



**COMPARATIVE STATISTICS FOR
THE UK, EUROPEAN AND US
BIOTECHNOLOGY SECTORS**

Analysis year 2003

February 2005



The DTI drives our ambition of 'prosperity for all' by working to create the best environment for business success in the UK. We help people and companies become more productive by promoting enterprise, innovation and creativity.

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Comparative Statistics for the UK, European and US Biotechnology Sectors – Analysis Year 2003

This report was prepared by Critical I Limited
for the Department of Trade and Industry

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Introductory note

This is the third report we have produced for the DTI under this programme. The first report covered 2001; the second report covered the 2001-2002 periods; and this report covers the 2001-2003 periods. The countries covered in each report are shown in the table below. As can be seen, the European country set has differed in each year in response to the DTI's requirements.

Countries covered in each report

		2001	2002	2003
European country set	Denmark	•	•	•
	Finland	•	•	
	France	•	•	•
	Germany	•	•	•
	Israel	•	•	
	Ireland	•	•	•
	Norway	•	•	•
	Sweden	•	•	•
	UK	•	•	•
	Switzerland			•
	USA		•	•

The extrapolations produced in the previous reports are not directly comparable with those for the 2003 European country set, given the different country sets involved.

In order to provide year-on-year comparability for the European countries in the 2003 set we:

- Ran new extrapolations for 2001 and 2002 for the 2003 European country set, in addition to a 2003 extrapolation.
- Incorporated original data for 2001 and 2002 that has become available since our last report was produced.
- Calculated changes in the key financial metrics for the UK in pounds sterling, rather than after conversion to Euros, in order to avoid the distorting effect of changes in the Euro exchange rate over the period covered. (US changes were likewise calculated in US\$ for the same reason. This was not required for the other countries outside the Euro zone, namely Denmark and Sweden, as their currencies have enjoyed virtual parity with the Euro since 2001).
- Have reported separately the 2003 metrics for Switzerland as the Swiss sector was not included in the study in the first two years.

Comparisons between the operational, as opposed to financing, metrics for the USA and the European sector are reported only for the 2002-03 period in the absence of 2001 data for the USA.

Executive Summary

The objective of this report is to provide the DTI with a robust and defensible analysis of the UK biotechnology sector's comparative standing against some of its key European competitors and the United States. The report analyses company performances in the calendar year 2003 and, on a country by country basis, compares that performance with metrics for 2002 (and 2001 where appropriate) calculated using the same methodology.

The European countries covered by this study are: United Kingdom, Denmark, France, Germany, Ireland, Norway, Sweden (for brevity, we refer to this collective set of seven as "Europe") and Switzerland.

Our study identified 1,484 companies in 2003 (1,581 including Switzerland), 1,511 in 2002, and 1,434 in 2001 in "Europe" whose primary commercial activity fell within the definition of biotechnology agreed with the DTI (the sector and sub-sectoral definitions used in this study are shown in Appendix D). This definition specifically excludes some companies that alternative definitions of biotechnology or life sciences often encompass (particularly clinical research organisations, suppliers of biological reagents for research purposes, medical device companies,

and those drug companies which use little biology). Consistent adherence to a transparent definition of the sector is key to any comparison of biotechnology data sets, either whether between nations or between different time periods for a single nation or region.

At the end of 2003 Europe's biotechnology industry:

- Employed approximately 73,600 people (82,400 including Switzerland) people (2002: 76,800; 2001: 75,000)
- Had 420 new drugs in clinical development or awaiting approval (2002:387)
- Generated €16.3 billion of revenue (2002: €16.8 billion; 2001: €16.4 billion)
- Raised €1.3 billion of equity investment in 2003 (2002: €1.9 billion;)
- Formed 100 new companies (2002: 115; 2001: 209)

As in previous years, the UK was the single biggest contributor to this picture. In 2003 the UK sector:

- Comprised 455 companies (2002: 494; 2001: 456)
- Employed approximately 22,400 people (2002: 24,400; 2001: 25,100)
- Had 224 new drugs in clinical development or awaiting approval (2002: 226) – half the European total

- Generated £3.6 billion of revenue (2002: £3.4 billion; 2001: £3.0 billion) - a 19% increase over the 2001-2003 period
- Raised £392 million of equity investment (2002: £440 million)
- Formed 36 new companies

The UK biotechnology sector in 2003 has continued the restructuring process that started in 2002. Employment in the UK sector fell 8% and R&D employment is also down. This restructuring has long been seen as inevitable following the sector's unsustainable growth in 2000 and 2001, but has proven less painful than many expected. R&D spending has been maintained overall, despite some heavy falls, particularly among younger companies. The restructuring achieved should strengthen the UK's growth potential for the future.

The European (non-UK) sector has also seen declines. German company numbers fell and employment was down, but not by as much as commentators had expected. The French biotech sector, albeit from a modest base, bucked the generally downward trend in employment as its governments' initiatives to stimulate the growth of innovative companies took hold.

Deeper preliminary analysis indicates that the UK post-restructuring has the most robust biotechnology sector in Europe and remains the most likely national sector to attract the large equity investments necessary for growth.

The United States continues to dominate the world scene and set the performance standards to which others aspire. In 2003, the US biotechnology industry:

- Comprised 1830 companies (2002: 1891)

- Employed approximately 172,400 people (2002: 168,000)
- Had over 1110 new drugs in clinical development or awaiting approval (2002:1164)
- Generated \$52 billion of revenue (2002: €42 billion)
- Raised \$9.2 billion of equity (2002:\$7.2billion), and a further \$5.4 billion of debt
- Formed 83 new companies

This report covers similar ground to those in previous years but differs somewhat in organisation. 2003 was a year of upheaval and realignment in the UK biotechnology industry. We start the **Key findings** part of the report, therefore, with a section on **Restructuring** which, in the context of movement elsewhere in Europe and in the US, charts the trends in company numbers, company formation and loss, and employee counts, and maps out some of the key events during the UK consolidation.

We then examine the **Financial health** of the UK biotechnology sector, again within a European and US context. The section covers private and public equity sources, debt provision and revenue generation. Our financial data is presented in the main in Euros. However, the strengthening value of that currency – it was 8% stronger in 2003 than in 2002 against Sterling and 20% stronger against the US Dollar - tended to devalue the performances of the UK and US. In evaluating financial performance year on year, therefore, we have made Sterling and dollar Dollar comparisons, where appropriate.

This leads into a section on **Value creation** in which we examine the relative investments by the UK sector in the UK and elsewhere and its peers in

research and development, and their success in creating products which represent the source of future revenues.

The body of the report concludes with a section on **Projecting the near future**. This, in essence, uses multiple-year data sets to determine indicators of the likely future health of the biotechnology sector. Although this part of the report which takes a forward view, is largely restricted to the UK, similar analyses could be applied elsewhere.

We have included two supplementary “chapters” in the report as well as a **Summary Data Set** for each of the nations we have studied.

The first supplementary section is on **Europe and the USA**. Here we have demonstrated the differing natures of the biotechnology effort in the two regions. Within the European universe, a group of companies established before 1975 accounts for over half of Europe’s biotechnology revenues and over a third of its employees. Such companies also exist in the USA industry but they account for only a tenth of US revenues and 9% of employees.

The second supplementary chapter is the **Country profile** section for Switzerland.

Throughout this year’s report, we have analysed our data in two distinct ways. The majority of analyses are drawn from extrapolated data totals based on a sub-sectoral and national division of the biotechnology universe. We believe that the extrapolated totals can be used with confidence, as in each case they are based on a solid foundation of real, verifiable data. For example, 84% (85% last year) of the Total employment figure for the nine countries studied is made

up of known, verifiable employee numbers, with only 16% being extrapolated. The corresponding ratios for Total revenues and Total R&D expenditure are 81% (up from 74% last year) and 69% (up from 51% last year), respectively.

For eight of the nine countries (all except Switzerland) we have metrics that can be compared directly between 2003 and 2002 at the individual company level. For companies in seven countries – the UK, France, Germany, Norway, Sweden, Denmark, and Ireland – we also have data for 2001. This, combined with the high penetration of data collection means that we can undertake dynamic analyses based on the year-to-year changes in a given metric at an individual company level, as well as static analyses based on a single year’s number. For instance, data on the proportion of companies in the UK, USA, France, and Germany that have increased their employee counts between 2002 and 2003 has been used as an early indicator of impending restructuring or likely future expansion.

Countries at a glance

USA

- IPO market opens in fourth quarter
- Revenues up to €42 billion, a 26% percent increase in dollar terms
- Employment expands but R&D employment falls

UK

- Sector achieves 6% revenue growth, but employment falls
- Company numbers down as British companies lead European biotech consolidation
- Remains Europe’s most sustainable biotech sector

- Leads product development race in Europe by a significant margin
- Public companies raise €161 million from PIPES

Denmark

- Danish biotech sector sees local currency revenue growth across all sectors
- Novo Nordisk's fortunes drive Danish biotech performance
- Denmark company creation is maintained, while attrition stays low

France

- Government initiatives boost employment and R&D spending
- Low equity investment and revenues indicate sector still fragile
- Flamel Technology raised €53 million in public offering

Germany

- Firms endure first restructuring wave as 30% of companies downsize
- Revenues fall back 8% while firms slash R&D budgets by 19%
- Venture financing holds up as investors back portfolio leaders

Ireland

- Elan raises €544 million in equity and debt for restructuring

Norway

- Revenues jump 45% to €118 million, employment rises by 5%

Sweden

- Consolidation pushes industry revenues and R&D budgets down
- BioVitrum signs €414 million diabetes deal with Amgen
- MediVir links marquee anti-HIV development deals with pharma majors

Switzerland

- Swiss biotech companies maintain strong product development effort
- Actelion signs €216 million co-development deal with Merck & Co
- Relatively moderate growth at Serono means it still lags its top tier US peers

Key Findings

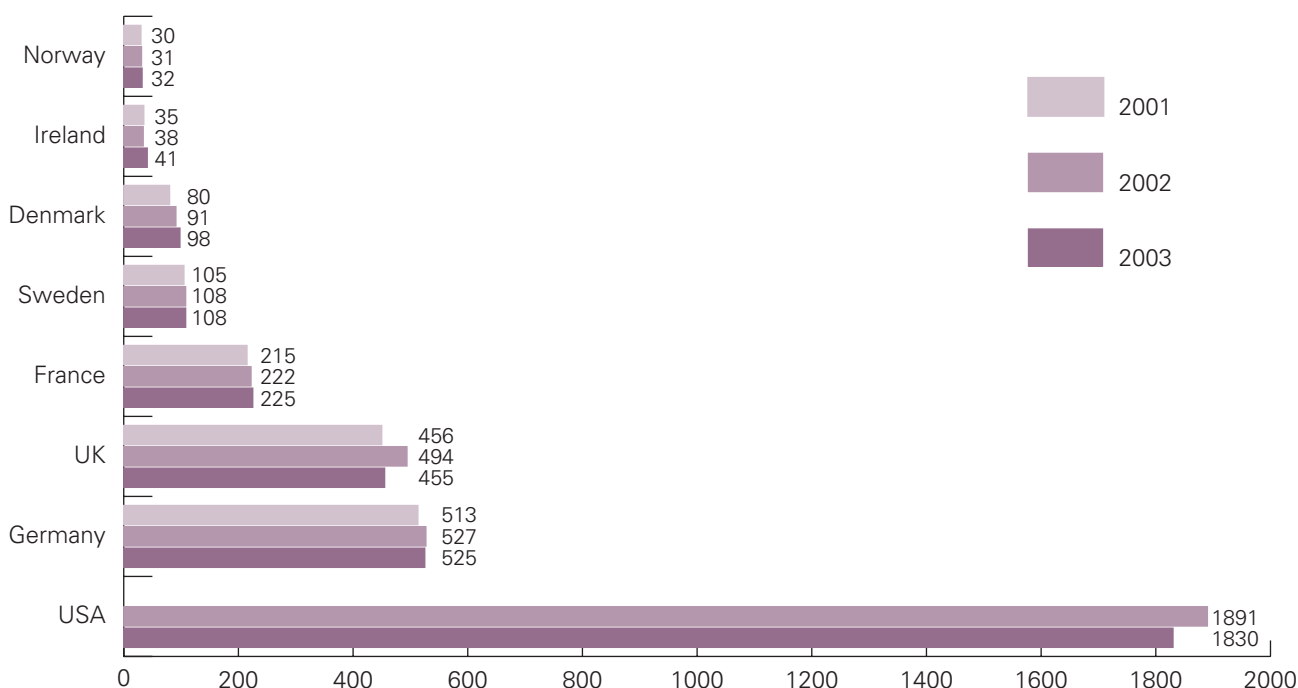
Restructuring the industry

Lack of financial support from the investment community for certain types of biotechnology company in 2002 triggered a wave of restructuring across the countries studied which continued throughout 2003. Many company management teams were forced to reorganise their companies to meet the demands of the industry's various stakeholders in the so-called post-industrial age of biotech drug discovery. The preliminary completion of the human genome map, and the efforts to

industrialise various processes involved in drug target discovery such as informatics, proteomics and functional genomics, and the ability of the major players to capture and build value, forced companies to rethink what is needed to build sustainably profitable businesses.

This reassessment resulted in companies engaging in both short term remedial activities as well as taking action that would have longer term implications. For many companies the need to conserve cash and cut spending resulted in some very heavy pruning of

Total number of companies by country in 2001 - 2003



staff numbers and non-core business operations. Others refocused their business models, while others engaged in mergers and acquisitions to build stronger foundations. Those that were unsuccessful in raising finance and/or revenues or failed to take adequate defensive action simply went out of business.

Number of companies by country: 2001-2003

Total # of companies	2003	2002	2001	2001-2003 % change
USA	1830	1891	na	
Europe:				
Germany	525	527	513	2
UK	455	494	456	0
France	225	222	215	5
Sweden	108	108	105	3
Denmark	98	91	80	23
Ireland	41	38	35	17
Norway	32	31	30	7
Europe total:	1484	1511	1434	3

Bloodletting continues apace

With the investment community showing few signs that it would once again favour the life biotechnology sciences sector, company managements were forced to pare back cash burn rates. The result was that approximately one in four biotech companies in the major markets of the US, UK, Germany and France laid off significant numbers of staff, while others also either dropped cash draining discovery programmes or switched focus completely.

Across all the countries studied, a significant proportion of companies had to lay off staff during 2003, with smaller and less mature companies faring worse. In all cases, however, more companies increased staffing levels than reduced them.

Year on year employment growth - source CIL employment survey

Country	Percentage of companies showing (2002-2003):		Percentage of employees in companies:	
	Increase in employee numbers	Decrease in employee numbers	Increasing employee numbers	Decreasing employee numbers
USA	45%	26%	59%	16%
UK	43%	24%	36%	21%
Germany	31%	30%	33%	32%
France	56%	17%	29%	21%

Across Europe, there was a 4% year-on-year decline in the numbers employed in the biotech sector between 2002-2003. While the Industrial & Environmental sector witnessed the largest proportional decline in employment, the Healthcare sector, which saw a 6% fall in total employment between 2002 and 2003, accounted for the greatest number of job losses. Companies in the Service Provider and the Technology Service Provider sectors, both very revenue-oriented, did expand their workforces in 2003. We estimate that the biotechnology industry in the European countries covered in this study employed 73,500 people in 2003, down from 76,800 in 2002.

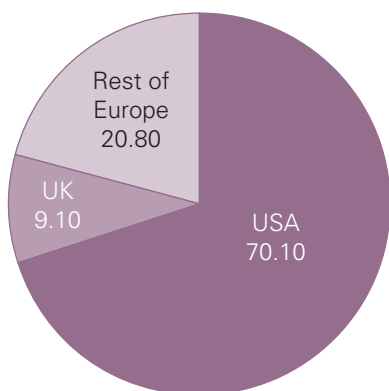
More worrying is the decline in the numbers employed in research and development in home territories. We estimate that there was a 5% decline in European R&D employment between 2002 and 2003. Again, companies in the Healthcare sector took the biggest hit with a 9% decline over the period, resulting in a 19,800 complement of European R&D employees. Service Providers and those engaged in biodiagnostics reported modest increases in R&D employment.

At the end of 2003 UK biotech companies were still the largest employer in Europe, employing 22,400

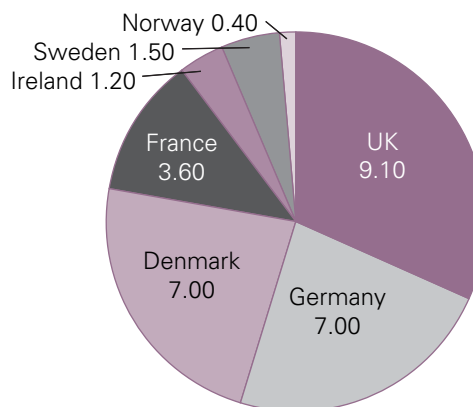
people, of whom 9,600 were engaged in research and development. They represented 30% and 34% of the European total, respectively. However, these totals represent 9% and 11% falls in UK total employment and R&D

employment respectively between 2002 and 2003. While one in four UK biotech companies had shed staff during the year, just over four in ten had increased their headcount.

Home employees: (Europe & USA) in 2003 as % of regional total



Home employees: (Europe) in 2003 as % of regional total



Number of employees by country: 2001-2003

Total home employees (rounded to nearest 100)	2003	2002	2001	2001-2003 % change
USA	172,400	168,100	na	
Europe:				
UK	22,400	22,400	25,100	-11
Denmark	17,300	16,800	15,300	13
Germany	17,300	18,600	16,200	7
France	8,900	8,500	8,300	7
Sweden	3,700	3,600	3,200	17
Ireland	2,900	3,900	5,800	-50
Norway	1,000	900	1,000	-7
Europe total:	73,600	76,800	75,000	-2

Selected European biotech industry restructuring 2003

Month	Company	Location	Staff cuts	Notes
Jan	Acambis	UK	14% to 280	Moving some R&D effort from UK to US
May	Axis-Shield	UK	10% to 400	Jobs lost in Norway as diagnostics business shifted to UK. Expects a €1.8M/year saving
Sep	Biolinvent	Sweden	19% to 105	Switching from biomanufacturing to developing antibody therapeutics
Jan	BioTie Therapies	Finland	26% to 40	Closed Vikki R&D unit, refocus on Turku
Aug	Celltech	UK	8% to 1660	Lay offs include EU 100 sales staff and downsizing of Californian manufacturing
Nov	Celltech	UK	129 jobs	Closed target discovery efforts in UK & US
Jan	GeneScan	Switzerland	43% to 52	BioChip Technologies division cut as company focuses on agrifood business
Oct	GPC Biotech	Germany	21% to 158	Reduces emphasis on technology research
Jan	IsoTis	Switzerland	31% to 107	Post-merger restructuring to contain R&D spending
Sep	IsoTis	Switzerland	29% to 60	Merged with GenSci OrthoBiologics to focus on orthobiologics
Jan	Karo Bio	Sweden	13% to 116	Focusing efforts on chemistry at expense of R&D biology.
Nov	Karo Bio	Sweden	Cut to 100	Shifting R&D from US back into Sweden
Nov	LION Bioscience	Germany	30% to 190	Cost cutting to achieve profits short-term
Jun	MediGene	Germany	30 jobs	Cut US subsidiary staff by 75% to 10
Jan	Pharmexa	Denmark	26% to 87	Cost cutting exercise to save €2.3M in 2003 and €4.6M in 2004
May	Pharmexa	Denmark	25% to 60	Curbing R&D by 20% to conserve cash
Sep	PPL Therapeutics	UK	20 jobs cut	Company put itself up for sale
Nov	PPL Therapeutics	UK	All 35 jobs cut	Additional cuts following for sale decision
Sep	PyroSequencing	Sweden	17% to 150	Hopes to save €5-6M annually following merger with Personal Chemistry
Jul	Shire Pharma	UK	6% to 1727	Return to late stage focus sees closure of Canadian lead optimisation effort.
Jan	SkyePharma	UK	11% to 420	Cost cutting looking to save €4.96 a year
Oct	Vernalis	UK	34% to 135	Wants to cut spending by €18.4M a year
Jul	Xenova	UK	38% to 66	Cut unpartnered preclinical projects to focus on late stage. €2.8M saving expected

No UK companies were immune from the need to consider restructuring whether to sustain profitability, as was the case for Acambis (which cut back on some early discovery programmes as well as shifting some R&D activity from the UK into the US) and SkyePharma (which wanted to get back into the black), or to conserve cash (as was the case with Xenova following its merger with KS Biomedix). Even the most successful UK groups were forced to lay off staff. Celltech closed down some of its target discovery activities in the UK and the US, resulting in a reduction of 262 jobs, while Shire Pharmaceuticals shed 104 jobs as it refocused on late stage development activities.

Restructuring in Europe was not restricted to the UK. Thirty per cent of German companies we analysed laid off staff in 2003, and 31% increased their headcount. The German sector witnessed an 8% decline in total employment between 2002 and 2003 to 17,200, and research employment fell by seven per cent. Major German biotech companies actively involved in this restructuring included GPC Biotech, which cut its workforce by 21% as it shifted its emphasis from technology platforms to more product oriented activities, and LION Bioscience which chopped its workforce back by 30% in a bid to meet profit targets. The scale of the retreat in German biotech employment levels is significant considering the level of employee security that exists in Germany. However, the drop also reflects the investment drought the German industry was enduring, exacerbated by the number of post-BioRegio companies chasing a finite pot of cash.

Among the major European nations, the French biotech sector appears, on the face of it, to have fared much better. More than half (56%) the French companies we analysed had increased reported a rise in staff levels, while only 17% had to cut numbers during 2003. Indeed, with the exception of the Service Provider section, France's biotech sector saw across the board increases in headcount between 2002 and 2003. Employment in the French biotech sector increased by 5% in 2003 to 8,900 people. The increase in French biotech employment reflects France's position in the life sciences growth cycle: government initiatives to stimulate the creation of new biotech companies were kicking in in both 2002 and 2003.

After a tough round of restructuring in 2002, the US biotech sector looked well on the road to recovery in 2003 with a 2% year-on-year increase in total employment levels. The US biotech sector employed 172,400 people by the end of 2003. Forty-five per cent of US biotech companies increased their headcount during 2003. However, restructuring had clearly not yet fully run its course and 26% of companies reduced their headcount during the course of the year. Much of this restructuring involved refocusing from discovery platforms towards later stage product developments (see Table *Selected US biotech industry restructuring 2003*). This had a major influence on the numbers employed in R&D which dropped by 6% in 2003 to 73,500 researchers.

Selected US biotech industry restructuring 2003

Month	Company	Location	Staff cuts	Notes
Apr	Aclara	US	32% to 65	Cuts in admin, marketing and some basic R&D to focus on commercialisation
Jan	AeroGen	US	30% to 61	Halted Aerodose insulin because unpartnered
May	Allos	US	34% to 61	Looking to cut cash burn by €20M-22M
Oct	Biopure	US	30% to 175	Seeking to save €9.5M in 2004
Oct	Cerus	US	25% to 120	Intention of ds to curbing 2003 spending by €16-20M
Aug	ChromaVision	US	30% to 70	Cuts aligned with revised sales forecasts
Apr	Corautus	US	47% to 17	Done to conserve cash for late stage projects
Jun	CuraGen	US	20% to 320	Shifting from discovery to preclinical and clinical development. Cut 25% jobs in 2002
Oct	Cygnus	US	60% to 30	Contract dispute with Sankyo forces cuts
Jan	Deltagen	US	38% to 200	Discontinued all discovery programmes
Apr	Deltagen	US	25% to 150	Third restructure since Oct 2002, closed all sites but base. Filed Chap 11 late 2003
Sep	Epimmune	US	23% to 37	Looking for savings of €1.35M per year
Jan	Geron	US	44% to 52	Focusing effort on lead GRN163 compound
Dec	HGS	US	7% to 1,100	Realignment of focus to drug development
Feb	Introgen	US	33% to 70	Cash conservation & cuts number of sites for Phase III cancer gene therapy trial
Jan	Keryx	US	48% to 19	Cutting back on early stage R&D, focus on Phase II diabetic neuropathy candidate
Jan	Lipid Sciences	US	35% to 20	Focus on viral pathogen inactivation platform
Jan	Lynx	US	25% to 90	Focusing effort on mass parallel signature sequencing genomics analysis
Jun	Millennium	US	26% to 1700	Seeking profitability, focus shift from discovery to product development
Jan	Onyx	US	25% to 71	Halted Phase III head & neck cancer gene therapy trial and attempt to conserve cash
Jun	Onyx	US	60% to 20	Cuts gene therapy activity, focuses on Phase III cancer compound
Jun	Orphan Medical	US	25% to 80	Reflects sale of Bisulfex to ESP Pharma
Jan	Texas Biotech	US	29% to 89	Early-stage R&D cut for more focus on clinic
Jan	Transgenomic	US	24% to 253	Bidding to achieve profitability in 2003
Mar	Transkaryotic	US	22% to 346	Refocuses R&D on rare genetic disorders
Jan	Trimeris	US	23% to 100	Restructuring following T-1249 delays
Jun	Vertex	US	13% to 737	Cuts early stage work to focus on partnerships
Jan	ViroPharma	US	70% to 139	Cash conservation, cutting early stage work

Failure historically by some US biotech companies to make genuine progress forced some technologies – such as gene therapy – on to the backburner. By the end of 2003, technology platforms had definitely lost their lustre and the spotlight was focusing more on product development. Investors were looking to back propositions that were most likely to provide robust returns on investment.

This realignment of business models included some of the USA's most enduring companies. Human Genome Sciences, Millennium Pharmaceuticals, CuraGen, and Vertex Pharmaceuticals all announced substantial reductions in staffing levels as they switched from early drug target discovery to much later stage biotech drug development and commercialisation. This trend of downstream movement into drug development which is also apparent in the UK, is likely to gain momentum throughout the rest of Europe in 2005 and beyond.

Merger & Acquisition and consolidation activity in 2003

Three distinctive trends drove biotech M&A activity in 2003.

First, there was evidence that fairly successful companies sought to consolidate their strengths by buying or merging with other robust businesses that added products, revenues and/or new markets. This was dominated by top tier US biotech companies. Success in developing a blockbuster product is no guarantee that the process is reproducible. Consequently, most biotech companies are always looking outside their own R&D efforts to achieve the growth rates sought by demanding investors.

The second trend saw companies that were relatively cash-rich but with weak technology and/or product pipelines being bought by cash strapped but technology- and product-rich businesses.

The third group of transactions were much more defensive, involving weaker companies combining with others in the hope that they would build stronger potentially sustainable businesses.

UK biotech sector consolidates

Britain's biotech sector witnessed some major upheavals in 2003. The number of UK biotech companies satisfying the agreed definition of biotechnology used for this study declined by 9% on the previous year from 494 companies to 455. Across all the geographies covered in this survey, this change represents the largest fall both in percentage and absolute terms. The table below shows the relative impact that M&A activity had on the change in company numbers in the 2002-2003 period. As can be seen, M&A activity in the UK significantly outpaced that occurring elsewhere in Europe.

While on the face of it this may suggest that the UK biotech sector is in trouble, there is plenty of evidence to the contrary.

During 2003, the UK was the focus of some very high profile mergers and acquisitions. The acquisition of PowderJect Pharmaceuticals' profitable vaccines business by Chiron, a US top tier biotech – the non-vaccines activities were later spun out in 2004 – was the marquee deal for the UK sector. Chiron saw the PowderJect acquisition as an opportunity to boost its own substantial vaccines activity.

Company count reconciliation 2002-2003

Country	# of companies 2002	Companies founded 2003	Companies removed through cessation of trading, receivership or dormancy	Companies removed through M&A	# of companies 2003
USA	1891	83	100	44	1830
UK	494	36	60	15	455
Denmark	91	10	2	1	98
France	222	11	5	3	225
Germany	527	31	28	5	525
Ireland	38	4	1	0	41
Norway	31	4	3	0	32
Sweden	108	7	5	2	108

Oxford GlycoSciences, a proteomics platform business with a promising biotech drug Zavesca for Gaucher's disease, was the biggest casualty in an all UK transaction. Celltech, at the time the undisputed bellwether of the UK biotech industry, beat off competition from Cambridge Antibody Technology to acquire OGS. Celltech used OGS's own cash pile to pay for its acquisition. By acquiring OGS, Celltech scooped a range of oncology targets that it considered to be novel and partially validated, picked up a product (Zavesca) with only €50-60 million in potential peak sales, but for which OGS or its owner would gain significant royalties, as well as a second generation compound in Phase I trials with a better side effect profile. Celltech was also able to enhance its oncology expertise. The acquisition did, however, result in 129 researchers being laid off by the year end.

Cash, a public listing, and critical mass were the main lures for RiboTargets' reversal into British Biotech and it was the promise of a marketed triptan migraine drug (Frova) that prompted the newly merged company to then acquire Vernalis. Through the three-way merger,

the backers of the three companies believed that they would be creating a potentially more sustainable company than if they tried to go it alone. There were similar defensive mergers taking place in the UK involving the consolidation of intellectual property with cash. From the reaction of the investment community – who in some cases had prompted the consolidation – such transactions were considered to be value creating and so worth backing. Investors backed the mergers in the expectation that the resulting combine would provide a greater opportunity for returns on investment.

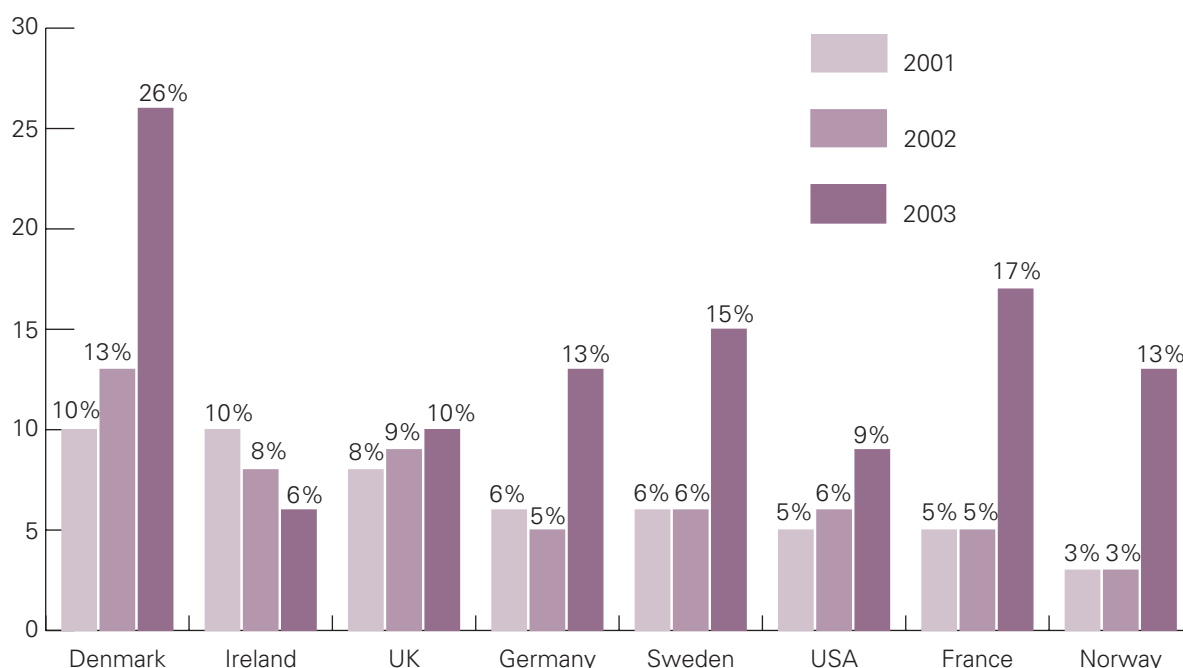
British M&A activity accounted for 15 companies disappearing from the country count in 2003. Not all companies were able to restructure or refinance themselves out of trouble, and went out of business. Notable casualties included PPL Therapeutics, forever associated with Dolly the Sheep, which failed to attract additional finance and could not save itself despite swingeing job cuts during the year, and Weston Medical, a drug delivery technology company that ran into development problems. Failure to raise finance forced others, including many recent start-ups,

into dormancy with the founders hoping that they might be able to revitalise the IP portfolio either in the same companies, in new companies, or through being acquired by others. During 2003, 75 UK companies were removed from the UK company counts as a result of losing their discrete identity through being absorbed in to another business operation through merger or acquisition, going out of business, or by becoming dormant. It should be pointed out that some of these dormant groups may re-awake in subsequent years if they can attract financial support.

Despite this drop off in biotech business activity, the UK was still the most active in Europe for creating new companies. We have identified 36 new biotech companies founded in the UK during 2003. Not surprisingly, the Healthcare group, with 20 of the foundlings, was the largest, accompanied by 11 new

companies planning to provide services – such as bioprocessing, biomanufacturing and custom research activities – and only four offering technology platforms. The UK also spawned with six companies planning to develop and sell healthcare diagnostics. No new companies emerged in the Agricultural & Marine Biotechnology sector whilst the Industrial & Environmental sector saw only one new company formed in 2003. With access to finance still tight, despite the availability of seed finance, the rate of new company formation in the UK declined in the three years from 2001. This is not an isolated UK experience, however, as similar patterns were observed in the other major markets.

New company formation 2002 - 2003 by country as a % of total number of companies



European M&A still to take off

M&A activity among the Europeans was much more muted than in the UK. There were no major deals involving French companies, and Zentaris, which was acquired by Canada's Aeterna Laboratories, was the only major German M&A transaction. This lack of M&A activity can be explained by the relative lack of immaturity of both the French and German sectors which are populated by companies that have yet to develop the musculature to be predators or enough mass to be attractive prey. Both sectors did conclude some important all private transactions as companies such as France's Hybrigenics and Germany's BioFrontera sought to extend their technology coverage.

During 2003, France lost only three small companies through acquisition, while Germany lost five small companies through M&A. France reported only 5 companies going bankrupt or dormant in 2003 and added 11 new companies to its tally. Unusually for the countries in this survey, less than half (5) of the new companies were focused on Healthcare applications, while one was a new biopesticides business.

Germany lost a further 28 companies either through bankruptcy or dormancy. The total German company count decreased by only two to 525 in 2003, following the creation of 31 companies. Fourteen of these new firms focus on Healthcare, 11 are Service Providers – including four biomanufacturing businesses and two bioprocessing businesses. Germany also saw the creation of a new bioremediation company, and three functional genomics and one high throughput screening

business, activities around which fewer companies now tend to be formed than in the past.

Scandinavian and Swiss companies, which are more likely to have spun out from pharmaceutical companies or to have been founded by teams with senior pharmaceutical industry experience, were much more active with sizable M&A deals. Switzerland's Actelion, regarded as one of the European biotech bellwethers, strengthened its pipeline when it acquired fellow Swiss firm Axovan in a cash plus milestone deal. Similarly, Switzerland's Straumann acquired Sweden's Biora AB to enhance its biomaterials activity, as did Isotis when it acquired GenSci, a US company. Novartis, the Swiss pharma major, acquired 51% of the US biotech company, Idenix Pharmaceuticals.

Sweden's Pyrosequencing AB made two major acquisitions in 2003 in its bid to become a profitable company in fiscal 2004. The first was the merger of the DNA sequencing company with fellow Swede and chemistry play, Personal Chemistry, in an all share deal valued at €20.9M. The second was the €27.8M cash acquisition of Biotage, a subsidiary of Dyax Corp which provided Pyrosequencing with a third product line and an enlarged sales force. Denmark's Lundbeck acquired the US biotech company Synaptic Pharmaceutical for €97.3M.

Selected Biotech M&A activities during 2003 (Confirmed value transactions >€20m)

Acquirer	Location	Target	Location	Value €M
Idec Pharmaceuticals	US	Biogen Inc	US	5082
Johnson & Johnson	US	Scios Inc	US	2137
Chiron Corp	US	PowderJect Pharmaceuticals	UK	697
Genzyme General	US	SangStat Medical	US	464
Gilead Sciences	US	Triangle Pharmaceuticals	US	368
Invitrogen	US	Molecular Probes	US	258
Versicor Inc	US	BioSearch Italia	Italy	207
Novartis AG ¹	Switzerland	Idenix Pharmaceuticals	US	202
Cell Therapeutics	US	Novuspharma	Italy	187
Allergan Inc	US	Oculex Pharmaceuticals	US	186
Celltech	UK	Oxford GlycoSciences	UK	143
ICN Pharmaceuticals	US	Ribapharm Inc	US	103
Lundbeck A/S	Denmark	Synaptic Pharmnaceutical	US	97
Actelion AG	Switzerland	Axovan	Switzerland	94
Serologicals Corp	US	Chemicon International	US	75
Johnson & Johnson	US	3-D Pharmaceuticals	US	70
British Biotech	UK	Vernalis	UK	68
Johnson & Johnson	US	OraPharma	US	67
Dendreon Corp	US	Corvas International	US	64
BioReliance	US	Q-One Biotech	UK	60
Caliper Technologies	US	Zymark Corp	US	58
Variagenics	US	Hyseq Pharmaceuticals	US	45
Straumann Holding	Switzerland	Biora AB	Sweden	44
GeneLogic	US	TherImmune Research	US	41
Aeterna Laboratories	Canada	Zentaris AG	Germany	41
British Biotech	UK	RiboTargets	UK	37
Celgene Corp	US	Anthrogenesis Corp	US	36
Isotis	Switzerland	GenSci	US	35
Angiotech Pharma	Canada	Cohesion Technologies	US	33
GenVec	US	Diacrin	US	32
Protein Design Labs	US	Eos Biotechnology	US	30
PyroSequencing	Sweden	Biotage	US	28
OSI Pharmaceuticals	US	Cell Pathways	US	25
Genta	US	Salus Therapeutics	US	24
Incyte Genomics	US	Maxia Pharmaceuticals	US	22
PyroSequencing	Sweden	Personal Chemistry	Sweden	21

¹ Novartis acquired 51% stake in Idenix

² Martek acquired biomanufacturing facilities from FermPro Manufacturing

³ Regenecor purchased PPL's US-based xenograft, stem cell and polyclonal antibody research division

US shies away from mass consolidation

US biotech engaged in sustained M&A activity through 2003 and this was topped off at the end of the year with the announcement that General Electric intended to acquire Britain's Amersham in an all stock deal valued at €7.4 billion. The deal merged GE's Medical Systems division with Amersham to create GE Healthcare, which focuses on the development of molecular imaging and personalized medicine. Although both companies fall outside this study's definition of biotechnology, the deal was regarded as perhaps the most significant that year in the wider life sciences arena. But apart from a few headline grabbing deals, much of the M&A activity that took place in the US was still fairly modest.

Pharmaceutical majors – including the European cohort – continued to have a small but selective appetite for biotech companies. Johnson & Johnson was the most active, acquiring Scios Inc, 3-Dimensional Pharmaceuticals and OraPharma for a total €2.28 billion in 2003. However, the most common relationship between pharma and biotech companies remains discrete biopartnering deals, rather than acquisition.

At the tail end of 2003, there were a number of big pharma announcements of deals that were not completed until 2004. These included Pfizer reaffirming its commitment to the cardiovascular area by announcing its intended acquisition of Esperion Therapeutics and adding some potentially important follow-on products to its acute cardiovascular disease treatment, Lipitor. Similarly, Eli Lilly's announced plan to build its own antibody capabilities by

acquiring Applied Molecular Evolution for approximately €320M included a pre-clinical pipeline of next generation products that include second generation Remicade and second generation Rituxan.

The biotech:biotech event of the year was Idec Pharmaceuticals' €5.1 billion all-share merger with Biogen, the second largest biotech/biotech deal ever after Amgen's 2002 €9.5 billion acquisition of Immunex. Through the merger, Idec and Biogen hope to emerge as the partner of choice for the biotech industry and are seeking to differentiate the business from conventional pharmacos by being more accessible, speedier in its partnering activities, and more attuned to biotech companies' needs than pharmacos. Both companies had blockbuster products reaching the end of their patented shelf lives but with poor internal scientific productivity, had no potentially big selling replacements moving through the pipelines. With a combined war chest of €1.2 billion, the merged company started scouting the biotech industry – particularly in Europe – for new product opportunities.

US biotech companies also demonstrated an appetite for going across the Atlantic to make European acquisitions. The biggest deal was Chiron's acquisition of PowderJect Pharmaceuticals, but other notable transactions were the raids on Italian biotech companies. Versicor completed its acquisition of the Italian anti-infectives business BioSearch Italia, while Cell Therapeutics bought the Italian oncology company Novuspharma. By acquiring SangStat Medical, Genzyme hoped to enhance its product portfolio and existing pipeline of products in development for immune-

mediated diseases. Similarly, Gilead boosted its anti-virals efforts by acquiring Triangle Pharmaceuticals. Most M&A transactions that were completed in the US in 2003 were, however, much more modest than these.

Beyond the 44 companies that disappeared through M&A activity during 2003, the US also saw an additional 100 companies cease trading or go bankrupt. While there were no obvious trends relating to either age or activity, high profile casualties included the biomaterials companies, Advanced Tissue Sciences, a company that actually had an approved product, BioTransplant, and Organogenesis. Nevertheless, entrepreneurial activity is still strong in the USA with 83 new companies – mostly in drug discovery – being created in 2003.

Financial health

In our previous report we presented an analysis that demonstrated that the comparative performance of the European and US biotechnology sectors was closely linked to their relative availability to raise equity finance. The ability to access appropriate levels of finance is of fundamental importance to the sector’s well-being. In this section we first review the availability of finance in the nine countries surveyed and then analyse their revenue generation performance in 2003.

Please note that Switzerland has, unless otherwise stated, been omitted from the European trend data presented as the Swiss sector was only added to the European country set in 2003. 2002 funding and performance data for Switzerland is therefore not included in the dataset upon which the following analyses are based.

Biotechnology fundraising in 2003 – the big picture

Biotech companies continued to struggle, relative to the peak period of 2000 to 2001, to raise capital in 2003. Across the nine countries surveyed in this report, companies raised €8.6 billion of equity and €7.0 billion of debt finance. This represented a year-on-year decrease, in Euro terms, of 1% in the level of equity and a 44% increase in debt funding compared to 2002.

Equity funding

The total equity raised in 2003 was split as follows:

Equity type	Amount (€billion)
PIPEs	1.6
Venture capital	2.8
Other private equity	0.4
Public equity	3.8
TOTAL	8.6

The year started slowly with PIPEs – private investment in public equity – being the most common financing vehicle. PIPEs usually involve a public company selling about 10-20% of its shares to one or more institutional investors at a discount price to the prevailing share price. The money raised is usually earmarked for a specific value-creating purpose such as an acquisition or a clinical trial. In 2003 US companies accounted for 87% of the total €1.6 billion raised in PIPEs.

The public equity markets did not open in the US until Acusphere floated on NASDAQ in October 2003. A further six US companies were able to float by the year end, although in all but two cases, Pharmion and Myogen, the companies were trading at below their IPO price as the year closed. Nevertheless, by the year

end a further 14 US companies had filed with the regulators to float. The NASDAQ Biotech Index and the BioCentury 100 Index both rose 45% percent over the year, outperforming the general US market indices by a factor of two.

By the third quarter, with positive news flow from some of the (US) industry's bellwethers, companies were able to conduct secondary and other follow-on offerings. However, once again, the US dominated the scene, accounting for 88% of the total. This reflects a major difference in investor attitudes on either side of the Atlantic. US investors have historically been prepared to give company management teams a longer leash, and hence more cash. European investors have tended to provide cash for specific projects at specific times.

The global biotech sector's value surge in 2003 was in part driven by newsflow from the US sector. In particular, the investor community reacted positively, in part due to the strong financial performances of the top tier biotech companies such as Amgen and Genzyme, and in part due to the approval of US FDA, and partly in response to the approval by the US Food & Drug Administration of a number of innovative biotech drugs.

Share prices of Europe's public biotech companies rose on the back of the US biotech industry, reflecting increasing investor confidence in the sector. However, the increases in Europe were more selective than the broad gains seen in the US, with the UK biotech sector faring much better than continental European biotech stocks. Sixteen European biotech companies (8 British and 8 continental) saw their market capitalisations more than double during the course of 2003.

Despite the IPO window opening in the US, the European market for IPOs was for all intents and purposes still firmly shut. In Europe, the closest to a biotech IPO was that of Sinclair Pharma, a UK-based niche pharmaceutical company pursuing a No Research Development Only (NRDO) business model and developing and commercialising patented products for oral health, oncology support and dermatology. , Sinclair raised €12.6M in new capital in a December 2003 AIM flotation.

In the meantime, across the nine countries surveyed €2.5 billion of venture capital was invested in Healthcare companies, €161 million in Technology Service providers, €57 million in Service Provider companies and the balance in Industrial & Environmental and Agriculture & Marine biotechnology companies. US companies attracted 77% of the total sum invested. Their share represented a 0.8% increase, in dollar terms, over the sum raised in 2002.

Debt funding

At the start of the second quarter, investors once more began to provide mature companies with access to convertible debt. Thus, during 2003 companies raised approximately €6.95 billion, again with the US taking the lion's share at 86%.

The UK and European funding picture

European equity financing

In 2003, the UK and its continental peers (excluding Switzerland) raised a total of €1.33 billion, split as follows:

Equity:	UK		Rest of Europe (exc Switzerland)
	£m	€m	€m
PIPEs	108	153	38
Venture capital	174	247	361
Other private equity	36	64	51
Public equity	64	91	293
Total equity:	382	555	743

The UK sector raised more equity in 2003 than any other European country, albeit that this was in sterling terms, 11% less than in 2002.

The sum raised via follow-on offerings (by companies such as Antisoma and Alizyme were involved) was 16% down on that raised in 2002. UK companies, however, raised three times more in 2003 through PIPE transactions than they had in 2002.

Venture capital support for the UK biotech sector remained relatively robust, with the sector raising more than any other European biotech sector. The €247 million raised was, however, 20% below that raised in 2002 – a fall pretty much in line with that across Europe as a whole. This sum was invested in 34 companies, all but two of whom were Healthcare-focused. Eighteen per cent of this sum was raised by companies under two years old, and 75% by those between three and five years old.

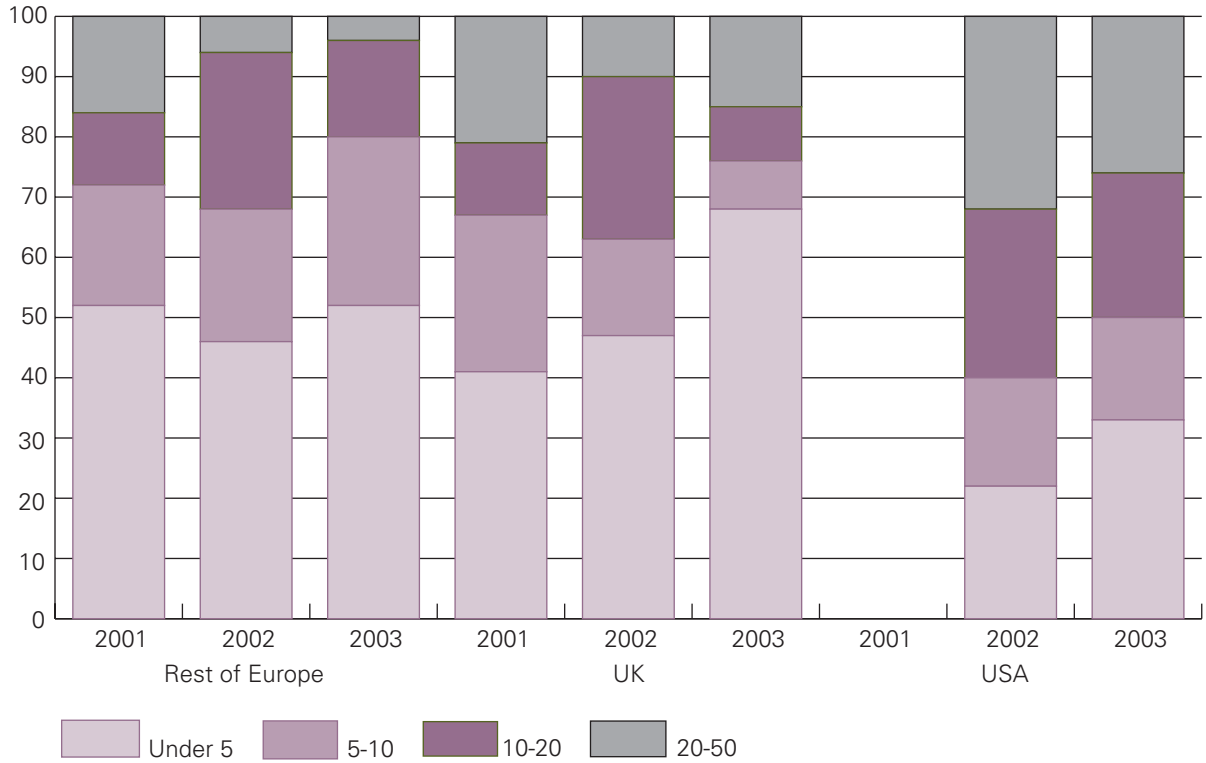
In 2002, by comparison, €335 million of venture capital was raised by 38 UK companies. A quarter of the companies were in the Service Provider and Technology Service Provider categories. Since 2000, a decreasing proportion of British venture finance has been put to work in platform technology companies. Half the money was being put to work in companies between three and five years old, and just under a third in companies less than two years old.

With 38% of the total, the UK biotech sector retained pole position in the European biotech venture fundraising league table. Germany’s biotech sector was still attracting significant sums – it actually saw a 10% increase on 2002, raising €179 million in 2003 – as venture capitalists sought to back winners around which they could coalesce and combine potentially less successful businesses with a view to creating more sustainable companies.

As the chart top right indicates, across Europe a similar picture was emerging: that of venture capitalists making fewer, but larger investments.

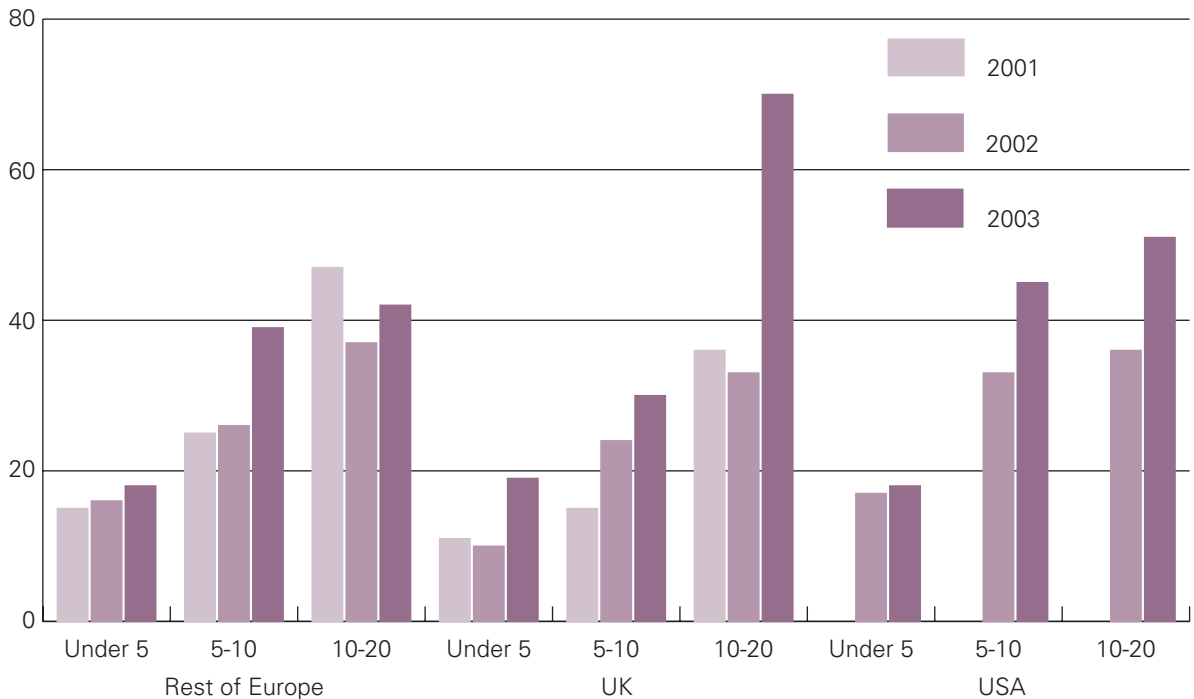
The next chart shows the benchmarks for receiving investment over the 2001-2003 period. Venture capitalists shifted their focus towards more developed companies, regardless of the size of tranche of investment concerned. For example, a company wishing to attract between €5-10 million of venture capital in 2003 would, on average, had to have 20-25% more employees than a company attracting the same amount of money in 2001. This theme is developed further later in this report (see **Projecting the near future** later in this report).

EU but not UK investors shy away from large tranches



UK and US investors were still willing in 2003 to invest large sums of money in individual companies (top part of bar). However such investments into companies in continental Europe have dwindled.

Number of employees as point of investment by region 2001 - 2003



The graph shows that in 2003 to attract any of three sizes of tranche - under €5 millions, €5-10million and €10-20m - companies must on average employ more people than they would have done to attract the same investment in 2001 or 2002. Interestingly, investors in UK companies are more willing to invest in small companies than those investing elsewhere.

Before leaving the subject of equity financing, it is worth noting that, although no UK companies floated during 2003, UK quoted biotech companies accounted for the three largest European share price increases and six of the leading ten value gains that year. This was a reflection of both the relative maturity of the UK sector over its continental peers and the UK's focus on therapeutic products rather than technology platforms. Germany's publicly quoted biotech companies averaged a 90% plus gain in market capitalisation, during 2003. This surge in valuations was first and foremost a market correction following the collapse of the Neuer Markt in 2002 when biotech stocks fell 97% on average.

European debt financing

During 2003, the amount of debt raised by European companies rose dramatically to €980 million. This was largely due to Ireland's Elan and the Swiss companies, Serono and Actelion. Elan, which pulled itself back from the brink of bankruptcy in 2003, raised substantial sums through a follow-on offering (€189 million) and a debt financing (€382 million). Serono and Actelion, with promising pipelines, together raised €465m through debt vehicles.

Partnering deals

Partnering deals are a further source of finance for biotechnology companies that, in some respects, straddle the divide between investment and revenue generation: many such deals involve a combination of equity investment and payments that, in effect, are in the form of revenue.

Outside the Healthcare sector the opportunity to strike such deals is relatively limited. Within it, however, the pharmaceutical majors, concerned about the impact their own innovation deficits will have on their future prospects, have maintained an appetite for late stage and marketed biotech products. Not surprisingly, US biotech companies have remained the most popular acquisition targets, reflecting once again the relative maturity of the US industry. On the biopartnering front, the US pharmaceutical major Bristol-Myers Squibb, clearly not put off by its experience with Imclone and Erbitux, struck three of the ten most valuable partnering deals in 2003. Biotech dealmaker of the year was undoubtedly Regeneron Pharmaceuticals with two deals worth potentially more than €683 million. Four European biotech companies – shown in bold text in the left-hand column of the table below - concluded top 10 deals in 2003.

The ten highest valued biopartnering deals in 2003

Biotechnology company	Pharma/Biotech Partner	Details of the transaction	Value €M
Millennium Pharmaceuticals	Johnson & Johnson	JNJ's Ortho Biotech Products acquired non-US global marketing rights to Velcade	425
Biovitrum	Amgen	Amgen acquired exclusive rights to develop and commercialize Biovitrum's small molecule enzyme inhibitors for treatment of metabolic diseases, included is BVT3498, which is in Phase II trials for type II diabetes	414
Regeneron Pharmaceuticals	Aventis SA	Partnership to develop & commercialise Regeneron's VEGF TRAP which is in Phase I trials to treat solid tumours and NHL	405
Regeneron Pharmaceuticals	Novartis AG	Partnership to develop Regeneron's IL-1 TRAP which is Phase II trials for rheumatoid arthritis	278
Actelion AG	Merck & Co	Co-develop and promote globally Actelion's oral rennin inhibitors to treat heart failure, renal failure and hypertension	216
Idenix Pharmaceuticals	Novartis AG	Novartis licensed two hepatitis B virus treatment candidates & has option to co-develop Phase I/II hepatitis compound	199
Corgentech	Bristol-Myers Squibb	Deal to co-develop and co-promote Corgentech's E2F Decoy currently in Phase III for prevention of vein graft failure	199
Medivir AB	Boehringer Ingelheim	Medivir has out-licensed to Boehringer, a Phase II inhibitor of reverse transcriptase as an HIV therapy	158
Lexicon Genetics	Bristol-Myers Squibb	Drug discovery, development and commercialization in neuroscience	152
Flamel Technologies	Bristol-Myers Squibb	Licensing and commercialization agreement to develop and market Basulin®, a controlled release insulin, developed as a daily injection.	131

While these deals, and the sums usually associated with them, make big headlines and can have a major impact on the companies involved, it is clear that they have little impact on the overall financial health of the biotech industry. Although their headline value may be very large, receipt of significant

revenues in the form of royalties may be many years hence and, of course, be heavily contingent upon the achievement of interim milestones. In short, for most companies, collaborative research revenues are rarely a substitute for equity as a solution to their financing requirements.

Revenue generation

UK & European revenues

Revenue by country: 2001-2003 in €[local currency]millions

Comparative revenue growth 2001-2003				
Revenues (€m)	2003	2002	2001	2001 -2003 % change
USA	41663 [52472]	39690 [41647]	na	
Europe:				
UK	5041 [3558]	5219 [3400]	4884 [2989]	3 [19]
Germany	3054	3311	2946	4
Denmark	4698	4459	4296	9
France	1944	1911	1634	19
Ireland	982	1305	2156	-54
Sweden	501	563	345	45
Norway	118	81	140	-16

Based on our analysis, European companies covered in this survey generated total revenues of €16.3 billion (€18.5 billion including Switzerland) in 2003. Taking European exchange rate movements into account the European sector's sales remained static over the 2001-2003 period, although this is largely attributable to the decline of Ireland's Elan.

The UK biotech sector's share of European total revenues remained close to 30% throughout the 2001-2003 period - a significant achievement when one considers that Sterling's value against the Euro fell by 13% during this time.

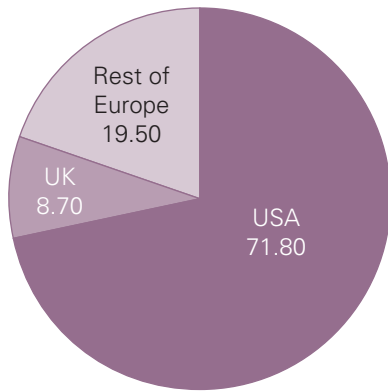
Despite the fall in employment referred to earlier in this report, UK Agricultural & Marine Biotechnology revenues (adjusted to reflect the fall in the £: exchange rate) increased by 2.5% to €543m (£383m) in the two years to 2003. Over the same period European sector revenues fell by 3% to just over €930 million. Revenue gains in the Animal Health and Food Technology sub-

sectors offset the €30+ million fall in European Crop Agriculture revenues. The European Agricultural & Marine Biotechnology sector shows some marked differences in revenues generated per employee. Thanks to the contribution of its Crop Agriculture and Horticulture majors, the €331k average revenue per UK employee in 2003 is significantly ahead of the European average of €264k per annum. Norway lies second, thanks to a strong contribution from Intervet Norbio, the animal health subsidiary of Akzo Nobel group. The corresponding figure for the USA was €210k, peaking at €300k per employee in the Crop Agriculture and Horticulture sub-sector.

2003 revenues in the UK Industrial & Environmental sector were £114.2m (€131m), compared to £99m (€162m) in 2001, a 15% increase over the period. This compares with an average fall of 19% across the European sector as a whole. UK revenues per employee increased from £100k to £121k (€171k) during this time. The corresponding European average in 2003 was €140k. Healthcare companies generated revenues of €12.4 billion in 2003 - three quarters of total European biotech revenues that year. UK companies accounted for €3.5 billion of this sum. Although European Healthcare revenues (excluding Switzerland) fell 3% in Euro terms between 2002 and 2003, the real sales movement was a drop of only 0.5% when the Sterling and Danish Kronur exchange rates are factored in.

Elsewhere, there were few surprises in the year-on-year performances of the other European sectors. Service Provider revenues increased 5% between 2001 and 2003 to €2.3 billion, of which €800 million was generated by UK companies in 2003. European Technology Service

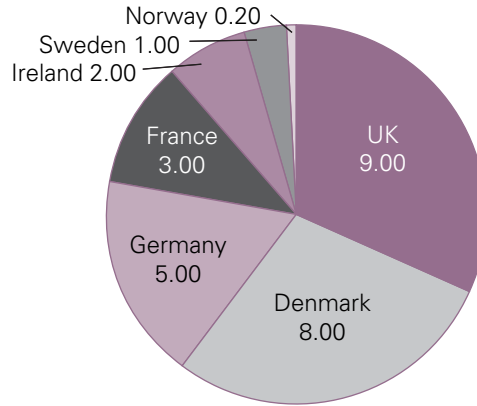
Regional revenues as % of 2003 total revenues



Provider revenues remained static over the period which may be regarded as quite an achievement given the significant cutbacks in spending that many of its customers were making during this period.

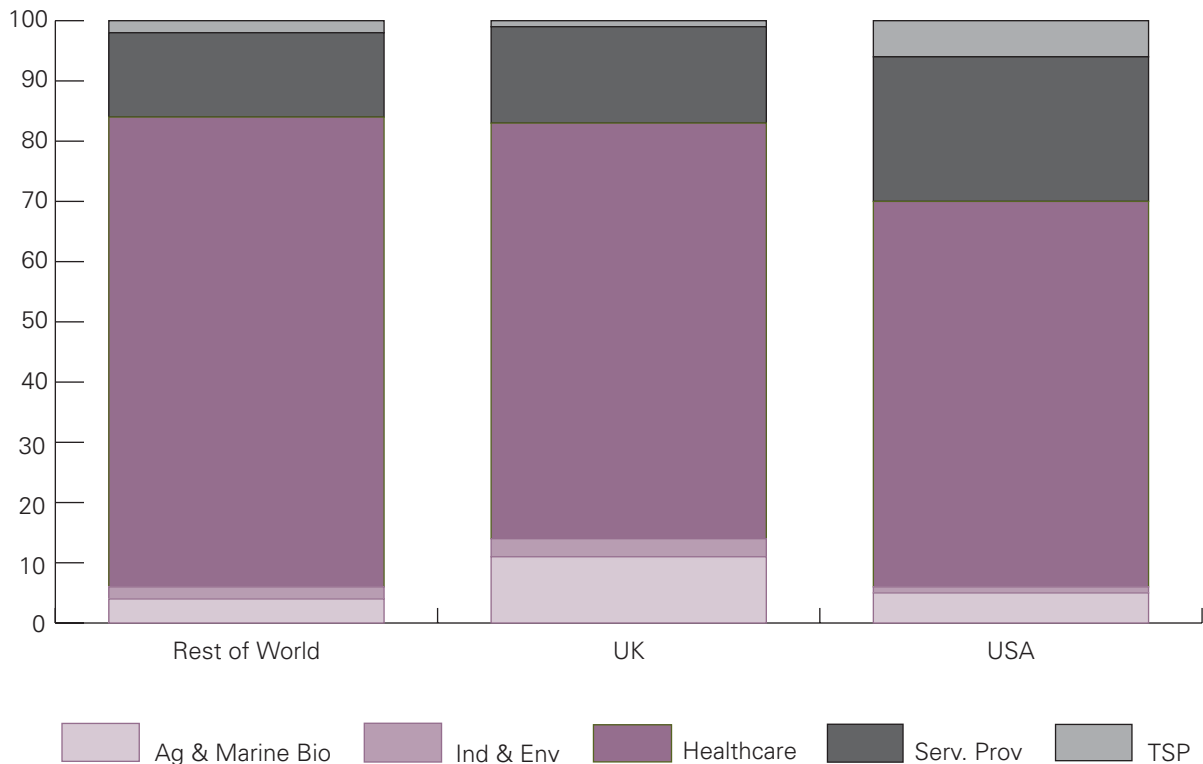
The chart above shows the contribution made to regional revenues by each sector in 2003. The most notable features are

National revenues as % of 2003 European total



the modest contribution made to UK revenues by Technology Service Providers compared to the domestic contribution made by their continental and US peers and the comparatively strong contribution made by the UK's Agricultural & Marine Biotechnology companies. The lack of any meaningful revenue contribution by US and European Industrial & Environmental companies

Revenues by sector as % of total revenues by region (2003)



may reflect the fact that most activity in industrial biotechnology takes place in companies which are primarily chemicals, food processing or environmental services companies that do not meet the definition of a biotechnology company used in this report.

Swiss revenue profile in 2003

Not surprisingly, Serono and Healthcare companies with substantial sales such as Actelion and Berna BioProducts dominated the Swiss performance. In 2003, we estimate that the Swiss biotech industry generated €2.16 billion of revenue, with the Healthcare companies contributing €1.90 billion (88%) of that total. This includes a sizable contribution from companies under five years old, reflecting the rapid maturation that is a feature of many Swiss start-ups, given their pharmaceutical industry origins.

US revenue profile in 2003

With its more mature and unarguably more successful biotech industry it is not surprising that the US sector reported a revenues advance between 2002 and 2003. Even with the US dollar weakening against the Euro, the US biotech industry was able to deliver 5% year-on-year growth between 2002 and 2003 in Euro terms. In local currency terms, however, the US sector increased revenues by 26% to nearly €42 billion.

Interestingly, while Healthcare sales account for the majority of the revenues, the split of revenues across among the US biotech industry is much more evenly spread than in Europe, as shown in the Figure above.

Agricultural and Marine biotechnology sales -, and crop biotech sales in

particular -, were up in dollar terms by 16% at €1.8 billion. Companies in the Technology Service Provider sector also fared much better than their European counterparts. This group reported a local currency adjusted sales improvement of some 35% at €2.2 billion, driven primarily by the uptake in bioinformatics services in their sizable domestic market. Similarly, US companies in the Service Provider sector saw a 50% plus boost (26% in Euro terms 2002-2003) in revenues. This was primarily driven by the outsourcing of activities such as contract research and customised biological raw materials which grew 74% and 61%, respectively, and to a lesser extent biomanufacturing outsourcing which advanced in dollar terms by 7 percent.

The greatest contribution to the growth in US biotech revenues came from the Healthcare sector and those commercialising biotech drugs, in particular. Drug discovery and development companies saw turnover increase by 19% during 2003 to €27.6 billion (\$34.7 billion). While more than 80% of these revenues are associated with companies founded before 1988, other age groups were still reporting substantial performances. Compared with their European counterparts, US drug discovery companies are quickly ramping up biotech drug revenues. The three to five year age band reported 2003 revenues of €670 million, while the six to ten year old group and the 11 to 15 year old group reported revenues of €1.8 billion and €1.9 billion, respectively.

With the current rates of successful biotech drug approval (see table overleaf), the US biotech industry, and its drug discovery and development sector in particular, is clearly expected to remain the primary driver of global biotech revenues for some time to come.

Selected FDA biotech drug approvals in 2003

Company	Drug	Approval body	Indication
Actelion/Celltech	Zavesca	FDA	Type 1 Gaucher disease
Biogen-Idec	Amevive	FDA	Moderate-to-severe chronic plaque psoriasis in adults
Cubist Pharma	Cubicin	FDA	Complicated skin and skin structure infections caused by Gram-positive bacteria, including MRSA and MSSA
Genentech/Novartis/ Tanox	Xolair	FDA	Asthma in adults and adolescents. The first humanized therapeutic antibody for the treatment of asthma
Genzyme/BioMarin	Aldurazyme	FDA and EMEA	Mucopolysaccharidosis
Genzyme	Fabrazyme	FDA	Enzyme replacement therapy for Fabry disease, a rare and potentially fatal inherited disorder
Gilead	Emtriva	FDA and EMEA	Once-daily nucleoside reverse transcriptase inhibitor for treatment of HIV infection in adults in combination with other antiretroviral medications..
GSK/Bayer	Levitra	FDA and EMEA	Oral PDE-5 inhibitor, for the treatment of erectile dysfunction
GSK/Corixa	Bexxar	FDA	CD20 positive, follicular, non-Hodgkin's lymphoma
Medimmune/Wyeth	Flumist	FDA	The first influenza vaccine delivered as a nasal mist available in the US for healthy people
Millennium	Velcade	FDA	New treatment for multiple myeloma, a cancer of the bone marrow
Roche/Trimeris	Fuzeon	FDA, EMEA and Swissmedic	For use in combination with other antiretroviral (anti-HIV) medicinal products for treatment of HIV-1 infection
Serono	Serostim	FDA	HIV patients with wasting or cachexia to increase lean body mass and body weight, and improve physical endurance
SkyePharma/ Sanofi-Synthelabo	Uroxatral	FDA	Relief of urinary symptoms associated with benign prostatic hypertrophy, a common condition affecting middle-aged males

Value Creation

While revenue and employment statistics can be regarded as indicators of the current status of a company or of an entire sector, the research and development (R&D) effort and the development of products to which that effort is directed provide a better guide to future prospects. Partly developed products and intellectual property by themselves do not generate revenues through sales, but they are the currency with which biotechnology companies, particularly those in the Healthcare sector, trade. Younger companies' revenue streams, in particular, tend to be slight but it is R&D that is the mechanism through which future value is built from their initial pool of intellectual property and technological advantages. The intermediate goal of research-oriented companies is, therefore, to secure a substantial portfolio of intellectual property and know-how.

Critical I has analysed the R&D effort in the biotechnology sector in two main ways. First, we have used our extrapolation approach to calculate figures for R&D spending and the number of R&D Employees across all companies in our survey. The extrapolation method generates multipliers from original data, on a country by country basis, in essence, to fill gaps in each country data set. Additionally, we use only the original data to ensure that the conclusions that we draw are not a function of the extrapolation process itself. As noted in the Executive Summary, the original data represents a high proportion of the totals generated by the extrapolation process.

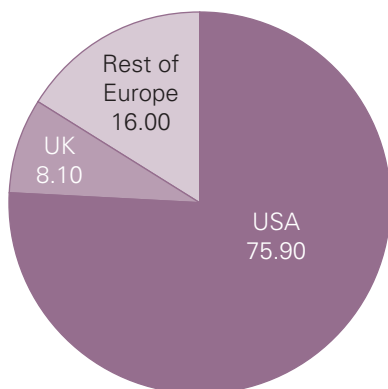
After a 15% rise in R&D spending between 2001 and 2002, the UK biotechnology sector's 2003 R&D spend was €1.76 billion (£1.24 billion), down 12% on 2002 and 1.8% above its 2001 level, after adjusting for the downward drift of Sterling against the Euro.

Half of that reduction stemmed from the Healthcare sector which, with a total spend of €1.53 billion (£1.08 billion), represented the most significant contribution to R&D spending. Although Healthcare R&D spending had fallen 10% during 2003, it nonetheless represented a 17% increase over its 2001 level (£926 million).

R&D spending trends by country: 2001-2003 €[local currency] millions

R&D Spend (€m)	2003	2002	2001	2001 -2003 % change
USA	16386 [20637]	18312 [19215]		
Europe:				
UK	1758 [1241]	2158 [1406]	1991 [1218]	-12 [2]
Denmark	943	933	861	10
Germany	1284	1577	1281	0
France	608	551	525	16
Sweden	314	355	289	8
Ireland	277	411	516	-46
Norway	34	63	78	-56
Europe total:	5217	6048	5541	-6

Regional R&D spend as % of 2003 total R&D spend

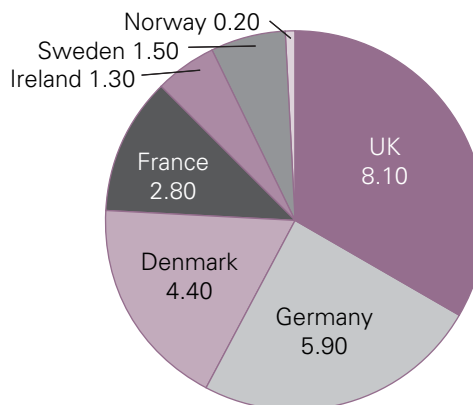


Over the 2002-2003 period however, 1,100 R&D net jobs were lost in the UK biotechnology sector, a fall of 10% to 9,600. Over 1,400 R&D jobs were lost in the Healthcare sector, with small gains in the Service (+300) and Technology Service Provider groups (+200) blunting those losses somewhat.

Our study indicates that 97 R&D posts were lost in the UK Agricultural & Marine Biotechnology sector during the 02-03 period – a 44% fall over the 2001-02 period. The majority of the losses fell at the UK Crop Agriculture majors. Although R&D spending fell by 26% over the period, UK R&D spending per R&D employee increased from £154k (€252k) to £233k (€331k). The corresponding European figures were €185k and €145k respectively.

Across Europe R&D employment fell between 2001 and 2003 by 15% to just over 800 posts, while the 2003 R&D spend of €120m was 30% below its 2001 level. All countries suffered in roughly equal measure, with the exception of Denmark that started from a very small Agricultural & Marine Biotechnology base anyway.

National R&D spend as % of 2003 European total R&D spend



Nearly half of the fall in Healthcare R&D spending arose as a result of the virtual demise of three relatively mature, or at least relatively old companies: British Biotech merged with RiboTargets (later to become Vernalis); Oxford Glycosciences was absorbed into the Celltech Group; and PPL failed to find significant new investors. The three companies spent around €120 million in R&D between them in 2002. Virtually all of that R&D effort fell by the way in the rationalisations. The 10-15 year old age group of which they had been members lost over 650 R&D staff in 2003. The R&D efforts at RiboTargets and Celltech did not increase significantly as a result of mergers, although some of the intellectual property base of those companies has been recycled. OGS's Gaucher's disease treatment received approval at the US FDA in 2003 and its proteomics business, for instance, re-emerged as a service business, Oxford Genome Sciences, after a management buy-out at the beginning of 2004. Some of British Biotech's facilities had been taken over in 2001 by US company, OSI Pharmaceuticals. OSI consolidated its UK operations in Oxford in 2002, but in 2003 drastically reduced the headcount, leaving just the staff supervising clinical research.

The disappearance of these familiar companies was the consequence of their failure to translate significant fundamental and clinical research programmes into tangible value in the form of advanced products. This is concerning, but perhaps to be expected. Drug development is still a stochastic process and company failure can be anticipated among companies which are dependent to a large part on the success of a few product candidates.

We compared directly the original data for 2002 and 2003, at the individual company level. Overall, and using a Sterling base, the UK R&D biotechnology spend was up 3% in 2003 compared to 2002, and among Healthcare companies it was up 4%. However, among companies outside Healthcare, R&D spend dropped 12%. The fall among younger companies was the most severe: across all sectors, R&D spending by 0-2 year old companies fell 8% and by 18% among the youngest Healthcare companies.

Average R&D spend by age band – source: employee data for 1650 companies

Age (years)	Average R&D spend in 2002 (€m)	Average R&D spend in 2003 (€m)	% change
0-2	4.5	4.1	-7%
3-5	8.1	7.4	-8%
6-10	17.6	14.8	-16%
11-15	26.6	19.8	-26%
Over 15	39.2	40.9	4%

Part of the explanation for the declines in R&D spending and employment among companies less than two years old lay in the shift of venture capital away from start-up companies to less-risky, more mature firms. In lean times, venture capitalists “feed their older children”, re-investing in existing portfolio companies. Consequently, fewer new companies were formed in the UK in 2002 and 2003 and those that were created tended to be poorly funded. Thus the number of 0-2 year old companies in the UK shrank in 2003 (10% from 138 to 126), and so did its research effort.

The UK bioscience sector, however, was not alone in having had to trim its R&D sails. The R&D spend across Europe in all biotechnology sectors fell by €850 million in 2003, with Germany experiencing a €300 million fall. (UK R&D spending in 2003 remained 37% higher than that of Germany, a ratio similar to that in 2001 after taking exchange rate differentials in to account). France bucked the trend, however, with a €50 million rise, albeit from a low base. Across Europe, over 1,500 R&D employees were shed but most were in the UK (1,100) and Germany (550).

The impact of venture funding starvation had a profound but uneven impact on biotechnology company R&D spending across Europe. Comparing individual company R&D spending year on year, among UK companies spending was up 3% in Sterling. Scandinavian companies maintained their R&D spending at roughly 2002 levels, and French companies increased spending by around 9% on average. (It should be said, however, that French R&D spending per company is still well below the European average.)

Most striking, however, was the 14% average fall in R&D spending among German companies, a clear sign that financial strictures there were biting hard in 2003. The number of German R&D employees dropped by 7% over all sectors in all age groups and by a third in the 0-2 year old group, largely due to the reduction in the size of that group (188 companies in 2002 but only 125 in 2003).

In the USA, overall R&D employment slipped 4,000 between 2002 and 2003 to 73,000, although the reduction in the US Healthcare sector was less than 1%. The overall US R&D spend rose 7% in dollar terms, from \$19.2 billion (€18.3 billion) to \$20.6 billion (€16.4 billion). It is clear that there was a shift in the pattern of R&D spending within the US biotechnology sector between 2002 and 2003. In 2002, companies 5 years old and under accounted for 21% of the overall spending. In 2003, the comparative figure was 15%. In the big-spending US Healthcare sector, these younger companies accounted for 18% of R&D spending in 2002: in 2003, the figure was 13%. Concomitantly, companies over 15 years old spent around one third of the US R&D budget, both in the biotechnology sector overall and in Healthcare: in 2003 the figures were 41% overall and 43% in Healthcare. Most of the shift was due to the reduced number of companies in the younger age-band (482 in 2002 but 355 in 2003) combined with an increase in R&D spending among older companies. An analysis of original R&D spending data for US companies in 2002 and 2003 indicates that the average R&D spend increased 9% between the two years.

Average R&D spend by region – source: original company data

Region	Average R&D spend in 2002 (€m)	Average R&D spend in 2003 (€m)	% change
UK	8.6 [£5.6m]	8.3 [£5.87m]	-3% [+4%]
USA	30.0 [\$31.4m]	27.3 [\$34.4m]	-9% [+9%]
Rest of Europe	11.7	10.71	-8%

In summary, after an 8% increase between 2001 and 2002, European R&D spending fell back in 2003 to 86% of that in 2002, and to 94% of its 2001 level. Much of the decline was due to the demise of companies that were previously higher spenders. Within individual companies, the picture was mixed. Although spending across Europe was maintained at least at 2001 levels in the 3-5 and 6-10 year old companies and amongst those over 15 years old, the investment in R&D among early stage companies (0-2 years old) and in 10-15 year-old companies declined since 2001 by 20% and 50%, respectively.

The number of R&D personnel employed in European biotechnology also fell – by 5% across the board in 2003 compared to 2002. There were large falls of 32% and 16% respectively amongst the youngest companies and those in the 10-15 year age group.

Investment and R&D spending

There is a circular relationship between investment capital and R&D spending, especially among younger companies who, particularly in Healthcare, usually cannot fund R&D from revenues. In essence, our data suggests both that companies who attract investment undertake increasing amounts of R&D and that companies that undertake more R&D attract investment.

Our analyses of three years of data from companies in Europe and two years of data from the US clearly shows that the value in building IP assets is recognised by both external investors and potential large company collaborators. In the UK and in the rest of Europe, 81% of the equity capital in 2003 went to companies who showed an increase in their R&D spending over the previous year. In the US, the proportion is lower (53%) but this is because huge amounts of equity capital go into mature companies to support commercial development. However, among US companies under 5 years old, who tend to still be heavily focused on developing their intellectual property, 85% of equity investment went to companies that increase their research effort year on year. For companies under two years old the figure was 93%.

At the same time, 60% of reported European R&D spending in companies under 10 years old occurred in the 25% of companies that received equity backing in 2001, 2002 or 2003. The situation is even more marked in the USA where 68% of R&D spending reported in 2003 occurred in companies that had raised equity in 2002 or 2003. Using football as an analogy, the biotechnology sector has its own Premier League, with a large band of envious wannabes looking on from down below.

The implication is clear. Unless more European companies can attract large-scale equity funding, they will find it very hard to increase R&D expenditure substantially, as Governments intend.

Products

The development of revenue-generating products is the ultimate goal of R&D in biotechnology. Products are an asset that can be readily valued on the basis of potential sales volume. In addition, the perceived ability of companies to successfully take therapeutic moieties through the development process is a key criterion in triggering equity investments. In the European Healthcare sector less than one third of biotechnology equity capital in 2003 went to companies without therapeutic products in development. Increasingly, venture capitalists will only invest in a young Healthcare company if they are convinced that it has the ability to get its products successfully from lab bench to market by using an astute combination of internal and external resources.

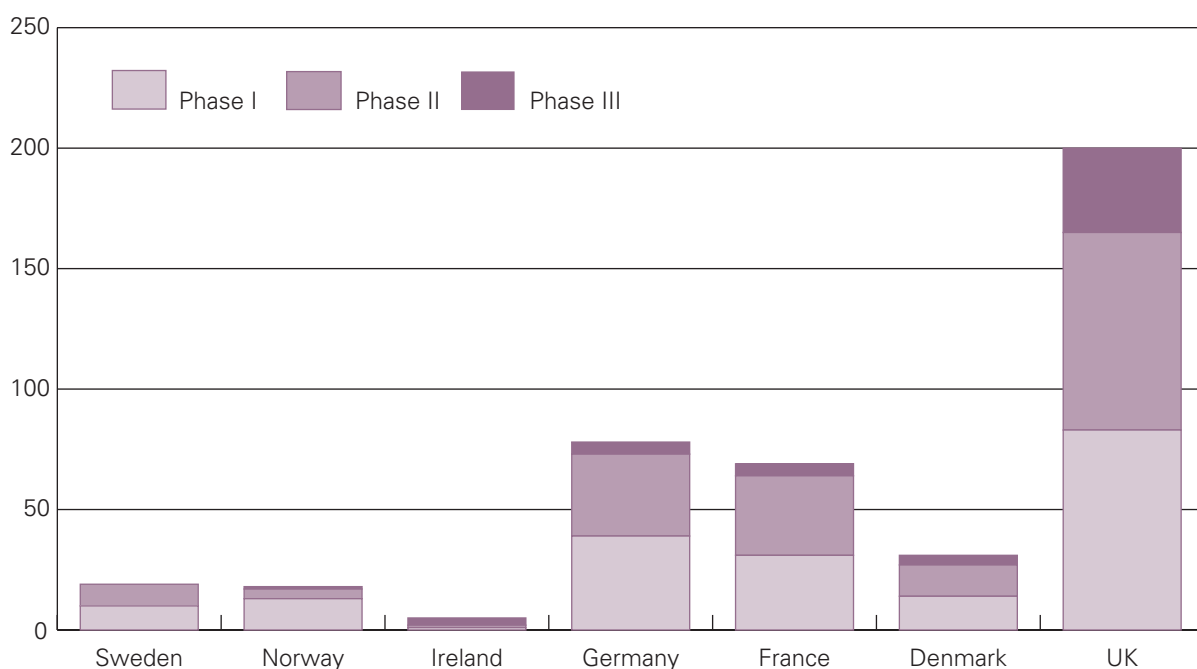
We have restricted our analysis of product development to therapeutic products in the Healthcare sector. Based on our knowledge of other product-generating activity in biotechnology, we estimate that the nations researched for this report represent about 80% of the European biotechnology product stream. Companies such as Zeltia in Spain, Newron in Italy, Innogenetics in Belgium and Octoplus in the Netherlands do have fairly late-stage products. However, other companies in those nations – and in Austria and Finland – are generally at a relatively early stage in product development.

We classify products according to the clinical indication they are designed to treat and track the progress of individual compounds from lab bench to market. However, we have not made any attempt to assign a value to any of the compounds in development. Nor have we attempted to ascertain how much of

the value of a given product a company has retained and how much has been traded to, for instance, large company marketing partners. Thus, a drug that might eventually reach sales volumes of €1 billion per year is assigned the same numerical value (1) as a compound on which a company expects to get an 8% royalty on sales of €50 million a year. As a crude guide to the revenues that

biotechnology companies can hope for, typical European (ex-UK) companies under 15 years old with products on the market show revenues of just under €80 million per product approved. UK companies generate around €50 million per compound. Revenues at similar US companies are around €100 million per product.

Europe: Healthcare products in Phase I to III clinical trials (2003) by country



The UK is still the dominant player in European therapeutic product development (see Figure above). In 2003, UK Healthcare sector companies had 132 approved compounds on the market, ten more than in 2002. This is half of the 263 marketed compounds developed by European biotechnology companies covered in this study. At the end of 2003, UK companies also had a further 24 products, 80% of the European total, awaiting approval.

Looking further back in the drug development process, the UK accounted for 60% of the compounds among European companies surveyed in clinical phase III, 50% of those in clinical phase II, and around 45% of those in clinical phase I.

Clinical development is an uncertain process and there is a risk, of course, that compounds in development will never make it to the market. To reflect this and to assess the relative future value of the compounds in the UK Healthcare sector's pipeline, we have assigned a discount value to products in various stages of development based on standard pharmaceutical industry failure rates. Thus an approved drug is worth 1; compounds awaiting approval are "worth" 90% of an approved drug; compound in phase III trials are worth 60%; Phase II, 30% and phase I, 10%. Compounds in preclinical development or earlier are discounted entirely.

The UK is also well-placed within the European context when it comes to the future value of its pipeline. At the end of 2003, the UK Healthcare sector had 200 compounds in clinical development, 35 of which were in phase III. Switzerland, with 12 compounds in phase III and 29 others in the clinic was the UK's nearest rival. Germany and France had 60-70 products each in phase I or phase II trials but only 5 each in phase III. Again using the products index, the UK's clinical pipeline is "worth" 54 approved drugs, the German pipeline 17, the French 16 and the Swiss sixteen.

The European and UK drug development effort is, of course, dwarfed by US achievements. US biotechnology companies at the end of 2003 boasted 740 products on the market compared with the UK and European totals of 132 and 261 respectively. The US index for products in clinical development (phases I, II and III) was 287 "approved product equivalents". On the basis of simply counting compounds on the market or in development, the UK appears to be holding its own against the US sector relative to the size of its biotechnology industry. The US Healthcare sector has five times as many companies than the UK (940 versus 185) and employs nearly eight times as many people (120,000 versus 15,500), and has generated five to six times as many products to date.

On this basis, the UK Healthcare sector at the end of 2003 had an index value of 208 "products" developed or in development, accounting for 53% of the total in the European companies surveyed. Germany had 20% of the surveyed total, France 8% and Switzerland 10%.

Projecting the near future?

Is the UK biotechnology sector sustainable?

In this and our two earlier reports, we have analysed the comparative standing of the biotechnology sector in the UK, the USA and leading continental European nations. In this section, in contrast, we will look somewhat into the future, using the body of validated and consistent data gathered year on year as a tool in assessing the prospects for a given nation's biotechnology sector.

We must emphasise that what is presented here is only a preliminary analysis, and illustrates but two of the sorts of insight that can be derived from this dataset. Nevertheless, we believe that what follows demonstrates the utility of the approach. Furthermore, we consider that it may provide a means of focusing policy thinking on the problems that are most germane to the future health of the biotechnology sector and of directing attention to some of the answers.

The background

The UK biotechnology sector did not thrive in 2003 relative to its performance in 2002 or, in some respects, to the performance of its European peers. The number of people employed in the industry fell, as did the number of R&D employees and revenues generated. With a few exceptions, the downward trend applied across all industry sectors and ages of company as firms endeavoured to maintain profitability, cut losses or channel resources towards product development. Some commentators, Critical I included, believe that the restructuring (a) was necessary and (b) has created a more

robust, if smaller, UK biotechnology sector. Furthermore, we believe that many companies elsewhere in Europe in 2003 still had not faced up to the need to distil their biotechnology endeavour into a form that was more sustainable and supportable.

To explore this further, we have focused on two questions:

- Did the restructuring of UK biotechnology in 2002/2003 create a sector that is more robust and sustainable than that of its European peers?; and
- Can the UK biotechnology sector expect to attract significant future investment?

Is the UK biotechnology sector more robust than its competitors?

In order to analyse the sustainability of the UK sector relative to its European peers, we sought to establish what proportion of Europe's top performing companies are based in the UK. For this purpose we identified those European companies under 15 years old who had increased their headcount during 2002 and 2003 (almost half the total), and whom might therefore be regarded as "growing". (We excluded companies over 15 years old as they have already shown themselves to be sustainable – at least for 15 years.)

We focused our analysis on the top quartile of the set of growing European companies because they accounted for two-thirds of the headcount increase: all of the 100 companies had taken on at least 10 extra staff between 2002 and 2003. For present purposes we refer to this sub-set as "fast growth" companies.

UK companies accounted for 28% of Europe's "growing company" group and a third of the fast-growth group. Germany accounted for 33% and 34% respectively of these groups. A further 21% and 16% respectively were French. Significantly perhaps, while UK and German companies had added an average of 27 employees per company, their French counterparts added an average of only seventeen.

Thus, the UK and its major European competitors each had a significant cohort of growing companies, despite a downturn in European biotechnology employment overall during the 2002-2003 period. The key question, however, is whether their growth is sustainable moving forward.

To address that question, we made a simple assumption: that companies could only sustain headcount growth in the future if they were funded by either revenues or investment capital, or both. We identified, therefore, what proportion of Europe's growth companies had either (i) received equity funding of €5 million or more in either 2002 or 2003, but not 2001, or (ii) had generated €5 million in revenue in 2003. The €5 million figure is not entirely arbitrary: it represents around 25 person-years of biotechnology Healthcare employment.

In 2003 only 30% of European growth companies had had access to either significant equity or significant revenue or both.

Twenty-nine per cent of UK growth companies had access to significant recent equity while 43% could call upon either equity or revenues to support their continued growth.

As seen earlier in the **Financial Health** section, our data indicate that revenues are likely to have to play a larger role in supporting continental European growth companies than is the case for their UK peers, given the comparative difficulty of raising significant equity finance on the continent.

For this reason, German growth companies appear unlikely to be able to support much further growth on the back of equity investments. Only 9% of German growth companies raised over €5 million equity in 2002 or 2003. However, revenue earnings increase the total of "sustainable" German growth companies to twenty-six per cent.

France fared little better than Germany on the equity front. Although over 20% of French growth companies received some equity backing in 2002 or 2003, the amounts were generally small. Only 9% of companies, as in Germany, received over €5 million. French companies are not as able as their German counterparts to call on revenues to sustain their growth: only 13% of French growth companies appeared in 2003 to be sustainable based on our access to equity or revenues criteria. France bucked the general European downturn in employment, adding 5% to its headcount in 2003. However, unless its companies can rapidly generate significant revenues or garner greater investor support, the continuing expansion of France's growth companies is under threat.

Only 19% of Scandinavian growth companies – those in Sweden, Denmark and Norway - raised €5 million or more in equity, although one quarter of them could draw upon €5 million or more of either equity or revenues.

In summary, 42% of European companies that might expect to sustain their growth on the back of significant equity or revenues were based in the UK. Germany accounted for 25%, Scandinavia for 19%, and France for only ten per cent.

This high-level analysis indicates that the growth that has occurred in the UK sector is probably more sustainable than that elsewhere in Europe. However, sustained growth in the UK will remain largely dependent on a continuing supply of external equity capital. Access to capital though, is likely to be an even more important determinant of growth in continental Europe.

Comparison with companies in the USA is instructive. Just over half of the US companies for whom we have data increased their headcount in 2003. Forty-three per cent of these growth companies appeared to be sustainable based on having received equity financing of €5 million or more in 2002 or 2003. This figure is boosted to 55% when one includes companies that earned €5 million in revenues during this period.

In 2003, 49% of the US fast-growth company group appeared to be sustainable thanks to the raising of equity capital. This increased to 69% when revenue generation is also taken in to account.

The UK does not match the US sector on these criteria. It is also true that the UK sector has lost more companies than elsewhere in Europe and, in many of those that remain, employment has been cut or R&D activities curtailed. However, UK biotechnology at the end of 2003 had more companies in a healthy financial state and able to support renewed growth through recent

equity funding or revenue generation than any other country in Europe.

Can the UK biotechnology sector attract future investment?

The second forward-looking question we addressed concerns the interplay between the biotechnology sector and the parallel universe that is the investment community. Although the previous analysis suggests that the UK sector is indeed more robust than those of its European neighbours, it is not entirely clear that the way that the UK sector is developing will enable it to attract future external investment. We address this question here.

Investment decisions in biotechnology are based on a complex interplay of factors that include the quality of science, the experience of the management team, the size of the markets that a company plans to address, its strategy for accessing those markets, the profile of the current investors in the company, and the age and size of the fund from which the investment is being made. The personal chemistries between investors and the management group may also be an important consideration. Despite the diverse range of factors that feed in to any given investment decision, we can discern patterns and trends in venture investment from our data. In the earlier section on the biotechnology sector's financial health, for instance, we described how biotechnology companies in 2003 needed more employees, on average, to attract a given size of investment than they did in 2002 or 2001.

The growth of the UK biotechnology sector, like that of the USA, is relatively highly dependent on equity investment. In looking to the future health of biotechnology, therefore, it is important

to gauge the readiness of UK companies for that investment. In particular, it is particularly important for companies to be able to raise finance between €10-30 million, a range that allows them to continue to tread the value-generating road to product development.

So, how many UK companies are ready for investments of €10 million or over? To answer that question we have to ask another: what does a company that can raise €10 million look like? There are a number of pertinent parameters.

First, in order to raise over €10 million, a company will usually have already received one or more tranches of seed capital or follow-on investment. That is certainly the case in the UK and Europe; in the USA, it is more common for a company to raise over €10 million the first time around. Secondly, the company will probably also have gained a reasonable number of employees in its first few years. The mean number of employees in companies that actually raised €10-20 million in 2002 or 2003 was approximately forty (see Figure: *Number of Employees at point of investment*). Thirdly, the company will very probably be in the Healthcare sector: in 2003, 90% of companies that raised €10 million or over were in Healthcare. It will also very probably have a product in clinical development (if only in a phase I trial). The simple query to our database of biotechnology companies, therefore, was "In which countries do we find companies that:"

- Are in Healthcare; AND
- Have at least one phase I clinical product; AND
- Have previously received venture capital (in 2001, 2002, or 2003); AND
- Have over 20 employees (we used half the mean of the historical data cited above)?

Note that we did not apply any age-linked criterion to the selection.

Nearly three-quarters of the companies that met these requirements were in the USA. Of the European set, 43% were in the UK, 25% in Scandinavia, and 14% each in France and Germany. Thus it appears, on this analysis, that the UK sector – although well behind the USA – has more companies than its European peers that might potentially attract relatively large sums of equity finance.

The results of this simple analysis are in alignment with reality. Of the companies that raised €10-30 million in 2003, 77% were from the USA. Of the European set, 52% were from the UK, 19% from Scandinavia 19% from Germany and 7% from France. Of the European companies in the group:

- 85% were in Healthcare;
- 75% of the Healthcare companies had at least one phase I clinical product;
- 90% of all companies had previously received venture capital; and
- Nearly 80% had more than 20 employees (60% had more than 40 employees).

The age of the companies was not completely irrelevant to their ability to raise finance, but nor was it a good guide. Sixty percent of the European companies who raised €10-30 million were founded between 1997 and 2000. But European companies founded in the mid-1980s and in 2002 also raised money in the €10-30 million range in 2003. In the USA, the range was wider still: from 2003 foundlings to grizzled companies that predate the solving of the triplet code of RNA.

Appendix A – Europe and the USA

The USA is the largest biotechnology power in the world. The best that European national pretenders can hope for is a distant second place. However, as a collective group, Europe has the potential – in science, financial muscle, and on a commercial footing – to challenge the USA. With moves afoot within European Union to create a centrally funded European Research Area, and the prospects of harmonised financial regulations leading to a more coherent investment climate, the obstacles to a more internationally-minded European biotechnology endeavour seem to be diminishing.

This section compares the status at the end of 2003 of the biotechnology communities on the two sides of the Atlantic. Since we will not make year-on-year comparisons here, “Europe” in this part of the report includes Switzerland, a country for which we only collected data in earnest for 2003. Most, if not all of the comparisons made here would, in essence if not in numerical detail, apply also to a Europe without Switzerland.

At the end of 2003, the US was home to 1830 biotechnology companies compared to 1581 companies in the seven European states which have been surveyed. In both cases, the numbers are little different from those in the

previous year. Europe created marginally more new companies in 2003 (106) than the US did (83) and lost fewer to merger and acquisition, bankruptcy and cessation of trading - 130 compared with 144.

The headline figures, therefore, seem to indicate that both the US and European biotechnology seemed to have reached a similar state of stability (or stagnancy, depending on your viewpoint). However, a deeper analysis shows not only that the two sectors are still very different from each other but also that they are diverging rather than converging. By virtually no parameter could it be said that the European biotechnology sector is catching the US one. And in many cases, the US is so far ahead that pursuit is technically impossible because the pursuers have lost sight of the quarry.

In our previous report, we suggested that European companies seemed to lag their US counterparts by 3-5 years (the “one age band behind” phenomenon) in the rate at which they are able to grow and gather resources. Collecting all sectors of the industry together, the typical European company of 0-2 years old:

- Employs 15 people, 11 of them in R&D
- Spends €1.7 million a year on R&D
- Has revenues of €1.73 million

In contrast, its US counterpart:

- Employs 22 people, 12 of them in R&D
- Spends €2.1 million a year on R&D
- Has revenues of €0.97 million.

Some of the difference between the two geographical blocs may be due to differences in the sectors in which these early companies are operating. In both regions, the agriculturally and environmentally oriented firms represent around 5% of the total. In the USA, though, around 68% of 0-2 year old companies are in Healthcare and 27% are providing services of some kind (Service Providers and Technology Service Providers). Among this youngest group of companies, Europe has a lower proportion (around 57%) of Healthcare companies and more (38%) service companies. Furthermore, in Europe a higher proportion of the Healthcare companies are in diagnostics rather than therapeutics development. Healthcare companies, and therapeutics companies in particular, are likely to spend more on R&D and generate lower revenues than early service-based businesses.

Nevertheless, the differences in resource-building between the USA and Europe continue to be apparent among the 3-5 year year-old firms, even though among this age band the proportions of businesses in the Healthcare, or Agriculture & Marine, and Industrial & Environmental or Service Provider sectors are now almost identical (56%-7%-37%, respectively, in the USA and 54%-9%-37% in Europe). The mean 3-5 year-old European firm:

- Employs 22 people, 14 of them in R&D
- Spends €1.9 million a year on R&D
- Has revenues of €1.61 million.

Apart from revenue generation, this profile is very similar to that of a 0-2 year old company. In the meantime, of course, the “average” US firm from the 3-5 year vintage has moved on and now:

- Employs 33 people, 19 of them in R&D
- Spends €3.4 million a year on R&D
- Has revenues of €2.66 million

The gap between the groups of US companies and European ones increases as the companies age. The average 6-10 year old US company employs twice as many people, nearly twice as many (1.9x) in R&D, and spends over twice as much on R&D as a European company of the same age. US companies between 11 and 15 years also have twice as many people employed as their European counterparts, but they are much more heavily committed to continuing research and development: they have three times as many R&D employees and are spending nearly five times as much on R&D. Much of that R&D spending is devoted to clinical trials of advanced compounds.

As we indicated in our report in 2004 and in the publication, *The Equity Gap*, we continue to believe that the significantly greater availability of risk capital (and debt provision) in the USA is a major influence on the way in which the growth of its biotechnology sector can be accelerated. In essence, the greater availability of risk capital in the USA means that companies there can get off the revenue-generating treadmill and focus to a much greater extent on the business of creating significant long-term value.

It is not that equity capital is unavailable to European companies: it is just that it is handed out in much smaller parcels. The 2003 data for early stage biotechnology companies of 5 years or younger illustrates this well. Some 129 US early stage companies raised equity capital in 2003, while a comparable number – 108 - in Europe did the same. But while the average US tranche size was nearly €14 million, the average European company in this group received only €6.1 million. Among the 0-2 year old group, US companies raised nearly 5 times as much per company (€10.8 million) than did European firms did (€2.2 million).

Not only was the average tranche for a European company much smaller in 2003, it was also being chased by many more companies. Among the 0-2 year old companies, for instance, there were 11 European biotechnology companies for every parcel of equity; in the US that figure was six. Notwithstanding the observation above that European companies tend to be more revenue-based on average in their early phases, it is clear that equity finance is a much rarer commodity in Europe than in the USA. Among the 6-10 year old and 11-15 year old groups, 3-4 times as many companies in the USA received equity investments in 2003 than did those in Europe. Moreover, the average size of equity tranches available to US companies within the 6-15 year old range in 2003 was 2-3 times higher than it was in Europe.

US companies almost totally dominate the 2003 fundraising table. There were only two European companies in the top 50 equity financings: Elan, the Irish specialty pharmaceutical group, which raised nearly \$190 million in equity and €365 million in debt to finance its

restructuring programme; and Flamel Technologies, the French drug delivery firm which raised €53 million in equity. Eleven European companies in addition made it into the top 100: nine were from the UK - Alizyme (#59), Lorantis (#63), Cambridge Antibody Technology (#75), Arrow Therapeutics (#84), Xenova (#87), Oxford Biomedica (#88), the UK end of Amarin (#89), Ardana Bioscience (#90), and GW Pharmaceuticals (#90) - and the other two were the German/UK drug discovery company, Cellzome (#86) and Sweden's Active Biotech (#100). If debt financing is added, Serono would come into the list at #7 but all the other European companies bar Flamel would fall out of the top 100 because of the preponderantly US nature of debt financing in biotechnology.

This distribution of biotechnology's elixir of growth had, and continues to have, a profound effect on the rate and the nature of the development of biotechnology in Europe.

Contrasts among mature biotechnology companies

Much of the discussion of biotechnology tends to focus on the early stage companies in the biotechnology sector. This is understandable since this is where many of the imponderables (and many unpondered ponderables) reside. However, the vast majority of the employment potential and economic contribution is vested in the more mature firms.

Over the whole sector, employment in the US was 172,000 in 2003 while the number of European jobs in biotechnology was 82,400. Around 90% of US employees worked in companies over 5 years old, and nearly three-quarters of the US total worked in

companies over 10 years old. In Europe, 77% of people were employed in companies over 5 years old, and 65% in companies over 10 years old.

The contribution to revenue generation by the older companies was even greater. Ninety-six percent of the US €43 billion revenue figure, and 87% of the €18.5 billion European (including Switzerland) revenue total arose in companies over 5 years old. For companies over 10 years old, the figures were 84% and 77% for the US and Europe, respectively.

There is a clear difference in the natures and histories of the companies that contribute the bulk of the revenue and jobs in the USA and Europe. At the top of the US lists for revenue generation are companies such as Amgen, Genentech, Chiron, Genzyme, IVAX, MedImmune, Gilead Sciences, Invitrogen, Cephalon, IDEXX, Genencor, Affymetrix, and Biogen Idec. These are companies formed in the late 1970s or 1980 which have grown rapidly from small beginnings, survived their own tribulations (product failure, merger, etc), and emerged to become new forces for wealth and job creation within a decade or two. It is their path that many of the newer generations of companies hope to follow.

The top 25 biotechnology earners in the USA contributed €23 billion in 2003, 53% of the total US revenues. Companies formed since 1980 (plus Genentech, which formed in 1977) contributed the majority of the revenues within the US top 25 - €19.5 billion or 85 per cent.

The list of European top 25 revenue earners had an entirely different profile. Companies such as the UK's Shire

Pharmaceuticals, Celltech, Warner Chilcott, Chiron Vaccines (PowderJect as was) and Acambis Plc, Sweden's Q-Med, and Ireland's Elan make the cut, as do relative newcomers such as Actelion Pharmaceuticals from Switzerland and Biovitrum from Sweden. However, European biotechnology revenues are dominated by companies such as biological pharmaceutical companies such as Novo Nordisk, Organon and Serono, diagnostic makers such as BioMérieux and Biotest, service companies such as Inveresk and Huntingdon Life Sciences, and the enzyme producer, Novozymes. These firms have evolved from an historical base in pre-recombinant biological technologies to maintain position high in the biotechnological firmament.

The top 25 European revenue earners contributed around €12.5 billion in 2003, about 68% of the European total. However, companies formed since 1980, accounted for only €4 billion, or a third of the revenues within the top 25 earners group (22% of the overall European total). Conversely, the older, established European companies in the top 25 earners contributed over €8 billion, or 44%, of the total earnings from Europe's biotechnology sector.

When the other pre-1975 European companies are added, the 52 older companies in Europe account for around €10 billion or 55% of European biotechnology revenues. They also account for some 30,000 or 36% of Europe's (including Switzerland's) biotechnology employees.

There is virtually the same number of pre-1975 companies in the US set which we have surveyed, but removing them from the counts has a very much lower impact. They collectively contribute some

€4.5 billion or around a tenth of the revenues and some 15,000 employees, which is 9% of the workforce.

We would certainly not want to discount the contributions of the older companies to the European (or US) biotechnology scene. The European biotechnology landscape in particular would be

impoverished without them.

Nevertheless, in comparing the pictures across the Atlantic, their impact needs to be borne in mind. The dynamics and the insecurities of these established firms are likely to be very different even to those firms founded in the early days of recombinant DNA (but since the resolution of the genetic code).

Europe (including Switzerland) & USA Summary Data Set

Key Performance Indicator	Agricultural & marine biotechnology		Industrial & Environmental		Healthcare		Service providers		Technology Service Providers		Sector overall	
	Europe	US	Europe	US	Europe	US	Europe	US	Europe	US	Europe	US
# of companies	105	87	126	42	800	1089	382	412	168	200	1581	1830
Age of company (% of sector total):												
0-2 yrs	12%	11%	11%	17%	29%	22%	26%	15%	39%	22%	27%	19%
3-5 yrs	26%	24%	24%	10%	35%	25%	32%	20%	44%	46%	34%	25%
6-10 yrs	25%	22%	27%	45%	18%	25%	18%	25%	14%	24%	19%	25%
11-15 yrs	17%	6%	21%	7%	8%	13%	13%	16%	2%	3%	10%	12%
Over 15 yrs	20%	37%	17%	21%	10%	16%	12%	25%	1%	6%	11%	18%
Total # of FTE employees (home)	3735	8548	2821	1194	56280	123136	15538	24607	4007	14907	82382	172392
# of new companies formed during calendar year 2003	2	1	2	3	56	55	32	16	14	8	106	83
Sector outputs:												
Overall R&D spend (M€)	124	136	22	1	4963	14721	387	554	361	975	5857	16386
Overall revenues (M€)	986	1818	422	54	14323	27561	2471	9982	294	2247	18496	41663
Sector productivity:												
Healthcare product development pipeline (# of prods by stage of development):												
- Concept/feasibility					443	1671						
- Preclinical					347	805						
- Phase I trial					198	468						
- Phase II trial					198	405						
- Phase III trial					65	199						
- Awaiting approval					29	38						
- Approved					286	741						
Equity raised - Total (M€)	4.8	92.1	11.2	2.4	1188.0	6851.3	58.2	95.8	78.9	260.5	1341.1	7302.08
0-2 yrs	0.0	6.9	0.0	0.0	77.1	624.6	22.7	4.7	5.7	33.3	105.6	669.52
3-5 yrs	4.8	0.0	0.0	0.0	500.8	1147.6	10.4	21.0	64.2	48.1	580.2	1216.76
6-10 yrs	0.0	12.4	9.9	2.4	194.0	1964.2	0.0	28.8	9.0	98.0	212.9	2105.74
11-15 yrs	0.0	0.0	1.3	0.0	151.0	1469.9	13.1	25.3	0.0	77.7	165.3	1572.91
Over 15 yrs	0.0	72.8	0.0	0.0	265.1	1645.0	12.1	15.9	0.0	3.5	277.2	1737.15

Appendix B – Switzerland

Switzerland has historically been at the forefront of life sciences development although it is only in the past few years that a genuinely entrepreneurial biotech industry has emerged. This is in spite of the Swiss Government launching its first national biotechnology programme as far back as 1991. Consolidation in the pharmaceutical industry appears to have been the trigger for the creation of the Swiss biotech sector.

Of the 97 Swiss biotech companies operating at the end of 2003, some 60% were less than six years old, and three in ten were less than three years old. With its strong pharmaceutical industry sector it is hardly surprising to see that Healthcare, Technology Service Providers and Service Providers account for 88% of the Swiss biotech sector.

Factors usually associated with successful biotech cluster development include a tradition in life sciences, an entrepreneurial culture, a strong academic base, access to capital and other professional services, and a supportive political and regulatory environment. As Switzerland ticks all of those boxes it is hardly surprising that it is fast emerging as a European biotech powerhouse.

Switzerland's biotech traditions start with the activities of the multinational life science companies located in Basel. For much of the 1980s and 1990s, companies such as Ciba-Geigy and Sandoz (which merged to create Novartis), plus Hoffmann La Roche were the focus of Swiss biotech efforts. This activity was not confined to Healthcare. Ciba-Geigy and Sandoz, and subsequently Novartis, were giants of the world agrochemicals industry and, consequently, were at the forefront of agricultural biotechnology. Roche has been a major player in the animal health, vitamins and diagnostics markets and has pioneered biotech's impact on these sectors.

Switzerland's pharma companies were not just focused on their own internal efforts. They have also been very active in their collaborations with biotech companies. Indeed, the first forays into biotech mergers and acquisitions were completed by Roche, which partly acquired Genentech in 1990, and Ciba which partly acquired Chiron in 1995. In both cases, the Swiss companies took a very relaxed attitude to how they managed their biotech acquisitions, ensuring that they did not stifle the innovative capacity of the existing teams. Sandoz and Ciba-Geigy were

both in the vanguard of gene therapy with a number of high profile acquisitions. Roche was also very influential in the industrialisation of the polymerase chain reaction technology which it acquired in 1991.

Biotech is clearly an important value driver for Roche, which has 13 biotech products in the marketplace including MabThera (Rituxan), the fifth best selling biotech drug worldwide, NeoRecormon (Epogin), Pegasys, Herceptin, and Nutropin which are among the company's ten best selling products. Indeed, MabThera, NeoRecormon and Herceptin are currently the company's best selling drugs. This means that the Roche Group is second in the global biotech drugs sales rankings behind Amgen and ahead of Johnson & Johnson, Novo Nordisk and Eli Lilly.

More recently, Novartis and Roche have been very active participants in biopartnering and biotech M&A, although the vast majority of their targets have been US biotech companies, reflecting the relative maturity of the US biotech sector over its European counterparts. During 2003, Roche concluded 40 product and technology deals while Novartis was second, completing 34 deals. More than a quarter of Roche's pipeline are biologicals.

Switzerland also boasts the presence of Serono, Europe's premier biopharmaceutical group and the third largest worldwide. Although the company was founded more than a century ago, its refocus into biotech means that it is now widely regarded as a biopharmaceutical group and as a consequence appears in our biotech count for Switzerland. Pharma multinationals such as Roche and Novartis, despite their significant biotech

efforts, do not.

Consolidation at the likes of Novartis and Hoffmann-La Roche have prompted the creation of a raft of new biotech companies which have a more mature profile than is usually seen in start-ups. The founding management teams are likely to have had senior pharmaceutical industry experience and are more likely to be focused on the discovery and development bottlenecks holding back the pharma giants.

Actelion, now regarded as both a bellwether of and inspiration to Europe's new generation of biotech companies, was only created in 1997 and yet it now has products in the marketplace. Indeed, following the successful launch of Tracleer, which has been approved as a treatment of pulmonary arterial hypertension, and Zavesca, a treatment for Gaucher's disease, Actelion saw sales rise 132% in local currency terms to €197m.

Bioterrorism threats boosted the performance of the Swiss vaccines company Berna Biotech which saw its net sales in 2003 rise 36%, in local currency terms, to €165m on the back of extraordinary sales of smallpox vaccine and the integration of Rhein Biotech, the German biotech vaccines company it acquired in 2002. Despite the strong sales performance, Berna Biotech reduced its headcount from 970 employees at the end of 2002 to 885 staff at the end of 2003.

Among the second generation of Swiss biotech companies making progress in 2003 were the Roche spin-off Basilea Pharmaceutica, which focuses on infectious and dermatological diseases, and which completed its IPO in 2004; Arpida which was founded in 1997 and had just completed a Phase II trial on its

lead hospital infection treatment Iclaprim in 2003; and Speedel Group, founded in 1998, with its lead hypertension candidate in Phase III trials.

Not all of Switzerland's new biotech companies have a pharma industry provenance. The state's Innovation and Promotion Agency (CTI) has been active in promoting the transfer of IP from academia to the marketplace, some of which, through the auspices of CTI Start-up, includes creating new companies such as Athelas SA, ESBATech AG, Glycart Biotechnology AG, and MyoContract Ltd. CTI Life Sciences funds innovative projects carried out by higher education in cooperation with industrial partners eager to commercialise the technology. CTI pays for half the entire project costs of employing the academics.

Switzerland boasts an excellent life sciences research base. In the past 25 years, Swiss researchers have won five Nobel Prizes for their work in the life sciences: Werner Arber (Medicine, 1978), Heinrich Rohrer (Physics, 1986), Richard R Ernst (Chemistry, 1991), Rolf Zinkernagel (Medicine, 1996), and Kurt Wuethrich (Chemistry, 2002). Indeed, Swiss scientists are still at the top of the citation index in the life sciences sector.

With its tradition in financial services it is not surprising that there is a significant investment community backing biotech in Switzerland. However, many of these investors are fairly conservative, backing mature top-tier biotech companies such as Amgen and Serono. Nevertheless, we have identified 10 Swiss-based specialist life sciences investors plus another five generalist investors with active life science interests. The Novartis Fund was the most active Swiss venture fund in 2003, making nine

investments - five of which were Swiss. Swiss biotech companies raised €44M from venture capital sources in 2003, the largest recipients being Glycart Biotechnology and Speedel Group. Serono, Actelion and Speedel were able to raise an additional €499M through convertible debt financing. The total finance raised by the Swiss biotech sector, €543M, placed Switzerland third behind Ireland and the UK in the financing stakes.

At the political level, Switzerland struggles to maintain a positive face for biotech. While a number of laws have been passed by the federal houses of parliament which are broadly supportive of the biotech industry they are under constant scrutiny and challenge. Under Swiss law it is possible to force a national referendum on any issue if 100,000 Swiss nationals petition for it. In recent years there have been such referenda on animal experimentation and other aspects of biotech activity. And while the Swiss politicians narrowly avoided the imposition of a moratorium on GM crops in Switzerland in 2003, the issue is clearly far from settled. Nevertheless, Switzerland has attempted to establish a regulatory framework that is compatible with the European Union.

Swiss Summary Data Set

Key Performance Indicator	Agricultural & marine biotechnology	Industrial & Environmental	Healthcare	Service providers	Technology Service Providers	Sector overall
# of companies	6	6	47	29	9	97
Age of company (% of sector total):						
0-2 yrs	17%	0%	34%	38%	11%	30%
3-5 yrs	17%	0%	32%	28%	56%	30%
6-10 yrs	17%	50%	17%	10%	22%	18%
11-15 yrs	0%	0%	2%	3%	0%	2%
Over 15 yrs	50%	50%	15%	21%	11%	21%
Total # of FTE employees (home)	203	183	6979	1214	240	8820
# of new companies formed during calendar year 2003	0	0	3	3	0	6
Sector outputs:						
Overall R&D spend (M€)	4	0	576	36	23	639
Overall revenues (M€)	52	54	1897	135	19	2158
Sector productivity:						
Healthcare product development pipeline (# of prods by stage of development):						
- Concept/feasibility			7			
- Preclinical			35			
- Phase I trial			7			
- Phase II trial			22			
- Phase III trial			12			
- Awaiting approval						
- Approved			25			
Equity raised - Total (M€)	0.0	0.0	32.4	0.0	11.5	43.9
0-2 yrs	0.0	0.0	0.0	0.0	0.0	0.0
3-5 yrs	0.0	0.0	32.4	0.0	11.5	43.9
6-10 yrs	0.0	0.0	0.0	0.0	0.0	0.0
11-15 yrs	0.0	0.0	0.0	0.0	0.0	0.0
Over 15 yrs	0.0	0.0	0.0	0.0	0.0	0.0

Appendix C – Country summary tables

USA Summary Data Set

Key Performance Indicator	Agricultural & marine biotechnology		Industrial & Environmental		Healthcare		Service providers		Technology Service Providers		Sector overall	
	2002	2003	2002	2003	2002	2003	2002	2003	2002	2003	2002	2003
# of companies	96	87	42	42	1120	1089	418	412	215	200	1891	1830
Age of company (% of sector total):												
0-2 yrs	19%	11%	10%	17%	26%	22%	18%	15%	43%	22%	25%	19%
3-5 yrs	22%	24%	19%	10%	25%	25%	20%	20%	35%	46%	25%	25%
6-10 yrs	21%	22%	36%	45%	23%	25%	25%	25%	14%	24%	22%	25%
11-15 yrs	6%	6%	12%	7%	13%	13%	16%	16%	2%	3%	12%	12%
Over 15 yrs	32%	37%	24%	21%	13%	16%	22%	25%	5%	6%	15%	18%
Total # of FTE employees (home)	8284	8548	1064	1194	120759	123136	25829	24607	12212	14907	168149	172392
# of new companies formed during calendar year 2003	2	1	4	3	88	55	23	16	9	8	126	83
Sector outputs:												
Overall R&D spend (M€)	202	136	8	1	16223	14721	414	554	1465	975	18312	16386
Overall revenues (M€)	1881	1818	31	54	27864	27561	7918	9982	1997	2247	39690	41663
Sector productivity:												
Healthcare product development pipeline (# of prods by stage of development):												
- Concept/feasibility					1000	1671						
- Preclinical					673	805						
- Phase I trial					458	468						
- Phase II trial					465	405						
- Phase III trial					183	199						
- Awaiting approval					58	38						
- Approved					646	741						
Equity raised - Total (M€)	7.7	92.1	7.6	2.4	6178.2	6851.3	173.2	95.8	247.6	260.5	6766.2	7302.1
0-2 yrs	46.4	6.9	4.8	0.0	1642.3	624.6	99.7	4.7	129.6	33.3	1884.0	669.5
3-5 yrs	4.8	0.0	2.9	0.0	1117.9	1147.6	39.1	21.0	57.0	48.1	1263.2	1216.8
6-10 yrs	0.0	12.4	0.0	2.4	1413.6	1964.2	5.6	28.8	56.4	98.0	1475.6	2105.7
11-15 yrs	0.0	0.0	0.0	0.0	972.5	1469.9	4.0	25.3	0.3	77.7	976.7	1572.9
Over 15 yrs	105.6	72.8	0.0	0.0	1031.9	1645.0	24.9	15.9	4.3	3.5	1166.7	1737.2

UK Summary Data Set

Key Performance Indicator	Agricultural & marine biotechnology		Industrial & Environmental		Healthcare		Service providers		Technology Service Providers		Sector overall	
	2002	2003	2002	2003	2002	2003	2002	2003	2002	2003	2002	2003
# of companies	38	34	53	46	264	239	99	98	40	38	494	455
Age of company (% of sector total):												
0-2 yrs	16%	9%	17%	15%	33%	31%	23%	27%	50%	42%	30%	27%
3-5 yrs	13%	21%	21%	22%	30%	26%	24%	28%	33%	45%	27%	27%
6-10 yrs	24%	26%	40%	28%	17%	22%	24%	16%	10%	8%	21%	21%
11-15 yrs	24%	15%	9%	20%	7%	6%	14%	18%	8%	5%	10%	11%
Over 15 yrs	24%	29%	13%	15%	12%	15%	14%	11%	0%	0%	12%	14%
Total # of FTE employees (home)	1798	1638	1056	941	15422	13199	5421	5840	702	788	24399	22405
# of new companies formed during calendar year 2003	1	0	1	1	34	20	9	11	5	4	50	36
Sector outputs:												
Overall R&D spend (M€)	90	81	25	5	1831	1529	172	91	41	51	2158	1758
Overall revenues (M€)	537	543	140	131	3718	3505	765	811	59	52	5219	5041
Sector productivity:												
Healthcare product development pipeline (# of prods by stage of development):												
- Concept/feasibility					151	118						
- Preclinical					112	100						
- Phase I trial					72	83						
- Phase II trial					96	82						
- Phase III trial					32	35						
- Awaiting approval					26	24						
- Approved					122	132						
Equity raised - Total (M€)	0.5	0.0	9.3	6.2	592.7	496.1	41.5	41.1	30.9	11.3	675.0	554.7
0-2 yrs	0.1	0.0	0.1	0.0	111.4	44.2	7.0	22.6	23.3	4.7	141.9	71.4
3-5 yrs	0.0	0.0	0.0	0.0	200.3	212.9	19.4	5.4	7.6	6.7	227.3	225.0
6-10 yrs	0.5	0.0	0.9	5.0	109.7	103.1	15.2	0.0	0.0	0.0	126.2	108.1
11-15 yrs	0.0	0.0	1.0	1.3	90.9	85.0	0.0	13.1	0.0	0.0	91.9	99.3
Over 15 yrs	0.0	0.0	7.3	0.0	80.4	50.9	0.0	0.0	0.0	0.0	87.8	50.9

Danish Summary Data Set

Key Performance Indicator	Agricultural & marine biotechnology		Industrial & Environmental		Healthcare		Service providers		Technology Service Providers		Sector overall	
	2002	2003	2002	2003	2002	2003	2002	2003	2002	2003	2002	2003
# of companies	4	4	4	3	52	57	20	22	11	12	91	98
Age of company (% of sector total):												
0-2 yrs	25%	25%	25%	0%	60%	47%	40%	36%	73%	58%	54%	44%
3-5 yrs	0%	0%	25%	33%	23%	32%	20%	27%	18%	33%	21%	30%
6-10 yrs	50%	0%	25%	33%	8%	9%	10%	9%	9%	8%	11%	9%
11-15 yrs	0%	50%	0%	0%	6%	9%	5%	5%	0%	0%	4%	8%
Over 15 yrs	25%	25%	25%	33%	4%	4%	25%	23%	0%	0%	10%	9%
Total # of FTE employees (home)	354	359	82	74	13511	13912	2625	2708	276	277	16849	17330
# of new companies formed during calendar year 2003	0	0	0	0	7	6	4	2	2	2	13	10
Sector outputs:												
Overall R&D spend (M€)	1	5	2	0	793	801	112	108	25	29	933	943
Overall revenues (M€)	59	59	20	18	3548	3775	825	839	8	8	4459	4698
Sector productivity:												
Healthcare product development pipeline (# of prods by stage of development):												
- Concept/feasibility					62	62						
- Preclinical					24	30						
- Phase I trial					11	14						
- Phase II trial					15	13						
- Phase III trial					3	4						
- Awaiting approval					2	1						
- Approved					11	12						
Equity raised - Total (M€)	4.7	0.0	1.1	0.4	111.3	45.9	35.3	0.1	6.5	9.8	158.9	56.2
0-2 yrs	4.7	0.0	0.4	0.0	62.2	7.0	35.3	0.1	6.4	0.0	109.0	7.0
3-5 yrs	0.0	0.0	0.0	0.0	40.0	35.4	0.0	0.0	0.0	7.8	40.0	43.2
6-10 yrs	0.0	0.0	0.7	0.4	9.1	0.0	0.0	0.0	0.1	2.0	9.9	2.4
11-15 yrs	0.0	0.0	0.0	0.0	0.0	1.7	0.0	0.0	0.0	0.0	0.0	1.7
Over 15 yrs	0.0	0.0	0.0	0.0	0.0	1.9	0.0	0.0	0.0	0.0	0.0	1.9

French Summary Data Set

Key Performance Indicator	Agricultural & marine biotechnology		Industrial & Environmental		Healthcare		Service providers		Technology Service Providers		Sector overall	
	2002	2003	2002	2003	2002	2003	2002	2003	2002	2003	2002	2003
# of companies	17	19	17	17	104	106	52	52	32	31	222	225
Age of company (% of sector total):												
0-2 yrs	18%	21%	35%	18%	40%	25%	37%	23%	59%	42%	40%	26%
3-5 yrs	29%	16%	24%	24%	28%	42%	19%	31%	34%	48%	27%	36%
6-10 yrs	29%	26%	18%	24%	16%	16%	21%	19%	6%	10%	17%	17%
11-15 yrs	18%	26%	12%	24%	7%	8%	10%	12%	0%	0%	8%	11%
Over 15 yrs	6%	11%	12%	12%	9%	8%	13%	15%	0%	0%	9%	9%
Total # of FTE employees (home)	279	390	257	391	6006	6182	1493	1378	476	582	8510	8923
# of new companies formed during calendar year 2003	0	1	0	0	6	5	3	3	4	2	13	11
Sector outputs:												
Overall R&D spend (M€)	19	9	7	3	451	505	44	40	32	51	551	608
Overall revenues (M€)	45	82	33	40	1518	1620	283	165	32	37	1911	1944
Sector productivity:												
Healthcare product development pipeline (# of prods by stage of development):												
- Concept/feasibility					59	58						
- Preclinical					33	48						
- Phase I trial					22	31						
- Phase II trial					22	33						
- Phase III trial					1	5						
- Awaiting approval					0	0						
- Approved					12	16						
Equity raised - Total (M€)	0.1	0.0	0.0	0.0	320.0	132.7	30.3	17.1	1.7	17.6	352.1	167.4
0-2 yrs	0.0	0.0	0.0	0.0	117.9	0.10	0.1	0.0	1.6	0.0	119.6	0.1
3-5 yrs	0.0	0.0	0.0	0.0	89.5	45.0	30.2	5.0	0.1	13.1	119.8	63.1
6-10 yrs	0.1	0.0	0.0	0.0	38.6	25.6	0.0	0.0	0.0	4.5	38.7	30.1
11-15 yrs	0.0	0.0	0.0	0.0	0.0	52.8	0.0	0.0	0.0	0.0	0.0	52.8
Over 15 yrs	0.0	0.0	0.0	0.0	74.0	9.3	0.0	12.1	0.0	0.0	74.0	21.4

German Summary Data Set

Key Performance Indicator	Agricultural & marine biotechnology		Industrial & Environmental		Healthcare		Service providers		Technology Service Providers		Sector overall	
	2002	2003	2002	2003	2002	2003	2002	2003	2002	2003	2002	2003
# of companies	24	24	44	44	249	245	147	149	63	63	527	525
Age of company (% of sector total):												
0-2 yrs	38%	17%	11%	9%	39%	26%	33%	23%	49%	32%	36%	24%
3-5 yrs	29%	42%	34%	32%	34%	40%	33%	37%	40%	44%	34%	39%
6-10 yrs	13%	17%	23%	20%	14%	18%	19%	22%	10%	22%	16%	20%
11-15 yrs	8%	13%	18%	25%	6%	8%	10%	11%	2%	2%	8%	10%
Over 15 yrs	13%	13%	14%	14%	7%	7%	6%	7%	0%	0%	7%	7%
Total # of FTE employees (home)	817	857	1716	990	11126	10434	3296	3342	1635	1654	18590	17277
# of new companies formed during calendar year 2003	2	1	0	1	14	14	9	11	4	4	29	31
Sector outputs:												
Overall R&D spend (M€)	47	19	26	9	1209	989	116	92	179	174	1577	1284
Overall revenues (M€)	163	197	268	151	2396	2183	383	422	102	101	3311	3054
Sector productivity:												
Healthcare product development pipeline (# of prods by stage of development):												
- Concept/feasibility					151	112						
- Preclinical					81	98						
- Phase I trial					42	39						
- Phase II trial					20	34						
- Phase III trial					3	5						
- Awaiting approval					3	1						
- Approved					86	61						
Equity raised - Total (M€)	8.0	3.1	7.2	4.5	560.4	195.7	20.4	0.0	48.2	18.9	644.2	222.2
0-2 yrs	5.0	0.0	0.0	0.0	434.0	25.7	11.9	0.0	0.5	0.8	451.3	26.5
3-5 yrs	3.0	3.1	6.8	0.0	87.1	134.7	8.5	0.0	47.7	18.1	153.1	155.9
6-10 yrs	0.0	0.0	0.7	4.5	39.3	32.4	0.1	0.0	0.0	0.0	39.4	36.9
11-15 yrs	0.0	0.0	0.0	0.0	0.0	2.9	0.0	0.0	0.0	0.0	0.0	2.9
Over 15 yrs	0.0	0.0	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0

Irish Summary Data Set

Key Performance Indicator	Agricultural & marine biotechnology		Industrial & Environmental		Healthcare		Service providers		Technology Service Providers		Sector overall	
	2002	2003	2002	2003	2002	2003	2002	2003	2002	2003	2002	2003
# of companies	4	4	8	7	16	19	9	9	1	2	38	41
Age of company (% of sector total):												
0-2 yrs	0%	0%	0%	0%	25%	32%	33%	22%	0%	50%	18%	22%
3-5 yrs	75%	25%	25%	14%	25%	26%	11%	22%	100%	50%	29%	24%
6-10 yrs	0%	50%	50%	43%	31%	16%	11%	11%	0%	0%	26%	22%
11-15 yrs	0%	0%	25%	43%	6%	16%	22%	22%	0%	0%	13%	20%
Over 15 yrs	25%	25%	0%	0%	13%	11%	22%	22%	0%	0%	13%	12%
Total # of FTE employees (home)	59	94	156	207	3438	2452	289	178	5	10	3947	2941
# of new companies formed during calendar year 2003	0	0	0	0	2	3	1	0	0	1	3	4
Sector outputs:												
Overall R&D spend (M€)	2	0	6	4	397	269	7	3	0	2	411	277
Overall revenues (M€)	8	11	31	27	1218	903	47	40	0	1	1305	982
Sector productivity:												
Healthcare product development pipeline (# of prods by stage of development):												
- Concept/feasibility					9	10						
- Preclinical					5	4						
- Phase I trial					3	1						
- Phase II trial					3	1						
- Phase III trial					3	3						
- Awaiting approval					1	1						
- Approved					16	19						
Equity raised - Total (M€)	0.0	1.7	0.0	0.0	6.3	197.2	0.0	0.0	0.0	0.0	6.3	198.9
0-2 yrs	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.2
3-5 yrs	0.0	1.7	0.0	0.0	3.8	0.0	0.0	0.0	0.0	0.0	3.8	1.7
6-10 yrs	0.0	0.0	0.0	0.0	2.5	7.8	0.0	0.0	0.0	0.0	2.5	7.8
11-15 yrs	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Over 15 yrs	0.0	0.0	0.0	0.0	0.0	189.3	0.0	0.0	0.0	0.0	0.0	189.3

Norwegian Summary Data Set

Key Performance Indicator	Agricultural & marine biotechnology		Industrial & Environmental		Healthcare		Service providers		Technology Service Providers		Sector overall	
	2002	2003	2002	2003	2002	2003	2002	2003	2002	2003	2002	2003
# of companies	6	6	1	1	17	17	5	6	2	2	31	32
Age of company (% of sector total):												
0-2 yrs	0%	0%	0%	0%	29%	12%	20%	33%	100%	100%	26%	19%
3-5 yrs	0%	0%	0%	0%	41%	53%	20%	0%	0%	0%	26%	28%
6-10 yrs	67%	67%	100%	100%	6%	12%	0%	17%	0%	0%	19%	25%
11-15 yrs	17%	17%	0%	0%	0%	0%	60%	50%	0%	0%	13%	13%
Over 15 yrs	17%	17%	0%	0%	24%	24%	0%	0%	0%	0%	16%	16%
Total # of FTE employees (home)	129	113	12	17	662	710	108	116	16	15	927	971
# of new companies formed during calendar year 2003	0	0	0	0	0	0	0	1	1	0	1	1
Sector outputs:												
Overall R&D spend (M€)	7	2	1	1	48	23	4	4	1	4	63	34
Overall revenues (M€)	51	32	0	0	21	76	9	9	0	0	81	118
Sector productivity:												
Healthcare product development pipeline (# of prods by stage of development):												
- Concept/feasibility					6	2						
- Preclinical					11	16						
- Phase I trial					10	13						
- Phase II trial					1	4						
- Phase III trial					1	1						
- Awaiting approval					3	2						
- Approved					2	2						
Equity raised - Total (M€)	0.0	0.0	0.0	0.0	0.9	2.1	0.0	0.0	2.8	0.0	3.7	2.1
0-2 yrs	0.0	0.0	0.0	0.0	0.9	0.0	0.0	0.0	2.8	0.0	3.7	0.0
3-5 yrs	0.0	0.0	0.0	0.0	0.0	2.1	0.0	0.0	0.0	0.0	0.0	2.1
6-10 yrs	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
11-15 yrs	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Over 15 yrs	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Swedish Summary Data Set

Key Performance Indicator	Agricultural & marine biotechnology		Industrial & Environmental		Healthcare		Service providers		Technology Service Providers		Sector overall	
	2002	2003	2002	2003	2002	2003	2002	2003	2002	2003	2002	2003
# of companies	9	8	2	2	69	70	16	17	12	11	108	108
Age of company (% of sector total):												
0-2 yrs	11%	0%	0%	0%	35%	29%	44%	24%	75%	45%	38%	27%
3-5 yrs	44%	63%	0%	0%	30%	34%	25%	47%	17%	36%	29%	38%
6-10 yrs	22%	13%	0%	0%	13%	14%	13%	6%	0%	9%	12%	12%
11-15 yrs	22%	25%	50%	0%	16%	14%	0%	6%	0%	0%	13%	12%
Over 15 yrs	0%	0%	50%	100%	6%	9%	19%	18%	8%	9%	8%	11%
Total # of FTE employees (home)	136	81	17	19	2328	2413	707	763	410	441	3598	3717
# of new companies formed during calendar year 2003	0	0	0	0	2	5	1	1	3	1	6	7
Sector outputs:												
Overall R&D spend (M€)	7	4	4	0	303	270	15	14	27	26	355	314
Overall revenues (M€)	21	9	13	1	399	364	48	50	82	77	563	501
Sector productivity:												
Healthcare product development pipeline (# of prods by stage of development):												
- Concept/feasibility					78	74						
- Preclinical					20	16						
- Phase I trial					15	10						
- Phase II trial					11	9						
- Phase III trial					1	0						
- Awaiting approval					0	0						
- Approved					14	19						
Equity raised - Total (M€)	0.0	0.0	0.8	0.0	38.3	85.8	32.2	0.0	21.4	9.9	92.8	95.6
0-2 yrs	0.0	0.0	0.0	0.0	0.8	0.0	0.0	0.0	21.4	0.3	22.2	0.3
3-5 yrs	0.0	0.0	0.0	0.0	17.4	38.2	32.2	0.0	0.0	7.0	49.6	45.3
6-10 yrs	0.0	0.0	0.0	0.0	8.2	25.1	0.0	0.0	0.0	2.5	8.2	27.6
11-15 yrs	0.0	0.0	0.0	0.0	6.2	8.7	0.0	0.0	0.0	0.0	7.1	8.7
Over 15 yrs	0.0	0.0	0.0	0.0	5.7	13.7	0.0	0.0	0.0	0.0	5.7	13.7

Appendix D – Methodology

Currencies

Prior to analysis all metrics were converted to Euros using the exchange rates below.

Currency to Euro	Exchange rate (31/12/2001)	Exchange rate (31/12/2002)	Exchange rate (31/12/2003)
Dkr	0.135	0.135	0.134
US Dollar	n/a	0.95	0.794
GBP	1.634	1.535	1.417
SKr	0.107	0.110	0.11
Nkr	0.125	0.138	0.119
CHF	n/a	n/a	0.641

Key challenges

There are many issues concerning collection of key performance indicators that are common to all emerging high technology sectors. They include:

- A lack of reliable data
 - ▶ Poor coverage of the sector by commercial databases, in particular:
 - Lack of revenue and R&D data
 - Poor or inconsistent categorisations of companies or data points
 - Difficulties in gaining access to information on new/emerging companies
- ▶ Inadequacy of SIC Codes as a means of classifying fast-moving R&D-based enterprises, in particular:
 - The range of classifications may not encompass the spectrum of activities in which subject companies are engaged
 - The introduction of new SIC Classes may lag the pace of technology development in the subject industry
- ▶ Reluctance of companies to disclose information - public disclosure of information by US quoted companies is very thorough and, generally speaking, better than that of their European peers. However, it is equally, if not more, difficult to obtain financial information on private US companies as it is for their European peers as they are under no obligation to publicly file or disclose their annual results. Furthermore, survey fatigue is a potentially significant barrier to data access on both sides of the Atlantic
- Lack of consistently applied definitions
 - ▶ This issue, perhaps more than any other, has inhibited meaningful comparisons of the European and international biotechnology industry in the past. As a result, government agencies and other stakeholder groups have found it difficult, if not impossible, to base their decisions upon reliable and informed analyses.

A consistently applied definition of biotechnology

The bedrock of our methodology lies in the consistent application of a definition of biotechnology that was agreed with the DTI at the outset of the study. Only companies whose **primary** commercial activity depends on the application of biological organisms, systems or processes, or on the provision of specialist services to facilitate the understanding thereof are included in the remit of this study.

Big pharma companies, other major corporates, and companies for whom biotechnology is an important but, nonetheless, minor part of their business are not included in this study. Dedicated biotechnology subsidiaries of major corporates are included, however. As a result, the study does not, and was not designed to reflect, the full scope and extent of biotechnology activity in the countries surveyed. This is particularly relevant in the Agricultural & Marine and Industrial & Environmental sectors where the number of pure-play biotechnology companies is extremely limited, albeit that biotechnology-based

techniques are both a widespread and increasingly vital part of their technology mix.

A rigorous application of this definition, likewise, means that many companies who might, and indeed, often do feature in reviews of the biotechnology industry have been excluded from this study. Examples include companies such as R&D Systems, Genetix, Applied Biosystems and Quest Diagnostics, to name a few. By the same token, companies such as Novo Nordisk have been included, notwithstanding their scale, because they do satisfy the definition above.

Sectoral analysis

Companies analysed in this study have been categorised according to their overall sector (e.g. healthcare, environmental) and according to their primary area of activity (e.g. vaccines, water and effluent treatment). The five overall sectors and 24 primary activities used for the purposes of our classification and analyses are as follows:

Activity category	Primary activity
Agricultural & Marine	Animal healthcare, Biopesticides, Crop agriculture, Food technology
Industrial & Environmental	Biocleaning, Bioremediation, Environmental diagnostics, Industrial diagnostics, Water & effluent treatment, Waste recycling
Human healthcare	Biomaterials, Drug delivery, Drug discovery, Gene therapy, Healthcare diagnostics, Genomics, Vaccines
Service providers	Bioprocessing, Chemicals, Contract research, Contract manufacturing
Technology service providers	Bioinformatics, Functional genomics, High throughput screening

To further enhance the flexibility of the data and increase the accuracy and range of analyses, companies were split into five age bands, namely:

- 0-2 years
- 3-5 years
- 6-10 years
- 11-15 years
- Over 15 years

These age-bands were selected for two reasons. Firstly, to ensure that companies for whom datapoints were not available were analysed on the basis of real metrics drawn from companies at a similar stage in their development cycle. Secondly, to build a composite picture of the sector based on an assessment of the dynamics and profile of clearly-defined market sub-segments. This approach resulted in analyses being generated from a universe of 120 sub-segments for each country covered in this report.

Data-gathering

To ensure that we included only companies that fall within the above definitions and sectors/sub-sectors, and that their data profile was complete as possible, an extensive data gathering process was undertaken, using the following approach:

- **Identification of companies for potential inclusion**

Our starting-point in each country was the universe of well-known, readily identified biotechnology companies. Each initial country list was then supplemented by identifying potential additional companies via:

- ▶ The identification and searching of the directories and web-sites of

university technology transfer offices, business incubators, regional development agencies, trade and industry bodies

- ▶ Contact with, and searches of the promotional materials issued by, investor groups
- ▶ Industry directory searches; and
- ▶ Contact with Critical I's own network of industry contacts

In 2002 for example, this resulted in an initial long-list of companies being compiled - in the case of the USA this extended to over 8,000 companies

- **Filtering of companies against the agreed definition of biotechnology**

- ▶ Information on the companies' operations and activities was then scrutinised, recorded in an Access database (to provide a record of activity transitions year-on-year) and used as the basis for deciding whether or not a company should be included and, if so, to which primary activity category (i.e. sub-sector) it should be assigned.
- ▶ Each selection and activity categorisation was approved by two members of our review panel. In the event of a split decision a third reviewer held a casting vote.
- ▶ The activities and primary activity category assigned to each company have been checked each year since to ensure that changes in company activity are tracked and accurately recorded.
- ▶ A check was made with the relevant national authority to identify a company's trading status to ensure that insolvencies, liquidations, cessations of trading and dormancy were recorded

Continuing with the USA example, in 2002 this stage of the process reduced the initial list down to 4,000 or so companies, and then the final

tally of just over 1,800 companies.

- **Gathering raw data** - this phase involved the
 - ▶ Obtaining and analysis of **all** available company annual reports & accounts
 - ▶ The detailed review of company web-sites & other public information sources to gather the required metrics
 - ▶ Confirmation of each company's Primary Activity category
- **Validation of data** - this phase involved
 - ▶ Inviting CEOs/FDs to review and validate the metrics gathered on their company via a secure and password-protected website
 - ▶ Checking company submissions for accuracy/consistency/completeness
 - ▶ Clarifying those returns as required with each company, before accepting their data in to the database and incorporating it in to the analysis data-set

As described at the front of the report, our previous extrapolations for 2001 and 2002 were re-run as part of the extrapolation process for this report in order to i) reflect the changed country set for which the DTI required analyses, and ii) make full use of the original data which has become available since the 2001 and 2002 extrapolations were originally run.

We shall be happy to provide further details of the methodology if required.

Extrapolation of original data for each KPI Analysis Year

The original data set was then used to generate a set of extrapolation multipliers from which to calculate proxy values for those companies in each sub-sector age group for whom original data was not available. Totals for each given metric covered in the study were then calculated by aggregating the original and proxy values for that metric for each sub-sector age group. Country sub-sector age group totals were then aggregated to build up composite metrics at sectoral and national sector level.

