology (ie, a route to new product development) and would be essential for future product innovation.

5.9 The strategies chosen by the large companies varied from company to company. All were concerned to build up in-house competence. Some chose to do this internally, using existing and new linkages into academic science; others bought-in competence through the acquisition of new biotechnology firms or through merger (and a subsequent reshuffling of assets) with American counterparts; yet others chose to retain external linkages with American and/or European DBFs. (See below, Section 6, for more discussion of this phenomenon.) All involved investments of $100m or more a year, building up internal teams of up to 700 researchers.[27] Initially many of these researchers were grouped together in special Biotechnology Divisions but as time went by these were disbanded and the biologists and biotechnologists within them disbursed among project based multi-disciplinary teams.[28] The investments in new plant and capacity brought the regulatory issues to the forefront for the first time. Most companies were prepared to accept the strict containment principles laid down by OECD guidelines of best (laboratory) practice (OECD, 1987) but the problems

[26]Burroughs Wellcome had established a research laboratory in Research Triangle Park, North Carolina in the late 1970s and used this as a launch pad for its links with the US academic base. Glaxo followed suit in 1983, establishing new research laboratories which were opened in 1986 at Research Triangle Park. Bayer expanded its operations on the site of the Miles Laboratories at West Haven, Conn, having taken over Miles in 1979. (Sharp 1985 a.)

[27]This was the number of researchers reckoned by Bayer to be engaged in biotechnology at the peak of its activities. See Sharp and Galimberti (1993).

[28]The timing of these moves and the way in which it was handled varied from company to company. Ciba Geigy, for example, made such moves fairly early; by contrast the Italian firm Carlo Erba/Farmitalia left the moves until much later and remarked on the difficulty of penetrating the 'chemical' traditions of the pharmacologists until this had happened. See Galimberti (1993).

encountered by the Hoechst in trying to bring their genetically engineered insulin plant on stream in Frankfurt in 1987 and the discussion of a five year moratorium on genetic research in West Germany caused uncertainty and raised fears about the future.[29]

5.10 Given the need to build up in-house competencies, the pressure from companies on government at this time centred on improving the indigenous science base and on issues of linkage into the science base. Governments, for their part, were anxious, insofar as funding was increased, to see it linked to technology transfer schemes which would ensure that companies used academic research, and that the research was 'relevant' to industrial needs. Hence the various Science & Engineering Research Council (SERC) schemes in Britain, the CRITT (Regional centres for Innovation and Technology Transfer) in France and the German Governments Biotechnology Centres, all aimed at establishing university/industry linkage.

The early 1990s - towards commercialisation

5.11 The third (and present) phase of the development of the new biotechnology sees products beginning to appear on the market and companies, both large and small, becoming more selective and targeting activities. Given the increasing emphasis on bringing products to market, the issues of regulation and intellectual property rights suddenly become very much more pressing and from the company point of view take precedence over all other issues of public policy.

5.12 There has been a steady trickle of new biopharmaceuticals on to the market. Nevertheless, even today (1996) the number of new products actually launched remains fewer than 50. But there are many in the pipeline, and many incorporating novel features. Jurgen Drews, head of R&D at Hoffman LaRoche, commented in 1993:

---

[29]For a full discussion of the regulatory problems encountered in West Germany, see Shackley (1993).

> While there are some redundancies among the 150 or so novel proteins in development, about 100 represent truly novel substances that have no precedent in medical therapy. Not all of these proteins will reach the market, but it is fair to assume that their attrition rate will be lower than that for small chemical entities because they should cause few unmanageable toxicological problems. A conservative estimate would expect 30-40 of the recombinant proteins now under development to become successfully marketed products over the next 5-6 years.
>
> (Drews, 1993)

Looking beyond the 10 year horizon, Drews foresaw the arrival first of the cytokine based drugs which will treat various kinds of cancer, many based on novel combinations of proteins and other chemical entities. Diseases such as Parkinson's and Alzheimer's and neural disorders are high on the list of targets. The most far reaching of current developments, however, come from another source - from work involved with understanding the human genome (and, concomitantly, unravelling genes' physiological function and roles in disease processes). Current initiatives in genome mapping will help identify many new proteins with therapeutic potential and also illuminate an even greater number of possible targets especially when linked to the new developments in combinational chemistry. Gene therapy itself - direct intervention to alter the genetic make-up of cells - may also have far reaching effect on both pharmaceutical and health care industries.

5.13 The implications of these developments are interesting . Although they show a maturing of biotechnology, it is still an area of active, indeed dynamic, development by both large and small firms in the industry. In the small firm sector, the early 1990s saw setbacks for some of the leading players of the 1980s. Genentech, the largest and in many ways the most successful of the new biotechnology companies, managed to launch its tissue plasminogen activator (tPA) in 1989 after 10 years of development, but ran into difficulties in the process and was therefore in no position to fight the effective take-over bid from Hoffman LaRoche the following year.[30] Centacor took its product Centatoxin (for treating septic

[30]One of the problems Genentech faced was that in order to recoup its heavy R&D spend it priced its tPA at the top end of the price spectrum. This led to Medicare and many insurance companies in the US refusing to pay for its use and insisting on cheaper alternatives, especially after a damming report which suggested it was no

shock) all the way but fell at the last hurdle of FDA (Food and Drug Administration) approval which entailed another year of testing which has had a crippling effect on the company.[31] Cetus, one of the first DBFs to emerge in the 1970s and one of the strongest during the 1980s has also hit difficulties in developing its products[32] and amalgamated with another DBF, Chiron, for survival. Chiron, always closely linked to Ciba Geigy, is now 49.9 per cent owned by the Swiss firm.

5.14 In their place a new generation of leading players have emerged. Amgen, for example, has succeeded in launching first its erythropietin (Epogen) and then its colony stimulating factor, Neupogen. It now has sales of over $1 billion per annum. (See Table 17) Human Genome Sciences is a leading firm in the gene sequencing business. Companies such as Affimix and Sphinx are leaders in combinational chemistry. But although most DBFs still aim to follow Amgen and become fully integrated pharmaceutical or chemical companies, none have so far made it.[33] Most DBFs continue to exist because they have established a synergistical relationship with the larger companies. Increasingly, as Table 17 shows, they are the source of new product ideas, but for their part the small companies depend on the larger firms not only to market these products but to carry them through the expensive development stages (which means taking them through Phase II and III trials). The large firms also remain a key source of finance. The two sectors of the industry remain therefore mutually dependent upon each other. Hence, while the DBF sector is as active as ever, the larger firms are also increasing commitments.

---

more efficacious than these alternatives. As a result sales were lower than anticipated, share prices fell and help had to be sought. See "An Appetite for Technology: Hoffman LaRoche", *BioTechnology,* August 1992.

[31]See "FDA flattens Centacor" and "What went wrong with Centoxin", *Bio/Technology,* Vol 10, June 1002, pp616 and 617.

[32]Cetus only survived because it sold its best innovation (its PCR patents) to Hoffman LaRoche for $300m in 1991. It could neither afford to develop them in-house nor to sit on them. They also funded a collaboration with instrument manufacturer Perkin Elmer to develop machines for PCR techniques. See *op cit* footnote 14 above. Se also "Hope and Hype in Biotechnology", *Bio/Technology,* Vol 10, September 1992, pp946-947.

[33]This is well illustrated in Barry Werth's *The Billion Dollar Molecule* (New York. Knopf 1994) which describes the frantic early years of the Vertex company in Boston.

Table 17 Top Ten Biotechnology drugs on the Market in 1993

Product	Developer	Marketer	1993 Net Sales ($m)
Neupogen	Amgen	Amgen	719
Epogen	Amgen	Amgen	587
Intron A	Biogen	Schering-Plough	572
Humulin	Genentech	Eli Lilly	560
Procrit	Amgen	Ortho Biotech	500
Engerix-B	Genentech	SmithKline Beecham	480
RecombiNAK HB	Chiron	Merck	245
Activase	Genentech	Genentech	236
Protropin	Genentech	Genentech	217
Roferon-A	Genentech	Hoffman LaRoche	172
Total sales of top ten			**$4,288**
Total industry sales			**$7,700**

Source: *Med Ad News,* quoted in Ernst & Young, 1994

5.15 While large firm investment has been growing, it has also become increasingly targeted. The last few years have seen a marked shift away from the broad learning strategies of the mid-1980s towards a more focused approach. Ciba Geigy, for example, in 1989, cut back on its portfolio of interests in biopharmaceuticals in order to concentrate more narrowly on the development of a few products with market potential. Since then, it has both increased in-house activity in those areas and concluded a number of research and licensing deals which strengthen its position yet further (see next section). For Bayer targeting involved pulling out of biotechnology research in agro-chemicals and concentrating on pharmaceuticals. Hoffman LaRoche has likewise pulled out of agro-biotechnology to concentrate its interests in the pharmaceuticals area. Rhône Poulenc, a relatively late entrant into mainstream biotechnology, has made up for lost time by an aggressive policy of acquisition and alliance. Like Ciba Geigy and Zeneca, it has maintained interests in both pharmaceutical and agricultural aspects of biotechnology and has bought itself into the seed industry. For most of the large companies, however, the most notable feature of the 1990s

has been the explosion of collaborations with American DBFs. This development is explored in more detail in the next section.

6 ALLIANCES, LINKAGES AND TECHNOLOGY TRANSFER

6.1 This section seeks to explore the degree to which the European chemical/ pharmaceutical industry is linked into the US biotechnology base, comprehending both the DBFs and the US university system. The main evidence is presented in Annex A which presents in tabular form the linkages of some of Europe's major pharmaceutical companies.[34] While not necessarily accurate in every detail, the weight of evidence points firmly to relatively deep penetration of the US biotechnology base by European companies.

Corporate alliances

6.2 The outstanding feature of Annex A is the very large number of corporate alliances with American DBFs undertaken by these European multinationals. Table 18 summarises the data. Ciba Geigy, the company which in the early 1980s broke with tradition in contracting out key research on biotechnology, leads the list with 29 known alliances, but Hoffmann LaRoche on 27 and Hoechst on 24 are close runners up. By contrast, the British companies ICI and Zeneca (de-merged in 1993) between them have only two listings.

6.3 Even more interesting is the second column in Table 18, the number of agreements concluded since 1990. This reinforces what has been said earlier about the continuing dynamism of the DBF sector - indeed if anything it suggests an increase in the number of alliances between these two sets of players in the last five years at a time when, as indicated in the previous section, these companies have themselves been investing heavily in biotechnology.

---

[34]This listing was compiled for another piece of research and does not give full details for companies dedicated to pharmaceuticals - eg, Glaxo or SmithKline Beecham.

Table 18 Alliances and Joint Ventures between US DBFs and leading European multinationals in the chemical/pharmaceutical industry

Company	Total Number of Alliances listed in Annex A	Number concluded since 1990
Ciba Geigy	29	17
Hoffman LaRoche	27	10
Hoechst	24	10
Rhône Poulenc	19	12
Sandoz	18	14
Bayer	12	7
ICI/Zeneca	2	1

Source: Data presented in Annex A

6.4 Examining the detail in Annex A shows that there has been a shift over the course of the last ten years from R&D agreements, which dominated in the early years, towards marketing and licensing agreements. In other words, whereas ten years ago the alliances were to supplement internal research work, today they fulfil a more important role, namely as a key supplier of potential new products. This suggests that in spite of their substantial investments in in-house biotechnology since the mid-1980s, these companies are still short of key biotechnology products for their new product portfolios. It also illustrates the complementary nature of the investments. In order to be able to exploit the new product ideas coming from the DBFs, the large companies also need in-house capabilities. Without such capabilities, they would not be in a position to license and market the new generation of biopharmaceuticals.

6.5 While Annex A illustrates how deeply some of these European companies are networked into the US biotechnology system, it gives little perspective of the relative position of European firms vis-à-vis those from other parts of the world. In particular, given fears in the early 1980s of the growing challenge from Japan it is interesting to compare European collaborations with those of Japan. Tables 19a and 19b, based on studies of the

Table 19A US-DBFs involved in biotechnology alliances 1982-91

		%
Total number of alliances noted	2079	
of which detailed data on	1303	100
of which involving a Japanese partner	183	14
of which involving a European partner	346	27
of which UK	76	6
Swiss	71	5.5
Germany	45	3.5
France	36	3.0
Italy	3.6	3.0
Sweden	27	2.0
Netherlands	9	1.0

Source: Dibner and Bulluck, 1992

Table 19B Biotechnology Alliances 1992-1994 (June to June)

	%	
Geography of deal partner	1992-3	1993-4
N America	63	65
Europe	24	24
Japan	11	8
Other	2	3

Source: Ernst & Young (1994), Table 13

geographical spread of DBF alliances; one by Dibner and Bulluck (1992) using Dibner's North Carolina database on biotechnology collaborations, the other from the latest (1994) Ernst and Young *Biotechnology Review* suggest that European firms are considerably more active than Japanese firms in linking up with US DBFs. While a majority of alliances are forged not with foreign companies but with US companies, both tables suggest that approximately 25 per cent of alliances are concluded with European firms compared to a 10-

12 per cent share with the Japanese and a 60 plus per cent share to North America (including Canada). It is notable that on the issue of technology transfer, Dibner and Bulluck comment:

> "Of the 346 alliances we were able to code the direction of technology or product flow in all but 36. Of the coded alliances, 71 per cent had the technology or product flowing to Europe, 25 per cent had the technology or product flowing to the United States, and the remainder (14 alliances) were bilateral. ... However, it should be noted that many of the alliances are licensing or marketing agreements ... Since the majority of these alliances involve smaller US firms not likely to have sufficient resources to market globally, they may provide these firms with opportunities not otherwise available."
>
> (Dibner and Bulluck, 1992, p632)

It is perhaps worth adding that in saying that the alliance "had the technology or product flowing to Europe", Dibner and Bulluck meant, of course, to *European-owned* firms. Most of these firms are major multinational companies and have a substantial presence in the US.

Mergers, Acquisitions and Overseas Laboratories in the US

6.6 The ownership of subsidiaries and affiliates overseas is given by columns 3 and 4 in the individual company tables in Annex A. Column 2 lists overseas laboratories in the US; Column 3 lists acquisitions and mergers. Often the two are related. Bayer, for example, acquired two medium-sized US pharmaceutical firms, Miles and Cutter, in the late 1970s and their laboratories in West Haven, Connecticut and California have formed the basis of Bayer's research presence in the US. Molecular Diagnostics, a DBF in New Haven established with help from Bayer, was absorbed within the Miles Laboratories in 1992. Ciba Geigy's animal health laboratory in the US is based on its acquisition from Bristol Myers Squibb in 1990. On the other hand its plant breeding laboratories in North Carolina and its Pharmaceutical Division in New Jersey derive from earlier decisions to develop these facilities in the US. Both are located close to university campuses. Indeed, Research Triangle Park in North Carolina where Ciba Geigy's plant breeding laboratory is located has proved a popular

location for European multinationals. Glaxo, Wellcome, Ciba Geigy and Roche all have research laboratories in the area. Rhône Poulenc is the company amongst those listed which has pursued the most aggressive policy of growth by acquisition. Together with its subsidiary Institut Mérieux it bought Connaught Biosciences, Canada's largest biotechnology firm, in 1989 to make the combined operation (Mérieux plus Connaught) the world's largest producer of vaccines. Then in 1990, it bought Rorer, a fairly substantial US pharmaceutical company which already had a fair track record in research and the company's work in pharmaceuticals is now led by Rorer. It was the Rorer laboratories which in 1994 spearheaded the company's 'network collaboration' Gencell of 14 companies in genome sequencing area. Rhône Poulenc, like Zeneca, has also been actively acquiring seed companies.

6.7 The detail of Annex A also demonstrates the extent to which these European multinationals have put down roots into the US science base. Table 20, derived from a study which analysed European and Japanese company research laboratories in the US (Dibner, Stock and Greis, 1992) located 76 sites where the companies concerned were engaged in biotechnology R&D; of these, 60 belonged to European parent firms and only 16 to Japanese parents. Even more revealing is the data contained in the second half of the Table which shows the average number of collaborations for the two different types of site - in particular the degree to which the European sites are linked into the American university system with (on average) over six linkages per site compared to the Japanese 2.4 average.

Academic Links

6.8 Table 20 highlights not only the large number of US laboratories run by European multinationals, but the extensive linkages which these laboratories have with US universities. The picture that emerges from this data for most companies is of extensive linkage through the DBFs and their overseas research laboratories into the US science base.

Table 20 Linkages between US-based facilities of European and Japanese companies involved in biotechnology research

	European-Owned Sites	Japanese-Owned Sites
Number of Sites	60	16
Linkages with		
Universities (av)	6.04	2.42
Biotechnology firms (av)	0.93	0.17
Other corporations (av)	1.00	0.58
Total collaborations (av)	7.42	3.17

Source: Dibner, Stock and Greis, 1992.

6.9 An exception to this general picture is Zeneca, which, although it has substantial laboratories at Wilmington, PA, has few linkages with DBFs. Other UK firms (Glaxo, SmithKline Beecham, Wellcome) have also been slow to develop such linkages, although Glaxo and SmithKline Beecham have recently been actively developing DBF links. By contrast Zeneca (formerly ICI pharmaceuticals and agro-chemicals) has been very deeply networked into the UK science base. An evaluation of the UK Science and Engineering Research Council's (SERC) Biotechnology Directorate (Senker and Sharp, 1988) found ICI the most active participant in the Directorate's programmes promoting university/industry links and the company itself had established and supported laboratories at the Universities of Leicester and Cambridge. Several of the products the company currently has under development derive directly from such linkages. This view of Zeneca (ICI) as a company linked into its home (UK) academic base rather than into the US is reinforced by recent work undertaken at SPRU on collaboration as revealed by jointly authored publications. Table 21 looks at the performance of the individual firms in 1989. ICI tops the league with 363 papers.[35] Of these 238 (66%) were collaborative and 203 of these (85%) were collaborative with universities most of these (190) being within the UK. As a whole the data show that

[35]Zeneca demerged from ICI in 1993. At this time (1989) therefore it was an integral part of ICI.

Table 21 Collaboration through publication - company profiles

	ICI	BASF	Bayer	Hoechst	Ciba Geigy	Total
Total No of publications	363	91	119	210	311	1094
Collaborative publications[a]	238	38	55	133	159	623
	(66%)	(42%)	(46%)	(63%)	(51%)	(57%)
of which						
- with universities[b]	203	23	40	99	120	485
	(85%)	(60%)	(46%)	(63%)	(51%)	(78%)
- domestic[b]	190	27	39	91	58	409
	(80%)	(71%)	(73%)	(75%)	(76%)	(65%)
- with Europe[b]	223	34	51	112	124	544
	(94%)	(89%)	(93%)	(84%)	(78%)	(87%)

a Collaborative publications shown as a percentage of total publications
b Publications shown as percentage of collaborative publications. Note: a small number of publications have been classified as both a domestic collaboration and a foreign collaboration where more than two authors are cited.

Source: Unpublished data from Hicks, Isard and Martin (93)

most of the collaborations were within Europe (94% for ICI - the lowest being Ciba Geigy with 78%). These figures suggest that there is very little co-authoring of work between European researchers and their US counterparts in corporate laboratories.

Implications for Technology Transfer

6.10 The evidence presented so far in this section suggests that in their need to access biotechnology expertise, many European based multinationals are linking into the American science base via DBFs and overseas laboratories. While, following Reich (1991), this need do no harm, ensuring production opportunities and profits for the multinational and high productivity jobs for the US, it does pose the question of how far these companies are shifting all leading-edge biotechnology research off-shore, thus depriving Europe of the necessary learning opportunities and training in newly emerging areas of biotechnology.

6.11 Recent research at SPRU funded under the Biotech programme (Senker, Joly and Reinhard, 1996) has explored this question through a series of case studies based on interviews with leading researchers in corporate laboratories. The answers are reassuring for they show that while a good deal of research is being conducted in the US, much of it is driven by the need to develop and test products for that market, in that market, and that in no way is there any systemic tendency for leading edge biotechnology research to migrate across the Atlantic. On the contrary, European laboratories have built up and are maintaining a strong core of research in biotechnology, using linkages with US DBFs mainly in areas where Europe has weaknesses - for example, gene therapy, genomics and combinational chemistry. In such cases the link was directly from the European HQ to the DBF and the technology transfer was from the DBF to the European firm. In this sense, the relationship remains complementary and the linkage, far from weakening European capabilities, is helping to reinforce them.

7 CONCLUSIONS

What conclusions emerge in relation to the innovativeness of Europe's pharmaceutical industry?

(i) Innovation is not easily measured in the pharmaceutical industry. It is a research-intensive industry, but R&D does not necessarily lend to innovative drugs. Indeed, given the oligopolistic nature of the industry and the need to block and counter advantage gained by competitors, too much R&D is devoted to producing me-too drugs and duplicating research undertaken by others. The same problem affects both patenting (too much defensive patenting) and counts of drugs under development (does a large count mean poor management or real innovation?). The best measure, which effectively leaves it to the market to 'pick the winners', is to take numbers of drugs in the top selling 25 or 50 drugs on the market, but even this has its drawbacks, measuring past rather than present innovation.

(ii) Using this measure, US companies, with 26 out of the top 50 best selling drugs, prove to be the most innovative with companies such as Merck, Eli Lilley and Pfizer, combining a strong innovative tradition with high re-investment from profits into R&D so that the system becomes self-reinforcing. Merck in particular stands out as a company which has kept itself at the forefront of the industry with a steady stream of attractive and innovative new drugs.

(iii) Europe, with 21 out of 50 top selling drugs, is not far behind, whereas Japan with only three of 50 lags well behind. Within Europe it is the British companies, with between them 14 out of the European total of 21 top selling drugs, which stand out as the success story. Their position in world rankings has risen steadily over the last two decades, they have a larger market share of the highly competitive US market than their European counterparts and they have been steadily increasing their share of European and South East Asian markets. Britain is also host to a large number of overseas laboratories for American pharmaceutical companies. These are almost wholly staffed and managed by British personnel and in this sense both reflect and reinforce innovative capabilities in this area.

(iv) By contrast, the German and Swiss companies, traditional market leaders in Europe, fare relatively badly, with Bayer and Ciba Geigy (each with two top selling drugs compared to Glaxo's six (Glaxo-Wellcome seven) and SmithKline Beecham's four) leading the field. It is notable, however, that it is Swiss and German companies that top the lists in terms of R&D and numbers of drugs under development. This could be seen as following a 'Merck strategy' - trying to buy themselves into the virtuous self-reinforcing cycle of high investment in R&D yielding high profit drugs which finance yet further investment.

(v) The key to the future lies with the biopharmaceuticals and biotechnology where European pharmaceutical companies were slow to develop in-house capabilities allowing the leading edge of the technology to be developed in the United States by the small, specialised dedicated biotechnology companies (DBFs). In contrast to the position in the 1950s and 1960s when the innovative new drugs were coming from the in-house research laboratories of

the major pharmaceutical companies, today's innovative drugs have been 'discovered' in academic laboratories or the quasi academic laboratories of the DBFs.

(vi) In some senses Europe's large pharmaceutical companies have shown surprising flexibility in this shift from chemistry to biology. Swiss and German companies have broken with tradition and bought into external research, both through linkages with the DBFs and through agreements of one sort or another which have given them access to the American science base. The French too have been active in developing such links, with Rhône Poulenc's merger with Rorer providing that company with an American base for the development of pharmaceuticals. These linkages, combined with heavy in-house investments in the new technologies, means they are now in a position to exploit developments in biotechnology. In the last few years in particular there has been a notable shift towards deals with DBFs which replenish product portfolios with drugs in development rather than the early deals involving exploratory research.

(vii) The exception, until recently, have been the British drug firms which have chosen to exploit linkages with the British rather than the American science base. British capabilities in molecular biology and molecular genetics, combined with a more mature venture capital market mean that Britain also has had a stronger and more active small firm sector in biotechnology than any other country in Europe. Substantial investments in the public science base and the development of venture financing in other European countries, means that Britain is no longer as distinct in this field as it was in the 1980s.

(viii) Significant changes have taken place in the last two-three years. The emergence of a new 'generation' of bio-pharmaceutical research with developments in genomics, bio-informatics and combinational chemistry have seen the British companies, SmithKline Beecham and Glaxo-Wellcome investing heavily in US capabilities, Rhône Poulenc Rorer developing its Gencell network and Pfizer now following suit. These developments suggest that all companies are now shifting from the old model of concentrated in-house R&D to one

which accepts a new extended division of labour, with specialist companies performing specialist roles.

(ix) These changes reinforce other cost cutting pressures on the major pharmaceutical companies, especially pressures from governments anxious to limit the public sector liabilities on drugs expenditure. The spate of mergers already seen in the industry, which seek to reinforce research and rationalise distribution systems, are likely to be followed by others as companies reassess capabilities and reposition themselves in the market.

(x) It is not yet clear where these trends will lead - to large, international companies whose main role is to co-ordinate specialist international teams? Or to tight knit organisations like Merck which, nevertheless, have the ability to assimilate and use information from a wide variety of sources?

(xi) Given continuing uncertainty, priority in terms of innovation means creating an environment conducive to innovation rather than pre-empting particular routes. For European countries and companies this means:

(a) continuing high level support for the public research base in the life sciences - so much of the creativity in the US has come from the exploitation of public research findings, it is vital that the squeeze of public finances does not 'kill' this 'goose which lays the golden eggs';

(b) exploitation of that science base as a *European* resource - at present too little is known, especially by the company sector, of capabilities that lie within Europe but outside national boundaries;

(c) the reinforcement of the Single Market in pharmaceuticals with the dismantling of *national* regulatory regimes and the development of Community institutions such as the EMEA. Developments to date have been too slow and hampered by too many national

sensitivities. In particular an efficient regulatory framework for biotechnology-based drugs is essential.

(d) The easing of financial restrictions on venture capital financing and the promotion of other mechanisms for the support and funding of new, technology-based companies.

REFERENCES

Archilladelis, B *et al* (1990): 'The Dynamics of Technological Innovation: The Case of the Chemical Industry', *Research Policy,* 19 (1), pp 1-35.

Brech, M and Sharp, M (1985): 'Inward Investment: Policy Options for the UK', Chatham House Paper No 21, Routledge & Kegan Paul for Royal Institute of International Affairs.

Burstall, M L and Senior, I (1994): *The Community's Pharmaceutical Industry,* Economists Advisory Group for the Commission of the European Communities.

Chetley, A (1990): *A Health Business,* Zed Publications.

Clark, C and Walton, F (1992): 'Europe's Emerging Biopharmaceutical Companies'. *Bio/Technology,* Vol 10, October, pp1108-1110.

Coleman, R F (1988): 'National Policies and Programmes in biotechnology', in *Biotechnology: The Changing Role of Government,* OECD, Paris.

Dibner, M (1991): 'Tracking trends in US biotechnology'. *Bio/Technology,* Vol 9, December, pp1334-1337.

Dibner, M and Bulluck, J A (1992): 'US/European Strategic Alliances in Biotechnology'. *Biotechnology Forum Europe,* Vol 9, October, pp628-635.

Dibner, M; Stock, G and Greis, N (1992): 'Away from Home: US sites of European and Japanese Biotech R&D'. *Bio/Technology,* Vol 10, December, pp1535-1538.

Dimasi, J A; Hansen, R W; Grabowski, H G and Lasagna, L (1991): 'The Cost of Innovation in the Pharmaceutical Industry: New Drug R&D Cost Estimates', *Journal of Health Economics*, June.

Drews, J (1993): "Into the 21st Century. Biotechnology and the Pharmaceutical Industry in the next 10 years", *Bio/Technology,* 11 March 1993.

Ernst and Young (1994): *Reform, Restructure and Renewal,* 9th Annual Report on the Biotechnology Industry.

Galimberti, I (1993): *Large Firms in Biotechnology: Case Studies on Learning Radically New Technologies,* DPhil Thesis, SPRU.

Gambardella, A (1995): *Science and Innovation: The US pharmaceutical industry during the 1980s,* Cambridge University Press, Cambridge, UK.

Griliches, Z (1990): 'Patent Statistics as Economic Indicators', *Journal of Economic Literature,* 28.

Hicks, D; Isard, P and Martin, B (1993): *University-Industry Alliances as revealed by joint publications,* Mimeo, SPRU.

Irvine, J; Martin, B R and Isard, P (1990): *Investing in the Future: An International Comparison of Government Funding of Academic and Related Research,* Edward Elgar.

Joly, P-B (1992): Organisational Learning, Diversity and Interactions in a Sectoral Innovation System. Paper presented at workshop on "Systems of Innovation", Bolgna, October 1992. Mimeo. Obtainable from INRA/SERD BP47 38040, Grenoble, Cedex.

Kenney, M (1986): *Biotechnology: The University-Industry Complex,* Yale University Press, New Haven.

Lake, A W (1976): 'Foreign Competition and the UK Pharmaceutical Industry', NBER Working Paper No 155.

Martin, P and Thomas, S (1996): *The Development of Gene Therapy in Europe and the United States: A Comparative Analysis*, STEEP Special Report No 5, SPRU, University of Sussex, September 1996.

MEFA (1992): Facts 1992: Medicine and Health Care, Copenhagen, July

Mossialos, E; Kanavos, F and Abel Smith, B (1993): *Policy Options for Pharmaceutical R&D in the European Community*, London School of Economics, November.

OECD (1987): Recombinant DNA Safety Considerations: For Industrial, Agricultural and Environmental Applications of Organisms Derived by Recombinant DNA Techniques, Paris, OECD.

Office of Technology Assessment (OTA) (1984): Commercial Biotechnology. OTA/US Government Printing Office.

Office of Technology Assessment (OTA) (1988): New Developments in Biotechnology: US Investment in Biotechnology, OTA/US Government Printing Office, Washington DC.

Office of Technology Assessment (OTA) (1991): *Biotechnology in a Global Economy,* Office of Technology Assessment, Congress of the United States, Washington DC.

Office of Technology Assessment (OTA) (1993): *Pharmaceutical R&D: Costs, Risks and Rewards*, OTA-H-522, Washington, DC: US Government Printing Office, February.

Patel, P and Pavitt, K (1995): 'Patterns of Technological Activity: their Measurement and Interpretation', in Stoneman, P (ed): *Handbook of Economics of Innovation and Technical Change"* Oxford, Blackwell.

Pavitt, K (1988): 'Uses and Abuses of Patent Statistics', in Van Raan, A (ed): *Handbook of Quantitative Studies of Science and Technology*, North-Holland, Amsterdam.

Rizzoni, A (1995): 'SPRU Database on Europe's new dedicated biotechnology companies', unpublished research, Science Policy Research Unit, University of Sussex.

Senker, J and Sharp, M (1988): *The Biotechnology Directorate of the SERC: Report and Evaluation of its Achievements,* mimeo, SPRU.

Shackley, S (1993): The Regulation of Biotechnology in Europe, DPhil thesis submitted to University of Sussex, UK.

Sharp, M (1985a): *The New Biotechnology: European Governments in Search of a Strategy.* Sussex European Paper No 15. Available from SPRU, University of Sussex.

Sharp, M (1985b): "Biotechnology: Watching and Waiting". Chapter 6 in Sharp, M (ed): *Europe and the New Technologies,* Pinter Publishers, London.

Sharp, M and Galimberti, I (1993): *Coherence and Diversity: Europe's Chemical Giants and the Assimilation of Biotechnology.* Case study undertaken for EC FAST Project: *Coherence and Diversity in Europe's Industrial System.* Mimeo, SPRU, University of Sussex.

Thomas, L G III (1994): 'Implicit Industrial Policy: The Triumph of Britain and the Failure of France in Global Pharmaceuticals', *Industrial and Corporate Change*, vol 3, No 2, pp 451-490.

Annex A

Company	Biotech Interests	Overseas Labs USA	Acquisitions and Equity Purchases in US DBFs	Alliances with DBFs and Universities USA	Biotech links in other countries
HOECHST inc Roussel Uclaf	Animal Health	USA		1981 Massachusetts Hospital - research into molecular biology (1)	1988 Bayer (Eur) - R&D into IDS diagnostics (4)
	Pharmaceuticals	1991 new R&D centre - neurological disorders (1)		1984 Immunex - drug development	1988 Glaxo (Eur) - cephalosporins (4)
	Diagnostics	Hoechst-Celanese Separation Products Div		1985 Genex - R&D serum proteins (1)	1988 Inra (Eur) - R&D fungicides
Sales					
$27.85bn (1993)		(2) (4)			
	Vaccines			1985 Cetus - R&D vitamins (1)(3)	1989 Nippon Kayaku (Jap) - drug R&D (4)
R&D:	Plant breeding	Other		Before 1986 Biogen - R&D antimalaria vaccine (1)	1990 DNARD (Jap) - joint venture develop/ market transgenic animal models (1)
$1865m (1992)				Before 1986 Chiron - R&D t-PA (1)	
	Pesticides	1988 Japan - drug research centre esp MABs (1)		1987 Integrated Genetics - development of EPO (1)	
		1989 Japan - biotech centre and production plant 91)		1988 Codon - vaccines for animal parasites (1)	
		1991 Japan - expansion of R&D/new research labs (1)		1988 Massachusetts Hospital - drug research (1)	
				1988 Calon - R&D into vaccines (4)	
				1988 Calgene R&D programme into plant genetics (1)	
				1989 Immunex - licensing (GM-CSF (3)	
				1989 University of Illinois - R&D into insecticides (1)	
				1989 Genex - veterinary (unspecified) (5)	
				1990 ImmunoGen - licensing anti-cancer drug (3)(c)	
				1991 Ecogen - R&D insecticides (1)	
				1991 Ecogen - marketing insecticides (3)	
				1991 Syntro - marketing vaccine (3)	
				1991 Syntro - R&D poultry vaccines (1)	
				1992 Triplex Pharmaceuticals - R&D anti-viral drugs (1)	
				1992 Syntro - R&D cattle and horse vaccines (1)	
				1993 Oncogene Science - D on transcription-based drugs (6)	
				1993 Vertex - R&D on anti-inflam drugs (6)	
				1994 Oncogene Science - D on drugs against Alzheimers (7)	

Company	Biotech Interests	Overseas Labs USA	Acquisitions and Equity Purchases in US DBFs	Alliances with DBFs and Universities USA	Biotech links in other countries
BAYER	Pharmaceuticals	<u>USA</u>	<u>Acquisitions</u>	Before 1986 Genentetech - factor VIII	1988 Hoechst (Europe) - R&D into AIDS diagnostics (4)
<u>Sales</u>: £24.70bn (1993)	Diagnostics	1988 major expansion of drug research centre (1)(2)	Before 1986 Molecular Diagnostics (1)	Before 1986 Genetic Systems - MABs v infections (1)	1988 Georg-Speyer Hans Research Lab (Europe) - R&D (4)
<u>R&D</u>: $1988m (1992)	Vaccines	1989 new experimental station - plant protection (1)	1988 Cooper Technicon - diagnostics (1)(5)	1988 Cutter Biological - production of therapeutics (5)	
	Plant protection	Cutter Biological (2)	1989 Agricon - veterinary vaccines (5)	1989 Calgene - research into plant herbicide resistance (1)	
	Agrochemicals	Miles Inc (2)	1989 Diamond Scientific - veterinarian vaccines (1)	1989 Chiron - licensing TNF (4)(5)	
		Miles Inc Diagnostic Division (2)	1994 Onyx Pharmacs (for Miles)(7)	1990 California Biotechnology - licensing therapeutics (5)	
		Molecular Diagnostics (2)		1991 California Biotechnology - CV disease drugs (1)	
		<u>Other</u>		1991 Iterex Pharmaceuticals - drug discovery (1)	
		1988 Japan - construction agchem research labs (1)		1992 Syntro - marketing vaccines (c)	
		1988 Japan - new drug research centre (1)		1992 Viagene - R&D on gene therapy for haemophia (b)	
		1990 Japan - new R&D facilities into CV disease (1)		1993 N American Biologicals - supply of plasma (6)	
				1994 Onyx Pharmaceuticals - joint research on cancer drugs (7)	

Company	Biotech Interests	Overseas Labs USA	Acquisitions and Equity Purchases in US DBFs	Alliances with DBFs and Universities USA	Biotech links in other countries
ICI Including Zeneca Sales: $22,634m (1993) R&D: $1328.6m (1992)	Pharmaceuticals Plant Breeding Agrochemicals	USA Cellmark Diagnostics (2) ICI Americas Inc (2) Other 1989 Japan - technical centre (1) 1990 Canada - technical centre (1)	1985 Garst Seed (6)	1989 Pfanstiehl Labs - licensing MANs (3) 1993 Liposome Technology - marketing of amphocil (Zeneca) (6)	Before 1990 Sumitoma Pharmaceuticals (Japan) - antibiotics (1) Société European de Semences - equity purchase (6) JV with Mitsubishi Kasei (6)

Company	Biotech Interests	Overseas Labs USA	Acquisitions and Equity Purchases in US DBFs	Alliances with DBFs and Universities USA	Biotech links in other countries
CIBA-GEIGY Sales: $15.32bn (1993) R&D: $1678m (1992)	Pharmaceuticals Diagnostics Plant breeding/ Pesticides	USA 1984 N Carolina - plant breeding (1)(2) Ciba Corning Diagnostic Corp (2) Ciba-Geigy Corp Agricultural Division (2) Ciba-Geigy Pharmaceuticals Division (2) Other 1987 Japan - research centre (1) 1990 Japan - research labs (1)	Acquisitions 1988 Cooper - therapeutics 1989 Ciba Corning Diagnostics buy out of joint venture (5) 1990 Bristol Myers Squibb (animal) health unit) (5) 1990 Biotrack (1) 1992 Sogetal - part of R&D programme on plants (1) Equity purchase 1988 Chiron (1)(5) 1990 ISIS Pharmaceuticals - therapeutics (5) 1990 Tannox - diagnostics and therapeutics 1991 Affymax Research Institute (1)	1984 Bio-Response - protein production project (1) 1985 Biogen - licensing yeast promoter (3) 1985 Unigene Laboratories - research protease inhibs (3) Before 1986 Chiron - R&D into insulin (1) 1987 joint venture Co with Chiron - vaccines (1)(3) 1988 Plant Technology - plant diagnostics (1)(3)(5) 1988 Synergen - marketing therapeutics (5) Before 1989 Agridiagnostics - fungal diagnostics (1)(5) Before 1989 Calgene - plant resistance to pathogens (1) 1989 Evans Biocontrol - marketing plant agricultural products (5) 1989 Tannox Biosystems - MABs v AIDS (1)(c)(5) 1989 Innovat - licensing drug delivery system (5) 1990 Univ California - funding research re arthritis (1) ISIS Pharmaceuticals - antisense technology (1)(c)(5) 1990 Biosys - marketing pesticide (3)(5) 1990 synergen - marketing elastase inhibitor (3)(5) 1990 ICI America - licensing plant agriculture (5) 1990 Tannox Biosystems - MABs v allergies (c) 1991 Biosys - marketing insecticide (3) 1991 Affymax - drugs v cancer/autoimmune disease (c) 1992 Sibia - research into CNS drugs (c) 1992 Biosys - R&D into insect control agents (c) 1992 Aphton Corp - development of drugs against parasites in animals (6) 1992 Genencor Int - development of enzymes for the pulp and paper industry (6) 1992 Glyco Tech - R&D on carbohydrates-based drugs (7) 1992 InCyte Pharmaceuticals - licensing of PN-1 (6) 1993 Biocryst Pharmaceuticals - licensing of one family of PNP inhibitors (6) 1993 Mycogen Corp - licensing and research on corn hybrids (Ciba Seeds) (6) 1993 Oncogene Science and Pfizer - R&D on chemoprotectant (6)	

Company	Biotech Interests	Overseas Labs USA	Acquisitions and Equity Purchases in US DBFs	Alliances with DBFs and Universities USA	Biotech links in other countries
RHONE POULENC inc Institut Merieux Sales: $14.33bn (1993) R&D: $1150m (1993)	Animal health Pharmaceuticals Diagnostics Vaccines Plant Breeding	USA Before 1988 R&D centre - agrichemicals 1988 veterinary lab (1) 1990 R&D lab - food additives (1) 1990 R&D centre - drugs (1)(2??) Rhône Poulenc Central Research (2) CelPril Industries Inc (2) Other 1989 Japan - research/ production centre agrochems (1)	Acquisition 1984 Callaghan Enterprises - soya and corn seeds (1) 1986 Select Laboratories - veterinary vaccines (3) 1989 Harris Moran Seeds (partial acquisition) (1) 1989 Connaught Biosciences - vaccines (1) 1989 Virogenetics - viral vector systems (1) 1990 Rorer - therapeutics (5) Equity purchases 1991 Sepracor - bioseparation (3) 1994 Applied Immune Sciences (1)	19?? Scripps Clinic - R&D antithrombotic (1) 1984 Calgene - sunflower genetics (1) 1988 Immune Response - AIDS immunogen (1) 1989 Calgene - plant herbicide resistance (1)(3) 1989 Cambridge Bioscience - veterinary *unspecified) (5) 1989 Molecular Genetics - R&D genetics of corn (1)(3) 1989 Cenzyme - drug development (1) 1990 ISIS Pharmaceuticals p R&D antisense (1) 1990 Medimune - drug research (1) 1990 Eastman Kodak - licensing veterinary products (5) 1990 Immune Response - licensing vaccines (5) 1990 ImmunoGen - licensing therapeutics (5) 1991 Wistar Institute - marketing rabies vaccine (1) 1991 Ecogen - marketing plant agricultural products (5) 1992 Merck - development of vaccines (1) 1992 Synbiotics - licensing of cat biological products (c) 1993 Enzon - licensing of Enzon's Oncaspar (1) 1994 Vical - development of vaccines (Institut Merieux) (4) 1994 Applied Immune Sciences, Darwin Molecular, Genopoetic, Genetix Pharmaceuticals, Introgen Therapeutics, and others - JV to develop an international network of cell therapy centers (PRP Gencell) (1)	1988 Allelix (Can) into interleukine 6 (4) 1989 Mochida Pharmaceutical (Jap) - drug development (4) 1989 Chugai Pharmaceutical (Jap) - drug development (4) 1989 Nissue (Jap) - diagnostic reagents (4) 1989 Limagrain Nestlé (Eur) - R&D (tomatoes) 1989 Biolafitte (Eur) - ultrafiltration (4) 1989 Condor Y cida De Cordoba (Eur) - R&D (4) 1989 Centre Int de Transfusion Sanguine (Eur) - R&D (4) 1990 University of Toronto (Canada) - vaccine research (1)

Company	Biotech Interests	Overseas Labs USA	Acquisitions and Equity Purchases in US DBFs	Alliances with DBFs and Universities USA	Biotech links in other countries
SANDOZ Sales: $10.21bn	Pharmaceuticals Diagnostics Agriculture - biopesticides, etc Equipment Veterinary	Research Centre: East Hanover NJ Stanton MN (plant biotech) Naples FL (plant biotech) Nampa ID (plant biotech)	198? Genetics Institute - equity investment $3m (6) 1987 - 60/40 joint venture Repligen (1993 Purchase Repligen's interest) (6) 1992 - 60% purchase SyStemix Inc 1992 - 6% Equity investment in Genetic Therapy Inc	1987 Incstar Corp - non-exclusive development agreement for MAb-based diagnostic 198? Wistar Institute - R&D agreement on MAbs to tumour antigens and infectious agents 1988(?) Columbia Univ - non-exclusive licensing agreement for patented rDNA extraction process 1990 AMRAD Corp Ltd - development and marketing agreement on leukemia inhibitory factor (LIF) therapeutics 1991 Athena Neurosciences Inc - exclusive licensing agreement for tizanidine to treat multiple sclerosis and other diseases 1991 Dana-Farber Cancer Institute - 10 year, $100m R&D agreement for signal transduction drugs 1991 Genetic Therapy Inc - development and marketing agreement for products based on GTI's gene therapy system 1991 Protein Design Labs Inc - development agreement on PDL's humanised mouse MAb 1992 Affymax NV - R&D agreement on catalytic antibodies 1992 Epitope Inc - development agreement on genetically engineered tomatoes 1992 Gensia Pharmaceuticals Inc - four-year R&D agreement on novel drugs to treat diabetes 1992 Magainin Pharmaceuticals Inc - development and marketing agreement for novel anticancer products 1992 Scripps Research Institute - 10-year, $300m research alliance 1992 SyStemix Inc - collaborative research agreement on stem cell growth factors 1993 Bio-Technology General Corp - exclusive worldwide rights to aminopeptidase enzyme for processing genetically engineered proteins 1993 Procept Inc - collaborative agreement on research and marketing for small-molecule drugs to treat immune system disorders 1993 SyStemix Inc - joint venture for development of somatic gene therapies for HIV infection	Research facilities in Austria, Netherlands Agri research station in Spain 59% holding SDS Biotech XK (Japan) 1989 Acquired Hilleshög - seed and plant genetic firm in (Germany?) Agreement with Royal Free Hospital (UK) to Agreement with Schering AG (Ger) for collaborative development on anti-anxiety agent

Company	Biotech Interests	Overseas Labs USA	Acquisitions and Equity Purchases in US DBFs	Alliances with DBFs and Universities USA	Biotech links in other countries
ROCHE Sales: $9.68m 1993 R&D:	Pharmaceuticals Diagnostics Fine chemicals	Research Centres at Nutlley NJ Burlington, NC Branchberg, NJ	1990 Acquired 60% Genentech for $2.1bn 1990 Sold plant protection business to Ciba Geigy 1994 Acquired Syntx for $5.36bn 1994 Equity Purchase and Research collaboration for Millenium (Cambridge MA) - $70m	1984 (extended 86) Immunex Corp and Ajinomoto Co Inc - collaboration agreement to research, develop (Immunex), and market (Roche), IL-2 1985 XOMA Corp - licensing agreement for MAb cell lines for diagnostics 1986 Angenics - licensing and sponsored research agreement on screening tests 1986 Immunomedics Inc - licensing agreement for radiolabeled MAbs for cancer diagnostics 1986 Scios Nova Inc - preclinical investigations for delivery system for Hoffmann's anti-obesity and growth hormone products 1987 Biogen NV - licensing agreement on screening tests 1987 Summa Medical Corp - licensing agreement for MAb for imaging blood clots 1988 Amgen Inc - copromotion agreement in Europe, to market Neupogen 1988 Boehringer Ingelheim Vetmedica GmbH - joint development agreement on antimicrobial substance aditoprim 1988 Chiron Corp - cross-licensing agreement on IL-2 patents 1988 Interferon Sciences, Inc - marketing agreement for alpha interferon treatment for genital warts 1989 Alpha 1 Biomedicals, Inc - licensing agreement to produce thymosin alpha-1 1989 Chiron Corp - five-year R&D agreement, for products based on ras-oncogene research 1989 Harvard Univ Medical School, Institute for Chemistry - five-year research agreement, for treatments for immunological diseases 1989 Protein Design Labs, Inc - licensing agreement for anti-Tac MAb to prevent organ rejection 1990 Chiron Corp - joint development and marketing agreement on IL-2 products 1990 Cortecs International Limited - collaborative R&D agreement for alpha-Interferon 1990 Dainippon Pharmaceutical Co Ltd - cross-licensing agreement for IL-1 alpha 1990 SangStat Medical Corp - supply agreement for pregnancy test kits 1990 Syntex Corp - joint development and marketing agreement for Toradol IM injectable analgesic 1991 Interferon Sciences, Inc - licensing agreement for injectable alpha Interferon 1991 Metpath Inc - development agreement for DNA	Nippon-Roche Research Centre (Japan) Cytolcine research group in Ghent (Bel) Roche Milano Ricerche Immunology (Italy)

Cont'd

probe assays
1992 Genentech Inc - 10-year development and marketing agreement DNase to treat cystic fibrosis and chronic bronchitis
1992 Xenova Ltd - exclusive rights to develop and market novel biochemical assay for immunosuppressant screening
1993 Celltech Group plc - four-year manufacturing agreement on humanised MAb
1993 Hybridon, Inc - R&D agreement (through Hoffman laRoche Inc) for antisense oligonucleotide compounds