CHAPTER V
The competitiveness of European biotechnology: a case study of innovation

This chapter reviews the state of innovation and production systems in European biotechnology and, in particular, its innovative capacity and related factors[86]. As such, biotechnology cannot be considered as an industrial sector but rather as a set of technologies developed in the field of life sciences. Its applications span over a number of other industrial or service sectors, and agriculture. This direct link with science makes innovative capacity a major determinant of competitiveness.

While large biotechnology firms are undoubtedly important[87], the emphasis of the chapter is on the role of the small and medium, research-intensive companies, which have emerged from the new opportunities opened up by the life sciences. In this chapter they are referred to as dedicated biotechnology firms (DBFs).

Inevitably, comparisons with the US biotechnology industry are made throughout. One notable difference between Europe and the US in the 1990s has been that, while in the US a new research–intensive industry in the life sciences has continued to develop, there has not been a comparable specialisation in entrepreneurial biotechnology in Europe (see also Gambardella, Orsenigo, Pammolli, 2001). Partly reflecting this difficulty in developing an industry of DBFs, the perception has emerged that the US has a competitive advantage over Europe in biotechnology.

The US have pioneered the rise of an effective division of labour between smaller and larger companies, which possess different comparative advantages in the "exploration" and "exploitation" of new innovation opportunities (March, 1991). Europe has been less effective in facilitating the growth of research–intensive DBFs. While large multinationals, such as biopharmaceuticals and agri-food, may not need local technology suppliers, the presence of a local industry of research–based firms and technology suppliers is critical, because the industry is, by itself, a powerful source of growth and social progress. The US biotechnology industry has, over the past two decades, created a large number of new jobs, and at least a dozen new world–class companies (e.g. Amgen, Chiron, Genzyme, and others), along with several new ones in the new tool technologies (e.g. Incyte, Millennium, Celera, Human Genome Sciences, and others). It has also produced a substantial stream of revenues, mostly in the form of royalties from licences or R&D contracts and collaborations.

As in many other technologies, innovation in biotechnology was first undertaken not by incumbents but by new companies. In the US, biotechnology was the motive force behind the first large–scale entry into the pharmaceutical industry since the early post-World War II period. Entry rates soared in 1980 and remained at a very high level thereafter, but with waves linked to both the stock market performance and to the appearance of successive new technologies. Despite the high rates of entry of new firms into biotechnology, it took several years before the industry started to have an impact on the pharmaceutical and agri-food markets. Many of the early research efforts proved to be dead-ends and/or much more difficult to develop than expected.

86 There are several statistical and methodological problems that affect the quality and reliability of data concerning the European biotechnology industry. This chapter uses data from the BID (Biotechnology Industry Databank) of the University of Siena, as well as statistics collected by publicly funded organisations such as the US National Science Foundation in the US and NUTEK in Sweden, from the most important patent offices, and from commercially available databases such as Windhover, Recombinant Capital, Pharmaventures and Bioscan. Reports and data from commercial sources like Ernst&Young, Decision Resources, SRI, McKinsey, the European Venture Capital Association, have also been used. For a detailed description of the data used in this Report, see the background study "Innovation and Competitiveness in Biotechnology: a European Perspective", July 2001, prepared for the present Report by a team of researchers coordinated by Prof. Fabio Pammolli and Dr. Massimo Riccaboni at the University of Siena (see Allansdottir et al., 2001).

87 These are the agri-seed firms such as Syngenta, Aventis, and Advanta, large chemical firms such as BASF, and large pharmaceutical firms like Astra- Zeneca, Novartis, Aventis, and GlaxoSmithKline.

These companies were primarily university spin-offs and were usually formed through collaboration between scientists and professional managers, backed by venture capital. Their specific skills related to knowledge of new techniques and to research capabilities in that area. The "function" of this type of national biotechnology firms has been to mobilise fundamental knowledge created in universities and to transform it into commercially useful techniques and products.

Section V.1 reviews the recent evolution of industrial biotechnology in Europe and the contribution of the new DBFs that entered the industry during the 1990s. Section V.2 provides a detailed analysis of R&D activities and research collaborations of European biotechnology companies. Section V.3 analyses the essential features of biotechnology clusters in Europe and the position of European biotechnology firms in the context of the international division of labour within the field. Section V.4 reviews briefly the institutional, legal, and cultural factors that have an impact on the evolution and performances of the biotechnology industry and Section V.5 surveys the adoption of biotechnology by large European firms. The final section V.6 summarises the main findings.

5.1. Innovation activities of the European biotechnology industry

This section provides an overview of the innovative performance of industrial biotechnology in Europe, on the basis of patent data and patent citations. A traditional indicator of innovative performance, patents are even more important in the context of biotechnology where they often represent the only tradable asset.

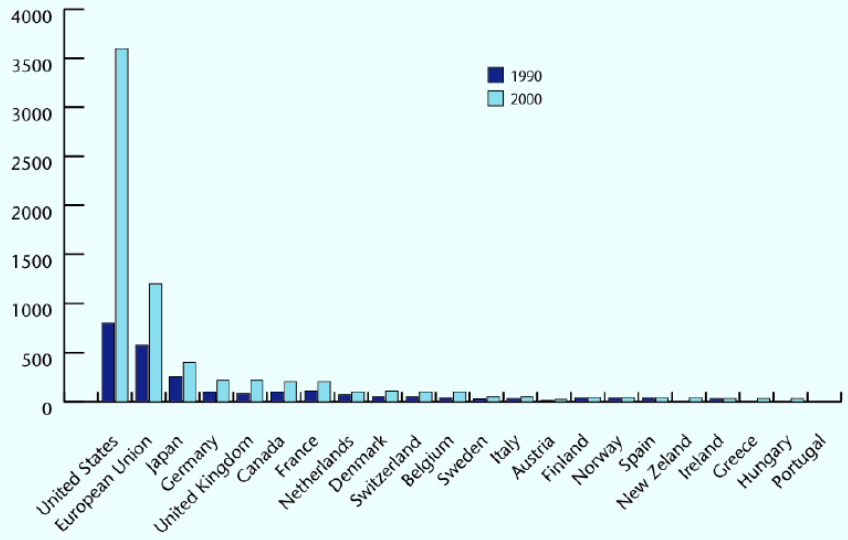
5.1.1. General observations and comparisons with the US

The available empirical evidence shows that the US is and continues to be the most important locus of innovation in biotechnology (see Graphs V.1 and Graphs V.2), followed by Japan, Germany, the UK and France.

Graph V.1 gives an account of the dominance of the US in biotechnology inventions. From 1990 to 2000, the US share in all biotechnology patents granted by the USPTO[88] increased by nine percentage points. The share of Japan declined by 11 %. A modest increase occurred in the case of Denmark (1.1 %), while Germany's share declined by 1.2 % The shares of all other European countries have remained generally stable over the last decade. Between 1990 and

88 Biotechnology patents are covered by class 435 of the USPTO classification system ("molecular biology and microbiology"). For a complete definition of class 435 see http://www.uspto.gov/web/offices/ac/ido/oeip/taf/moc/435.htm.

Graph V.1: Biotechnology patents granted by the USPTO, 1990 and 2000



Source: OECD, calculations based on data from USPTO and EPO

1997, national shares of biotechnology EPO patent applications[89] have been stable (see Graph V.2), with the exception of Japan, which saw a decline of 6 %. The UK shows the best performance with an increase of 2.1 %.

Patent citations data provide a better measure of the potential technological and economic value of innovative activities than patent counts. Citations are a measure of the importance or impact of inventions and a proxy for knowledge flows among patenting institutions. Widely cited patents tend to be "seminal" patents, i.e. key inventions to which further patents must refer. Moreover, high citation rates have been shown to correlate with the economic value of patents. Thus, a high number of citations received by a given firm or country can be interpreted as a measure of the quality and relevance of its innovative activities.

Allansdottir et al. (2001) show that the share of citations to US patents is substantially higher (around 55 %) than the share of US patents in total patents, suggesting that on average US patents are more important. Moreover, among European nations only UK patents show a higher share for citations than for patent counts. On the basis of a subset of "highly cited" patents (i.e. patents receiving at least 10 citations not counting self–citations) in the period 1978 – 1995 (with citations up to 1997) the US lead increases further to 65.4 %.

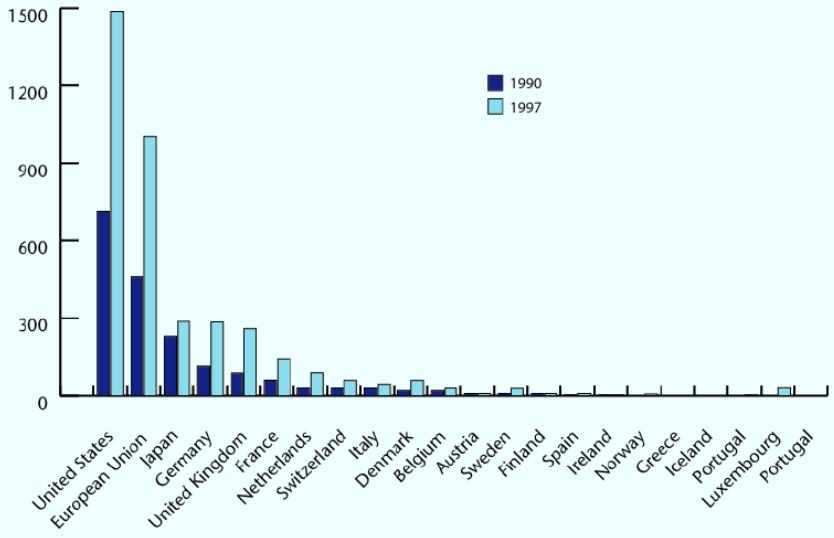
National biotechnology firms (DBFs) hold a disproportionate share of these highly cited patents (48 %), and US DBFs account for more than 80 % of highly cited patents of DBFs. In Europe (including Switzerland), around 65% of the highly cited patents belong to large incumbent firms and around 20 % to DBFs (almost all of them British). Considering the top 20 institutions in terms of patent citations, eleven are American (four DBFs, three incumbents, four universities and other research organisations), two are, respectively, German, British and Japanese, while Switzerland, France and Denmark are represented with one institution. Almost all of these European institutions are large corporations, the only exceptions being one British DBF and one French public research organisation.

Finally, the US appears to be more specialised in the pharmaceutical segment of biotechnology. The US share in highly cited agri–food patents is 13.5 % compared to a total of 17%. However, only two European countries have agri–food patents, Germany (35 %) and the UK (33 %), among their total highly cited patents.

The importance of biotechnology depends to a considerable extent on the size and the growth of downs-

89 European biotechnology patents are covered by 5 IPC codes: C12M: Apparatus for enzymology or microbiology; C12N: Micro-Organisms or Enzymes; compositions thereof; C12P: Fermentation or enzyme-using processes to synthesise a desired chemical compound; C12Q: Measuring or testing processes involving enzymes or micro-organisms; C12S: Processes using enzymes or micro-organisms to liberate, separate, or purify a pre-existing compound or composition. For complete definitions of these IPC codes, see http://classifications.wipo.int/fulltext/new_ipc/index.htm.

Graph V.2: Biotechnology patent applications to the EPO for priority years 1990 and 1997



Source: OECD, calculations based on data from USPTO and EPO

Table V.1: International patterns of specialisation in related industries: share of food, pharmaceutical and chemical industries in GNP, 1978-1997

		Average share of GNP (%)		
		1978-1985	1986-1993	1994-1997
United Kingdom	Food	19.11	17.97	17.00
	Chemicals	19.03	18.00	19.66
	Pharmaceuticals	1.50	2.14	2.78
Germany	Food	14.46	12.82	11.77
	Chemicals	20.31	17.71	18.61
	Pharmaceuticals	1.11	1.32	1.43
France	Food	17.79	17.01	16.68
	Chemicals	19.47	16.40	18.11
	Pharmaceuticals	1.65	2.24	2.65
Sweden	Food	4.06	2.78	2.81
	Chemicals	12.87	10.69	10.25
	Pharmaceuticals	0.85	1.67	2.72
US	Food	14.27	14.36	13.35
	Chemicals	19.42	16.69	16.59
	Pharmaceuticals	1.17	1.83	2.21
Japan	Food	11.07	10.90	11.11
	Chemicals	14.47	9.52	11.28
	Pharmaceuticals	1.26	1.42	1.56

Note: " "Chemicals" excludes Drugs.

Source: OECD, STAN Database (2000)

tream industries, which demand biotechnology products and technologies (see also Gambardella, Orsenigo, Pammolli, 2001). Table V.1 shows, over a period of twenty years, the shares on GNP of the most important industries related to biotechnology: food, chemicals, and pharmaceuticals, for the US, Japan, and four major European countries: Germany, France, the UK and Sweden.

The data in Table V.1 show a continuous growth of the share of pharmaceuticals, while the shares of the food industry and of chemicals in GNP decreased significantly. The countries that recorded the highest growth in the GNP share of pharmaceuticals are the US and the UK, while Germany and Japan experienced a much slower growth. As for chemicals, the UK, Germany and France have the highest share in GNP.

5.1.2. R&D activities and r esearch collaboration: Inter–country and inter–regional comparisons

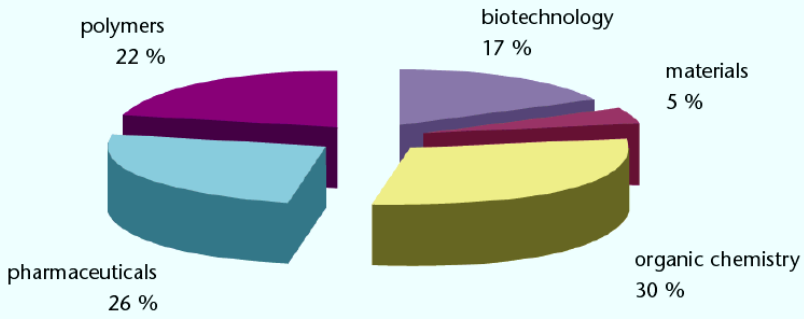
Patent data provide important information about the geographical distribution of biotechnology research across macro-regions (Europe and the US) and across countries. The extent to which companies locate biotechnology research outside of their home country (internationalisation of research) is also important. To put the analysis in perspective, biotechnology is compared with four other branches of the chemical industry (materials, organic chemistry, pharmaceuticals, and polymers). It is assumed that the location of the inventors of the (97,785) patents and the location of the (7,264) chemical R&D laboratories coincide with the location of the inventive activity.

The data suggest that the US iscomparatively more specialised in biotechnology innovations, and that smaller European countries show greater specialisation in biotechnology compared to larger European countries.

Graph V. 3 shows the sectoral break down of patents by chemical subsectors. In 1987–1996 biotechnology patents were 17 % of the total chemical patents, rising from 16 % in 1987–1991 to 19% in 1992–1996. Clearly, these EPO patents include patents developed in Europe and in the US and Japan. Graph V. 4 shows the share of patents attributed to each country.

The biotechnology patents invented in Europe represent 14.4 % of the total number of chemical patents invented in Europe, compared to 22.5% of the EPO biotechnology patents invented in the US over the total number of chemical EPO patents invented in the US. This suggests that the US chemical companies

Graph V.3: Share of EPO patents by chemical class, 1987-1996



Graph V.4: Share of 1987-1996 EPO patents in chemicals by country of invention

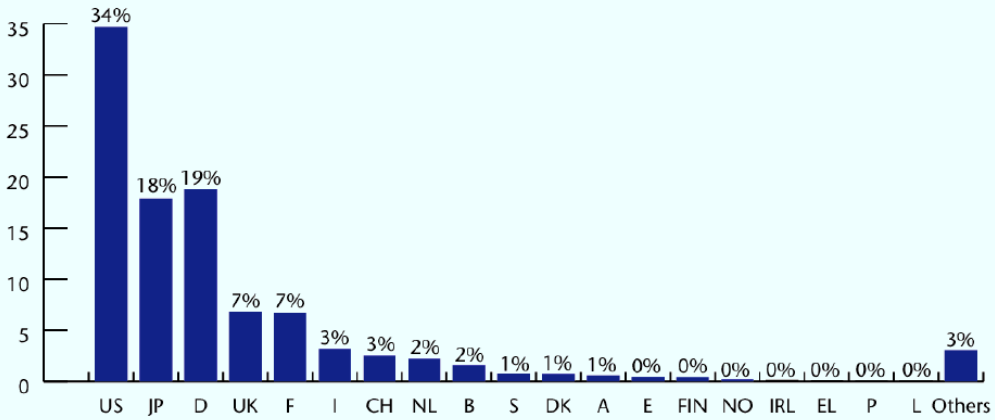


Table V.2: Standardised Revealed Technological Advantages of Eur ope, US and Japan in biotechnology , materials, organic chemistry, pharmaceuticals and polymers (97 785 patents in 1987-1996).

(RTA-1) / (RTA+1)

Country	Biotechnology	Materials	Organic chemistry	Pharmaceuticals	Polymers
EU total (*)	- 0.09	0.01	0.06	0.02	- 0.05
US	0.13	- 0.06	- 0.08	0.01	- 0.01
JP	- 0.12	0.08	0.01	- 0.11	0.15
OTHERS	0.22	0.02	- 0.08	0.11	- 0.39

Note: (*) This is EU-15 plus Switzerland (CH) and Nor way (NO).

Source: European Patent Office (1998)

are relatively more focused than European ones on biotechnology. To examine this issue further, the Revealed Technological Advantage Index (RTA) was computed for different countries. RTA is a country's share of all patenting in a given technology/sector relative to the share of patents in that technology/sector over all technologies/sectors, and it gives an account of the specialisation of a country or region in a technological field.[90] Table V.2 shows the Standardised Revealed Technological Advantage Index (SRTA) = (RTA-1)/(RTA+1), for Europe, the US and Japan. The standardised index varies between –1 (non-specialisation) and 1 (specialisation). The evidence in Table V. 2 suggests that the US has a stronger specialisation in biotechnology than Europe (and Japan). The biotechnology RTA index for the US is 0.13 compared to –0.09 for Europe, and –0.12 for Japan.

90 RTA = $(P_{ij} / \Sigma_i P_{ij}) / (\Sigma_j P_{ij} / \Sigma_i \Sigma_j P_{ij})$, where P_{ij} denotes the number of patents in country/region i and sector j.

Table V. 3 reports the standardised RTA by individual European country. It suggests that it is the larger European countries that show no specialisation in biotechnology compared to the other branches of the chemical industry. The standardised biotechnology RTA for Germany (–0.31), Italy (–0.24), France (–0.03) and the UK (0.01) are negative or very close to zero. By contrast, the standardised biotechnology RTA for the smaller European countries – Denmark (0.41), Ireland (0.23), the Netherlands (0.15), Sweden (0.25), Finland (0.12) and Norway (0.45) – is positive and has a high value. Germany and the UK have dominated the traditional chemicals industry for many years, while Italy and France have also been important world–wide. The RTA results indicate that whereas the larger countries continue to focus their activities on traditional chemicals, smaller European nations have taken advantage of the new opportunities opened up by biotechnology research. Thus, the traditional dominance of the larger European nations in chemicals does not provide them with a critical advantage in the new biotechnology industry.

The results shown by Tables V.2 and V.3 are confirmed by simple ratios of the total biotechnology patents over the total number of patents by country of invention. Table V.4 shows that 45.4% of the total biotechnology patents in the sample were invented in the US and 36.5% of biotechnology patents invented in Europe. However, in all chemical sectors the US share is 34.5% while Europe's share is 44.8%.

The data on the R&D laboratories also shed light on the comparative specialisation of European countries in biotechnology. Of the 7 264 chemical R&D labs in the sample, 32% perform biotechnology research[91]. Smaller countries (Denmark, Finland, Ireland, and the Netherlands) are more focused on biotechnology than the larger countries (Italy, Germany, and France), thus confirming the results seen earlier.

Finally, in Europe about 72% of the biotechnology laboratories are public (government research institutions, universities, and hospitals). This share is slightly lower in pharmaceuticals (71%), and much lower in the chemical sectors (40%). The evidence across countries is mixed. In Finland and in Ireland, 82.9% and 80.6% of the biotechnology labs are public. This percentage drops to 67.7% in Denmark, and to 56.8% in the Netherlands. It could be said, therefore, that the entry of Finland and Ireland is related to public

91 Each R&D lab in our sample can perform more than one activity. For example, only one third of the 32% of labs carrying out biotechnology research perform only biotechnology research. The other two thirds perform research in biotechnology and in one or more other chemical sectors.

Table V.3: Standardised Revealed Technological Advantages of European countries in biotechnology, materials, organic chemistry, pharmaceuticals and polymers (97 785 patents in 1987-1996)

(RTA-1)/(RTA+1)

Country	Biotechnology	Materials	Organic chemistry	Pharmaceuticals	Polymers
Germany	- 0.31	0.05	0.12	- 0.08	0.07
France	- 0.03	0.08	0.01	0.12	- 0.22
United Kingdom	0.01	- 0.14	0.04	0.16	- 0.37
Italy	- 0.24	- 0.07	0.00	0.09	0.05
Switzerland	- 0.17	- 0.40	0.25	- 0.06	- 0.27
Netherlands	0.15	0.16	- 0.14	- 0.18	0.15
Ireland	0.23	0.02	- 0.30	0.19	- 0.24
Belgium	0.02	0.14	- 0.23	0.06	0.12
Sweden	0.25	- 0.07	- 0.28	0.26	- 0.55
Denmark	0.41	- 0.29	- 0.12	0.06	- 0.80
Spain	- 0.02	- 0.21	0.19	0.05	- 0.54
Austria	0.34	0.19	- 0.19	- 0.10	- 0.16
Finland	0.12	- 0.08	- 0.29	0.01	0.18
Norway	0.45	0.42	- 0.30	- 0.14	- 0.54
Greece	0.39	0.02	- 0.31	0.03	- 0.28
Luxembourg	- 1.00	0.31	- 0.24	- 0.14	0.42

Note: Portugal is excluded because it had too few patents.

Source: European Patent Office (1998)

funding and public research in biotechnology. By contrast, in the Netherlands and to some extent in Denmark, the share of activities in biotechnology is more closely associated with private research. No single model emerges. Either private or public research can be the means by which newcomer countries can take advantage of the opportunities opened up by biotechnology.

The data can provide information on the extent to which patent assignees locate research activity in their home country. It is assumed that the locus of the innovative activity is the location of the inventors of the patent and that the location of the patent assignee is given by the nationality of the ultimate owner of the assignee[92]. The results show that, in general, the home country is the preferred location of inventive activities in all countries and sectors; and that biotechnology is a partial exception, with the European countries locating a sizeable share of their inventive activity in the US.

Table V.4 shows that European assignees invent 86.3 % of their chemical patents in Europe and US assignees 87.8 % of their patents in the US. When European companies locate their patenting activity outside Europe, they develop almost all of their "foreign" chemical patents in the US - the total share of patents by European assignees invented either in Europe or in the US is 98.2 %. Thus, the US is the favoured foreign location of the European assignees.

92 The need to control for the ultimate owner of the assignees was the reason why the smaller sample of 10,000 patents was used here. It would be very difficult to examine the complete sample of 97,785 patents for the purpose of this Report.

Table V.4: Share of patents by region of the assignee, region of the inventor and by sector (10,000 sample patents).

	Country of the assignee		
Country of the inventor	EU	US	Total
ALL CHEMICAL SECTORS			
EU	86.3 %	9.0 %	44.8 %
US	11.9 %	87.8 %	34.5 %
Total	98.2 %	96.8 %	79.3 %
BIOTECHNOLOGY			
EU	82.1 %	4.9 %	36.5 %
US	14.6 %	92.7 %	45.4 %
Total	96.7 %	96.6 %	81.9 %
MATERIALS			
EU	90.7 %	8.0 %	44.9 %
US	7.8 %	90.1 %	30.9 %
Total	98.5 %	98.1 %	75.8 %
ORGANIC CHEMISTRY			
EU	89.1 %	10.8 %	50.8 %
US	9.5 %	87.4 %	28.4 %
Total	98.6 %	98.2 %	79.2 %
PHARMACEUTICALS			
EU	85.0 %	11.5 %	47.3 %
US	13.3 %	86.2 %	36.0 %
Total	98.3 %	97.7 %	83.3 %
POLYMERS			
EU	85.4 %	8.3 %	40.1 %
US	12.9 %	84.6 %	33.5 %
Total	98.3 %	92.9 %	73.6 %

Source: European Patent Office (1998)

Table V.5: Share of biotechnology patents invented by Eur opean assignees in the home country, in the US and in other Eur opean countries (10,000 patents in 1987-1996)

	Country of the assignee					
	Switzerland	Germany	France	Italy	Netherlands	UK
Patents invented in the home country	30.6	76.2	81.5	73.3	70.7	76.9
Patents invented in the US	48.2	7.6	11.0	4.9	4.4	8.1
Patents invented in the other EU countries	18.4	11.2	4.2	21.8	24.8	12.8

Source: European Patent Office (1998)

Finally, there seems to be a fairly balanced interchange of research between the two continents in chemicals since the share of EPO patents by European assignees invented in the US (11.9%) is very close to that of the EPO patents by US assignees invented in Europe (9.0%).

As shown also in Table V.4 this pattern of cross-location between Europe and the US is also similar across the chemical subsectors with biotechnology being the only exception. The result that really stands out is the share of biotechnology patents by US assignees invented in Europe, which is only 4.9 %, while the share in the other direction is 14.6 %, suggesting that the US is an attractive location for biotechnology research by European assignees.

Therefore, the data do not show that European assignees perform a disproportionately large amount of biotechnology research in the US – they do almost as much biotechnology research in the US as they do in the other chemical sectors – but that Europe is not attracting similar levels of biotechnology research by US assignees. Even in pharmaceuticals, which is the closest to biotechnology, Europe attracts 11.5 % of the patents applied for by US assignees. The apparent European lack of attractiveness to US research seems to be specific to biotechnology.

Table V.5 shows the shares of biotechnology patents invented by European assignees in their home country, in the US and in European countries other than the home country. The table confirms that the assignees locate research largely in their home country, although inter–country differences exist. The most important difference is that Swiss assignees invent almost half of their biotechnology patents in the US, while assignees from all the other countries in Table V.5 (Germany, France, Italy, the Netherlands, and the UK) invent over 70 % of their biotechnology patents at home. Apart from the US, the latter countries have a sizeable share of biotechnology patents invented in other European countries and, moreover, these patents are not concentrated in the leading nations – Germany or the UK – but are spread across European countries. When Swiss multinationals are excluded from the sample, the share of biotechnology patents by European assignees invented in the US declines from 14.6 % to 11.3 %. This is closer to the similar share for the other chemical sectors presented in Table V.4.

5.1.3 Division of innovative labour and markets for technology

The ability of firms to access and make efficient use of markets for technology and networks of collaborative relations has become a crucial source of competitiveness in the new markets for technology (Arora, Fosfuri, Gambardella, 2001; Arora, Gambardella, Pammolli, Riccaboni, 2001). As a consequence, in the last 25 years, collaborations in biotechnology have increased dramatically world-wide (Science and Engineering Indicators, 2000; Orsenigo, Pammolli, Riccaboni, 2001).

The very existence of dedicated biotechnology firms (DBFs) depends on their ability to participate in networks of collaborative relations and markets for technology. Most exploit their basic competence and act primarily as research companies and specialised suppliers of high technology intermediate products, performing contract research for, and in collaboration with, established corporations in downstream sectors. Collaboration allows DBFs to survive and – in some cases – to pave the way for subsequent growth. First, collaboration with large companies clearly provides the financial resources necessary to fund R&D. Second, it provides the access to organisational capabilities in product development and marketing.

The latest generations of DBFs (and the new "stars" like Affymax, Incyte and Celera) were created on the basis of specialisation into radically different new

technologies like genomics, combinatorial chemistry, bioinformatics and what is now called "platform technologies". These technologies are essentially research tools and their developers do not aim to become producers but providers of tools and services to corporations involved in drug discovery and development. They may thus be able to sell customised services to a wider range of potential buyers.

Established companies face the opposite problem. While they need to explore, acquire and develop new knowledge, they have the experience and the structures necessary to control testing, production and marketing. Confronted with expanding innovative opportunities, no individual company, irrespective of its size, can consider originating and controlling the whole relevant knowledge on its own. Thus, participation into the network of collaboration and in markets for technology becomes a crucial ingredient for sustained technological and economic performances.

Assessing the involvement of European firms and institutions in these networks is a crucial exercise for an evaluation of the state of the European biotechnology industry.

5.1.3.1. Collaboration across assignees

A review of the multiple assignee patents shows that in biotechnology the share of patents assigned to multiple assignees is higher than in the other sectors. On the basis of the 10 000 patent sample, there are 11.2% biotechnology patents with multiple assignees against 8.9% in pharmaceuticals, 5.4 % in organic chemistry, 3.8% in polymers, and 3.1% in materials[93]. Biotechnology appears to be more open to collaborations. This is still the case when it is compared to pharmaceuticals which is technologically closer to biotechnology and is a more collaborative field (8.9 % multiple assignee patents) than the other fields in traditional chemicals. Furthermore, the evidence suggests that there are no country–specific factors that could account for this.

5.1.3.2. Collaboration among inventors

Single inventors develop only 18.3% of the sample's 97 785 chemical patents, the remaining (81.7%) are developed by two or more inventors. Hence, while there are few patents with multiple assignees, there is a great deal of collaboration among individuals. These teams of inventors are mostly national. Overall, 90.8 % of the patents in the sample developed by multiple inventors refer to inventors from the same country.

To review further the question of the nature and characteristics of research teams in biotechnology patents a sub–sample of 4 649 patents from the EPO sample of 10 000 patents was selected on the basis of their having at least one inventor located in Europe. The focus on inventions carried out in Europe is related to the finding that Europe does not appear to be a very attractive location for biotechnology research. It is therefore interesting to understand in greater depth the characteristics of the research located in there.

The data show that single inventors develop 788 patents (16.9 %) and multiple inventors the remaining (83.1 %). Furthermore, there is no major difference across countries or sectors in the size of the research team.

Table V.6 reports the average number of supplementary classes of these patents. Again, this is broken down by sectors and by some leading countries. This table shows that the biotechnology patents by US assignees that were invented in Europe have a significantly higher degree of interdisciplinarity compared to the biotechnology patents by the other countries in the table (Germany, France and the UK). This suggests that the US assignees in Europe patent research outputs with a greater degree of generality compared to the others. The difference is particularly striking with Germany. The average number of IPC classes in German biotechnology patents invented in Europe is 1.8, compared to 2.7 for the US. The figures for France and the UK are respectively 2.4 and 2.5.

The greater interdisciplinarity of the US biotechnology patents might reflect the fact that, for US assignees, patents in Europe are inventions patented abroad. Since patenting abroad is more costly, one may patent abroad only the more important patents, which are likely to be the more interdisciplinary ones. But Table V.6 shows that in biotechnology the US patents are relatively more interdisciplinary compared to other countries than are the US patents in the other sectors. For example, even in pharmaceuticals, which is the sector closest to biotechnology, the average number of IPC classes of the US patents is 1.2 as against 1.7 for Germany, 1.2 for France, and 1.5 for the UK. This suggests that US biotechnology patents

93 Overall in our sample of 10,000 patents, the shae of single assignees is 93.2%, for the same as in the 97,785 sample. This is suggestive of the comparability of the statistics computed by using either of the two samples. In this case, we are using the 10,000 sample because, as we shall see below , we need to use the information on the countr y of origins of the ultimate par ent of the assi - gnees.

Table V.6: Mean number of supplementary classes by patent. Inter-country (country of the assignee) and inter-sectoral differences

Sectors	Germany	France	UK	US	TOTAL
Biotechnology	1.8 (0.17)	2.5 (0.18)	2.4 (0.18)	2.7 (0.3)	2.1 (0.08)
Materials	1.02 (0.19)	1.2 (0.31)	1.5 (0.38)	1.5 (0.54)	1.3 (0.13)
Organic chemistry	2.4 (0.07)	2.4 (0.13)	2.7 (0.15)	2.9 (0.21)	2.5 (0.05)
Pharmaceuticals	1.7 (0.09)	1.2 (0.13)	1.5 (0.14)	1.2 (0.2)	1.6 (0.06)
Polymers	1.8 (0.09)	1.5 (0.19)	1.7 (0.23)	1.6 (0.26)	1.7 (0.07)
Average by country	2.0 (0.05)	1.8 (0.09)	2.0 (0.09)	2.3 (0.12)	2.0 (0.03)

Note: Standard errors in parentheses.

Source: Our elaboration from the EPO data.

invented in Europe may indeed be broader on average. Trajtenberg (1990) suggests that more general patents are also more cited, and they are more valuable. If so, this would indicate that US biotechnology research in Europe play a beneficial role, as US assignees are likely to perform research that leads to more valuable inventions than European assignees.

Finally, there is evidence that large firms are less involved in interdisciplinary biotechnology. This is consistent with the existing literature about this industry, which has stressed that competencies for producing innovations with greater breadth (and value) are often associated with smaller academic labs or smaller research-intensive firms (e.g. see Gambardella, 1995). In other words, it is the quality of the team rather than the size of the organisation that matters in this case. Moreover, biotechnology appears to be a more internationalised research process and this is consistent with the view that, as a modern science-based industry, its knowledge foundations are being developed in different areas on rather "global" basis.

5.1.3.3. Networks of collaborative relations

Table V.7 shows the nationality of origin and development of collaborative agreements (CA) in biotechnology for selected years. A crucial difference between Europe and the US becomes immediately apparent. The overwhelming majority of the biotechnology collaborative projects originate (70.07%) and are developed (66.12%) in the US. However, European biotechnology organisations have gradually increased their role both as originators (from about 14% in 1990-94 to 20% in 1998-00) and as developers (from 12.46 to 21.61%) of new projects.

In the second half of the 1990s, the number of DBFs rose in Europe but remained substantially unchanged in the US. However, European DBFs are still not as active in the networks of division of innovative labour. Age is not the only factor underlying the lower participation of European DBFs in markets for technology. The background study contends that the following structural differences between Europe and the US may affect the collaborative capabilities of DBFs.

- American DBFs develop a larger share of projects originated by domestic public research organisations (PROs) and DBFs and by European DBFs than their European counterparts. In Europe, DBFs tend to be replaced as developers by established companies. Interestingly enough, the only exception is for projects originated by European PROs, which are developed mainly by co-localised DBFs or by European PROs.

Table V.7: Number of organisations and number of originated and developed collaborative agreements (CAs), by nationality.

Nationality	Total	Number of Organizations						Number of CAs as Originators		Number of CAs as Originators	
		EFs		DBFs		PROs					
		No.	%	No.	%	No.	%	No.	%	No.	%
1990-1994											
EU15	112	41	36.61	36	32.14	35	31.25	274	14.05	243	12.46
US	496	154	31.05	241	48.59	101	20.36	1 463	75.03	1 459	74.82
Japan	25	23	92.00	1	4.00	1	4.00	65	3.33	84	4.31
Other	93	31	33.33	36	38.71	26	27.96	148	7.59	164	8.41
Total	726	249	34.30	314	43.25	163	22.45	1 950	100.00	1 950	100.00
1995-1997											
EU15	226	89	39.38	95	42.04	42	18.58	510	17.90	553	19.41
US	652	196	30.06	338	51.84	118	18.10	1 989	69.81	1 830	64.23
Japan	47	41	87.23	6	12.77	0	0.00	61	2.14	173	6.07
Other	195	59	30.26	73	37.44	63	32.31	289	10.14	293	10.28
Total	1 120	385	34.38	512	45.71	223	19.91	2 849	100.00	2 849	100.00
1998-2000											
EU15	447	117	26.17	223	49.89	107	23.94	838	20.19	897	21.61
US	1 124	334	29.72	587	52.22	203	18.06	2 819	67.91	2 629	63.33
Japan	81	64	79.01	8	9.88	9	11.11	119	2.87	212	5.11
Others*	313	78	24.92	151	48.24	84	26.84	375	9.03	413	9.95
Total	1 965	593	30.18	969	49.31	403	20.51	4 151	100.00	4 151	100.00
1990-2000											
EU15	785	247	31.46	354	45.10	184	23.44	1 622	18.12	1 693	18.92
US	2 272	684	30.11	1 166	51.32	422	18.57	6 271	70.07	5 918	66.12
Japan	153	128	83.66	15	9.80	10	6.54	245	2.74	469	5.24
Others*	601	168	27.95	260	43.26	173	28.79	812	9.07	870	9.72
Total	3 811	1 227	32.20	1 795	47.10	789	20.70	8 950	100.00	8 950	100.00

Note: *Argentina, Australia, Bermuda, Brazil, Canada, China, Costa Rica, Croatia, Cuba, Czech Republic, Egypt, Hong Kong, Hungary, Iceland, India, Indonesia, Israel, Malaysia, Mexico, New Zealand, Norway, Philippines, Poland, Puerto Rico, Russia, Singapore, Slovenia, South Africa, South Korea, Switzerland, Taiwan, Thailand, Yugoslavia.
EFs: established firms; DBFs: dedicated biotechnology firms; PROs: public research organisations

Source: BID, University of Siena.

• European PROs increased their relationships with both European and American DBFs in the period 1996-2000. On the contrary, US-based PROs collaborate more and more directly with established companies and act more frequently as developers of projects originated by DBFs. In general, universities and research institutes increasingly reach out and collaborate with delocalised partners both as originators and as developers. European DBFs do not seem to be able to attract US established pharmaceutical companies as developers of projects originated in Europe, and they turn in preference to European partners.

• Only a minority of European DBFs in Europe participates as developers in collaborative projects originated by other organisations. Established companies have the lion's share of bio-pharmaceutical products in Europe.

• European companies tend to access markets for technologies later on during product development (clinical research and marketing), while they are less active in the early stages of research. Product innovation in therapeutic biotechnology is highly dependent on both the originator and developer capabilities of US companies. European DBFs, still young and small, do not take part in the division of innovative labour in product development, particularly with American PROs and established companies.

• Finally, PROs in Europe tend to be focused on the generation of new research opportunities, while they tend to be absent from the downstream stages of product development.

5.2. Characteristics of the new European biotechnology industry

It was suggested in the previous section that European biotechnology is lagging significantly behind the US. However, encouraging signals related mainly to the good performance of some small (mainly northern) European nations and to a recent impressive increase in the number of DBFs was also stressed. This section examines the characteristics of European DBFs.

DBFs are widely considered to be the most efficient available organisational solution for the development of innovative activities in biotechnology:

• First, DBFs are fundamental organisational devices for exploring an enormous, quickly expanding and incredibly complex space of new innovative opportunities.

• Second, they perform a crucial function of transforming fundamental scientific knowledge into technological and commercially valuable knowledge. They intermediate in the transfer of knowledge from universities to established large corporations which cannot be always at the forefront of scientific discovery but which have the downstream capabilities needed for commercialisation (Orsenigo, 1989; Henderson, Orsenigo and Pisano, 1999).

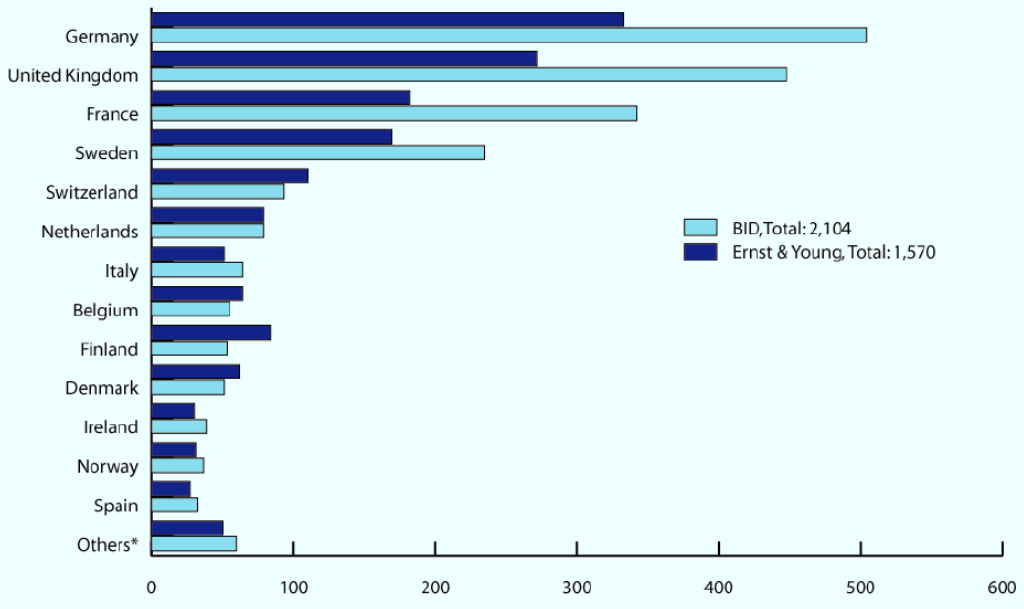
• Third, DBFs promote and are crucial agents in the process of division of labour in innovative activities that emerges in response to the increasingly codified and abstract nature of the knowledge bases on which innovations draw (Arora, Gambardella, 1994; Gambardella,1995).

5.2.1. The structure of the industry

This section uses data from the Biotechnology Information Databank (BID), maintained at the University of Siena, which includes 3669 organisations active in biotechnology. Among them, there are 2092 independent dedicated biotechnology firms (DBFs). More specifically, there are 1730 core biotechnology firms (according to the OECD classification) and 362 specialised suppliers. Detailed data for each of these have been collected.

Graph V.5 shows the number of independent dedicated biotechnology firms in major European countries at the end of year 2000. The data do not consider public research organisations, or companies whose

Graph V.5: Number of independent DBFs (December 2000)



Note: *Others: Austria, Czech Republic, Estonia, Hungary, Iceland, Lithuania, Luxembourg, Poland, Portugal, Romania, Russia, Slovakia.

Source: BID, University of Siena.

main activities are in fields other than biotechnology or biotechnology divisions of larger firms. They represent the 'inner core' of the European national systems of innovation in biotechnology. According to the data collected in BID, Germany leads the league with more than 500 small independent dedicated biotechnology firms (DBFs), followed closely by the UK. Taken together, Germany and the UK account for about one half of the total number of DBFs in Europe registered in the database. France ranks third with 343 biotechnology companies, followed by Sweden.

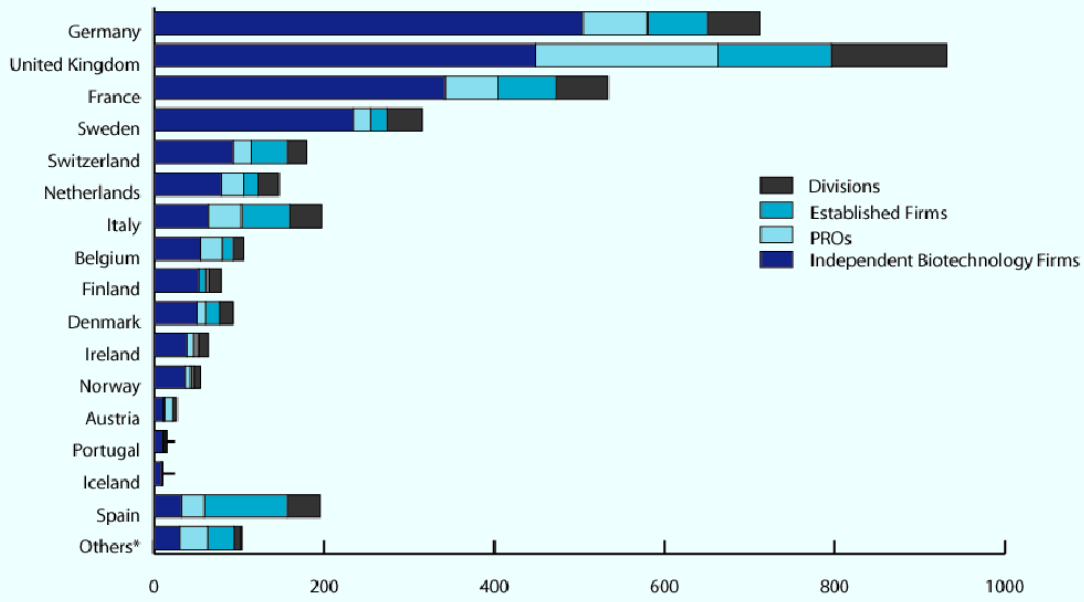
If one calibrates the number of DBFs using population or GDP numbers, a clear representation emerges, with Sweden ranked first according to both measures, followed by Switzerland, Ireland, Finland, and Denmark. The UK, Germany and France have similar values, while Italy and Spain have the lowest ratios.

Graph V.6 shows the European biotechnology innovation and production systems in terms of the types of active organisations. There are important differences in the composition of the industry across European countries. In particular, the UK differs from Germany, both because of the high number of divisions of companies focused on biotechnology and because of the higher number of large firms. Moreover, in the UK one observes a higher number of non-industrial research institutes in the fields of molecular biology and biotechnology. In Italy and Spain the number of DBFs is particularly low when compared to the number of large firms or of divisions of large firms.

Graph V.7 shows the distribution of currently existing European DBFs by year of foundation. Peak years of entry were 1997 and 1998. In 1999 and 2000, after a 4–year period of intense entry, in which the overall number of EU biotechnology firms almost doubled, the rates of company formation decreased. This slowdown is not corroborated by the Ernst & Young data. If it were confirmed, it could be similar in nature to the one observed in the US at the beginning of the Nineties and it could prefigure a period of stabilisation, consolidation, and selection, with mergers, acquisitions, and exit offsetting new company formation. As a consequence, the impact of intense entry on the long–term evolution of the industry is not known, and the industry seems to be far from any equilibrium configuration.

Table V.8 shows the distribution of currently existing dedicated biotechnology companies in Europe, by cohorts of entrants. It is clear that there are important differences in terms of the generational composition

Graph V.6: Number of organisations active in biotechnology by type (December 2000)



Note: *Others: Czech Republic, Estonia, Hungary, Lithuania, Luxembourg, Poland, Romania, Russia, and Slovakia.

Source: BID, University of Siena

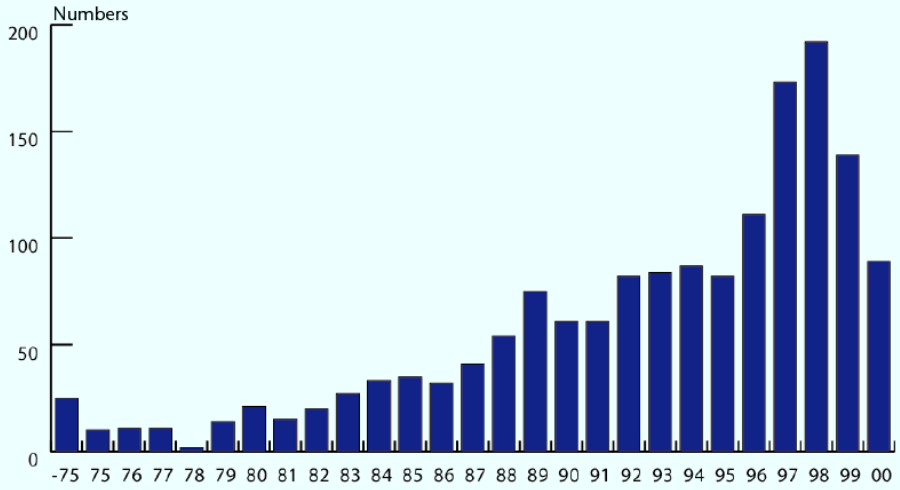
of DBFs in major European countries. Nordic countries like Sweden have experienced a relatively stable pace of entry of new firms, while in other countries, particularly Germany, the upsurge of the number of new firms has occurred in the last five years. At present, Germany accounts for a third of the total number of new European firms (i.e. those which entered the industry after 1995), followed by UK and France. The three countries, taken together, account for more than three quarters of the new biotechnology firms that entered the industry between 1996 and 2000.

Graph V.8 shows the size distribution of European DBFs, in December 2000, divided into classes according to the number of employees. As is evident, most European DBFs are either micro or small research–intensive firms. Only approximately 10 per cent of active European DBFs have more than 50 employees, while the majority (about 57 %) has less than 20 employees[94]. It is worth noting that despite general similarities in the shape of business size distributions, European national systems of innovation in biotechnology rely on quite different mixtures of small and medium biotechnology companies. Surprisingly enough, when compared to general figures about business firm size in manufacturing, the size of French DBFs is well above the mean for EU–15, while the opposite is true for Sweden. Moreover, while UK and Germany look similar in terms of shares of micro business units in the total number of firms active in biotechnology, Germany has a higher proportion of firms in the middle size range (10 to 50 employees), compared to the UK, which relies upon a higher number of medium and large DBFs.

The sustained flow of entry shown in Graph V.7 has changed the relative importance of agri–food and pharmaceuticals as areas of application. The share of new DBFs that entered the agri–food industries declined from 1995, from about 15 % to less than 5 % in the year 2000; this fall is likely to reflect regulatory factors and growing public opposition to genetically-modified crops. During this time, the number of dedi-

94 Presumably, the real number of small biotechnology companies is even higher. In particular, some of the youngest firms have barely enough people to run early-stage research activities, not revealing themselves through alliances, venture capitalist, company Internet sites, participation in public programs, surveys, directories and the like. Moreover, the BID also includes about 40 virtual companies (0 employees), concentrated mainly in Sweden. Virtual companies have been excluded from the analyses discussed in this chapter.

Graph V.7: European dedicated biotechnology firms: Distribution by year of foundation (firms per year)



Source: BID, University of Siena.

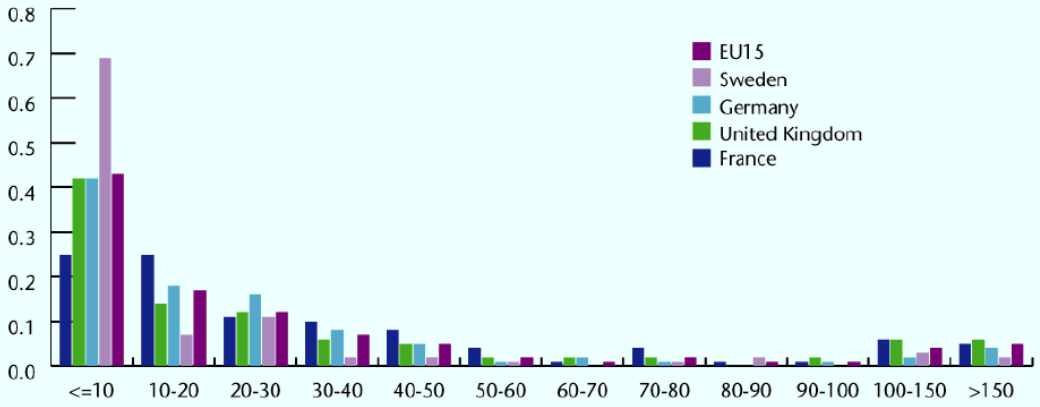
Table V.8: European dedicated biotechnology firms: distribution by cohorts of entrants

	EU15		United Kingdom		Germany		France		Sweden		Others*	
	No.	%	No.	%	No	%	No.	%	No.	%	No.	%
below 91	600	31.09	147	32.81	102	20.24	112	32.18	89	37.87	150	37.97
91-95	487	25.23	113	25.22	114	22.62	86	24.71	61	25.96	113	28.61
above 95	843	43.68	188	41.96	288	57.14	150	43.10	85	36.17	132	33.42
Total	1930	100.00	448	100.00	504	100.00	348	100.00	235	100.00	395	100.00

Note: *Others: Austria, Belgium, Denmark, Finland, Ireland, Italy, Luxembourg, Netherlands, Portugal, and Spain

Source: BID, University of Siena.

Graph V.8: European Dedicated Biotechnology Firms: distribution of employment by size class



Source: BID, University of Siena

Table V.9: European Dedicated Biotechnology Firms: distribution by areas of activity

Country	Therapeutics		Diagnostics		Agriculture		Food		Veterinary		Environnent		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
EU 15	809	40.03	415	20.53	282	13.95	228	11.28	137	6.78	150	7.42	2021	93.35
Germany	221	44.56	123	24.80	63	12.70	35	7.06	27	5.44	27	5.44	496	22.91
United Kingdom	185	39.36	96	20.43	55	11.70	45	9.57	31	6.60	58	12.34	470	21.71
France	150	35.05	68	15.89	77	17.99	73	17.06	39	9.11	21	4.91	428	19.77
Sweden	79	48.77	22	13.58	21	12.96	10	6.17	17	10.49	13	8.02	162	7.48
Switzerland	35	53.85	14	21.54	9	13.85	4	6.15	3	4.62	0	0.00	65	3.00
Italy	37	34.58	22	20.56	18	16.82	19	17.76	3	2.80	8	7.48	107	4.94
Others[4]	30	37.97	16	20.25	4	5.06	14	17.72	10	12.66	5	6.33	79	3.65
Total	874	40.37	445	20.55	295	13.63	246	11.36	150	6.93	155	7.16	2165	

Note: Other: Czech Republic, Estonia, Hungary, Iceland, Lithuania, Norway, Poland, Portugal, Romania, Russia, and Slovakia.

Source: BID, University of Siena.

cated biopharmaceutical companies rose from 35 % to more than 50 % of the total number of new firms. Thus, the dramatic increase in the number of European DBFs from 1996 to 2000 reflects, to a large extent, the entry of new DBFs that entered the industry to exploit the therapeutic application of genomics and new techniques, such as combinatorial chemistry and bio-informatics, which can be used to improve and speed up the development of new therapeutic treatments.

Table V.9 summarises the technological profiles of EU DBFs according to broad areas of interest in biology, chemistry and medicine. It shows the existence of differences among European countries concerning the areas of specialisation of national DBFs in main fields of application.

German biotechnology companies are active mainly in human health care (therapeutics and diagnostics), Swedish firms concentrate on human and animal therapeutics, while France, Italy, and Switzerland have a higher proportion of companies active in agri-food. A large proportion of French and German DBFs entered the industry, both in pharmaceuticals and agri-food, to explore the commercial value of recent technological advances at the lowest levels of the organisation of the living organisms in genomics, proteomics and bioinformatics. The UK keeps a strong technological basis in cell and tissue engineering, process biotechnology, instrumentation, and devices. Moreover, new UK DBFs are more active in combinatorial chemistry and in other general–purpose research techniques applied to drug discovery and development. Italy's specialisation is in targeting sub–cellular organisms, while Swedish companies tend to focus mainly on manufacturing of biomaterials and on innovative technologies in drug discovery, such as combinatorial chemistry and chiral synthesis.

Table V.10: European Dedicated Biotechnology Firms: distribution by technological field

Country	Cell and Tissue Culture and Engineering		Subcellular Organisms		DNA		Proteins and Molecules		Process Bio-technology		Chemical Synthesis[1]		Bio-informatics		Other Devices[2]		Analysis[3]		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
EU 15	436	18.72	189	8.12	349	14.98	504	21.64	218	9.36	177	7.60	126	5.41	233	10.00	97	4.16	2329	92.53
Germany	93	14.03	60	9.05	114	17.19	170	25.64	38	5.73	62	9.35	44	6.64	50	7.54	32	4.83	663	26.34
United Kingdom	117	22.90	30	5.87	60	11.74	87	17.03	53	10.37	34	6.65	25	4.89	88	17.22	17	3.33	511	20.30
France	82	16.94	41	8.47	85	17.56	107	22.11	61	12.60	36	7.44	30	6.20	24	4.96	18	3.72	484	19.23
Sweden	47	26.26	7	3.91	20	11.17	24	13.41	14	7.82	20	11.17	12	6.70	19	10.61	16	8.94	179	7.11
Switzerland	25	22.32	5	4.46	11	9.82	17	15.18	11	9.82	4	3.57	7	6.25	27	24.11	5	4.46	112	4.45
Italy	24	21.24	16	14.16	13	11.50	18	15.93	16	14.16	8	7.08	3	2.65	14	12.39	1	0.88	113	4.49
Other[4]	16	21.05	4	5.26	13	17.11	19	25.00	8	10.53	4	5.26	5	6.58	5	6.58	2	2.63	76	3.02
Total	477	18.95	198	7.87	373	14.82	540	21.45	237	9.42	185	7.35	138	5.48	265	10.53	104	4.13	2517	

Notes:
1. Chemical Synthesis: Includes Combinatorial Chemistry, Chiral Chemistry, Molecular Synthesis.
2. Other Devices: Includes Medical Equipment, PCR.
3. Analysis: Environmental and Agri-Food Test.
4. Other: Czech Republic, Estonia, Hungary, Iceland, Lithuania, Norway, Poland, Portugal, Romania, Russia, Slovakia.

Source: BID, University of Siena.

Finally, Table V.10 shows the extent to which biotechnology applications and research technologies are integrated at the firm level in key European countries. French and British companies have the highest degree of integration between technologies and applications. The higher level of integration of UK firms could well reflect a difference in the composition of industry in terms of cohorts of entrants, since the UK has a higher fraction of early entrant DBFs, which had sufficient time to implement their technologies in specific domains of application.Conversely, German firms and a significant fraction of Swedish firms, in particular, tend to be vertically specialised either in terms of technologies or domains of application.

5.3. Geographical clusters in European biotechnology

5.3.1. Clustering

IIn the US, biotechnology has been characterised, historically, by a relatively high concentration of firms, employment and activities in a restricted number of regions, mainly in San Diego, the Bay Area, Boston, Seattle, New Jersey, the New York metropolitan area and the Houston area in Texas. Based on this, economists, analysts and policy–makers have argued that spatial concentration of innovative and industrial activities is fundamental for successful development of biotechnology. To this effect, policies have been devised (e.g. the German BioRegio Program) with the explicit aim of supporting not so much the birth of new DBFs but rather the development of clusters of biotechnology activities.

Why is such concentration observed? As this is fundamentally a science-based technology, involving abstract and codified knowledge, it should in principle be available to everybody. What forces lead to the agglomeration of biotechnology activities in specific clusters? Different explanations have been suggested.

• The (partially) tacit nature of knowledge means that personal contacts, imitation and frequent interactions are necessary for knowledge transmission. These are clearly possible at lower cost for firms located within the same city or region. The transmission of tacit knowledge requires mutual trust, a sharing of language and culture and intense non-business relations are aspects which are made easier by co-location.

• Discoveries in this technological area are characterised by high degrees of natural excludability, i.e. techniques for their replication are not widely known and anyone wishing to build on new knowledge must gain access to the research team or laboratory setting having that know–how. In these circumstances, inventor–scientists tend to enter into contractual arrangements with existing firms or start their own firm in order to extract the supranormal returns from the fruits of their intellectual contribution. And they

tend to do so within commuting distance off their laboratories.

• However, empirical evidence suggests that there might be a threshold effect: local sources of knowledge are key in determining success in the development of new products and processes only in areas with a large accumulation of knowledge (Silicon Valley). Innovations by firms located in other areas depend on distant relationships with universities and other high–technology firms (suppliers and customers) located elsewhere, especially in urban centres.

Trying to draw some conclusions from this discussion, it would appear that clustering might be the outcome of different factors, but mainly:

– the existence of a strong critical mass of scientific knowledge, in absolute terms: in other words, excellence in scientific research is a basic precondition for attracting innovative activities. Where this is lacking, firms (incumbents and/or prospective entrepreneurs) might look for other locations for tapping the relevant knowledge. Moreover, diversity is also important. Insofar as innovation rests on the integration of different fragments of knowledge, the presence of a diversified scientific base becomes a key issue.

– The existence of a strong and diversified industrial base, with accumulated capabilities and organisational structures enabling them to actually participate in the network of cognitive and social relationships that are necessary to get access to, absorb and integrate the new knowledge and, on these bases, to engage in successful innovative activities.

– The existence of specific and often formal organisational devices (including markets for know-how) that allow flows of knowledge to take place.

5.3.2. Geographical concentration of biotechnology in Europe: Evidence from patent data

Table V.11 shows the regional distribution of the 4 649 patents invented in Europe from our sample of 10 000 chemical patents and lists the top 20 among the 146 European regions[95].

The top 20 regions (13.7 % of the total number of regions) account for 77.5 % of the sample of chemical patents invented in Europe. The top 10 regions (6.8 % of the total) host 59.5 % of these patents. The distribution of chemical patents across European regions is highly concentrated[96].

There are many German regions among the top 20, ranging from five in biotechnology to nine in pharmaceuticals. This is consistent with the well–known leadership of Germany in chemicals, although the smaller number of German regions among the top 20 regions in biotechnology confirms earlier remarks about its lower specialisation in this field. Other studies show that, in general, many of the most innovative European regions are in Germany (Paci and Usai, 1998). Overall, 52 % of the patents invented in the top 20 regions were invented in Germany, followed by France (with 13.8 % of the patents in the top 20 regions), the UK (13.8 %), the Netherlands (5.3 %) and Italy (4.6 %).

Although the data in Table V.11 show that patenting concentrates geographically in all five chemical branches, biotechnology shows the least geographic concentration. In the sample, the top 20 regions account for 68.6 % of the biotechnology patents invented in Europe. There are some regions that appear in all five listings in the top 20 positions. These are South–East England, Île de France, Bayern, Hessen, West-Netherland, Nordrhein-Westfalen, Baden-Württemberg, Vlaams Gewest and Rhône-Alpes. There are other regions, such as Rheinland-Pfalz and Sachsen, which are in the top 20 in all the chemical sectors, except in biotechnology

There are also regions that are ranked in the top 20 in biotechnology, but that are not among the top 20 in any of the other four chemical fields. This suggests a peculiarity of biotechnology within the overall chemical sector, and in particular that biotechnology is a technology which facilitates the entry of new actors. Specifically, it is opening up opportunities for regions that have not been active in developing innovations in the traditional branches of the chemical sector, including pharmaceuticals. The new regions in our top 20 for biotechnology are Københavns in Denmark, Uusimaa in Finland, Stockholm in Sweden, and the area around Madrid in Spain. This suggests that biotechnology offers opportunities for new entries in technologically dynamic fields.

5.3.3. Clusters of biotechnology activities in Europe

Data on firms and research centres in the BID database permit identification of the principal biotechnology clusters in Europe. These are presented in the

95 Based on the Eurostat classification at the NUTS1 and NUTS2 level.
96 Paci and Usi (1998) and Caniels (1999) report similar results for total patenting activity in Europe.

Table V.11: Distribution of patents acr oss European regions (region of the inventor): cumulative frequencies and Herfindahl index, top 20 r egions (10 000 patent sample in 1987-1996)

Biotechnology		Materials		Organic chemicals		Pharmaceuticals		Polymers	
Regions	Cum. Freq.	Regions	Cum. Freq.	Regions	Cum. Freq.	Regions	Cum. Freq.	Regions	Cum. Freq.
South East Engl. (UK)	8.6	Nordrhein-Westfalen (D)	14.3	Nordrhein-Westfalen (D)	15.3	Nordrhein-Westfalen (D)	12.9	Nordrhein-Westfalen (D)	20.8
Ile de France (F)	15.9	Hessen (D)	22.3	Hessen (D)	24.9	Ile de France (F)	23.7	Rheinland-Pfalz (D)	33.9
Bayern (D)	21.5	Ile de France (F)	29.0	Rheinland-Pfalz (D)	34.4	South East Engl. (UK)	31.5	Hessen (D)	40.5
Hessen (D)	26.9	Rheinland-Pfalz (D)	34.4	Switzerland	42.2	Hessen (D)	37.0	Switzerland	44.2
West-Nederland (NL)	31.5	West-Nederland (NL)	39.3	South East Engl. (UK)	49.5	North West Eng. (UK)	41.7	Rhône-Alpes (F)	47.9
Switzerland	35.6	North West Eng. (UK)	43.8	Ile de France (F)	55.7	Switzerland	46.2	Lombardia (I)	51.5
Eastern (UK)	39.5	Vlaams Gewest (B)	47.8	Lombardia (I)	59.8	Lombardia (I)	50.5	Ile de Fance (F)	54.8
Nordrhein-Westfalen (D)	42.9	Baden-Württemberg (D)	51.8	Sachsen-Anhalt (D)	62.6	Rheinland-Pfalz (D)	54.6	Sachsen (D)	57.6
Københavns amt (DK)	46.2	Sachsen (D)	55.4	Rhône-Alpes (F)	65.5	West-Nederland (NL)	57.7	West-Nederland (NL)	60.4
Baden-Württemberg (D)	49.2	Zuid-Nederland (NL)	58.5	Sachsen (D)	68.2	Baden-Württemberg (D)	60.4	Zuid-Nederland (NL)	62.9
Niedersachsen (D)	52.0	North East Eng. (UK)	61.6	Baden-Württemberg (D)	70.9	Sachsen-Anhalt (D)	62.7	Sachsen-Anhalt (D)	65.4
Vlaams Gewest (B)	54.5	Bayern (D)	64.3	Bayern (D)	73.0	Bayern (D)	65.1	North West Eng. (UK)	67.9
Ostösterreich (A)	56.6	Niedersachsen (D)	67.0	West-Nederland (NL)	75.1	Berlin (D)	67.3	Vlaams Gewest (B)	70.1
Rhône-Alpes (F)	58.6	Sachsen-Anhalt (D)	69.2	Vlaams Gewest (B)	77.2	Vlaams Gewest (B)	69.3	Bayern (D)	72.3
Berlin (D)	60.4	Rhône-Alpes (F)	71.4	Sachsen (D)	78.7	Eastern (UK)	71.2	Région Wallonne (B)	74.4
Lombardia (I)	62.2	South East Engl. (UK)	73.7	Alsace (F)	80.2	Lazio (I)	73.0	Emilia-Romagna (I)	76.4
Alsace (F)	63.8	Ostösterreich (A)	75.0	Eastern Eng. (UK)	81.5	F Rhône-Alpes	74.7	Baden-Württemberg (D)	78.3
Uusimaa (FIN)	65.5	Bruxelles (B)	76.3	Berlin (D)	82.9	Hamburg (D)	75.9	South East Engl. (UK)	80.1
Stockholm (S)	67.1	Région Wallonne (B)	77.7	Scotland (UK)	83.9	North East Eng. (UK)	77.1	Niedersachsen (D)	81.5
Comunidad de Madrid (E)	68.6	Haute-Normandie (F)	79.0	Cataluña (E)	84.7	Sachsen (D)	78.2	Bruxelles (B)	82.9
Herfindahl index	0.03		0.05		0.07		0.05		0.08

Source: Commission services.

detailed Annex Graphs V.1 to V.6. The data show that a process of clustering is taking place in Europe where a small number of local clusters are capturing a dominant majority of biotechnology firms and of public research organisations.

Some of these clusters (i.e. Oxford, Cambridge, Munich and Stockholm) are older and can rely upon sound research background and high international reputation, coupled with a critical mass of both young and established spin–off companies and international contacts. Other biotechnology clusters – the Medicon Valley between Copenhagen and Lund, the German bio-regions of Rhine/Neckar and Rhineland, and French districts – are younger. They took off during the 1990s, mainly thanks to a supportive policy environment, availability of public and private finance, new infrastructures, the presence of large companies active in related downstream industries and institutes of research in biomolecular biology, biomedical sciences and biochemistry. Biotechnology activities in Germany, UK, France, Sweden and Switzerland are concentrated in a handful of clusters. Apparently, most of the factors that contribute to the growth of the national systems of innovation and production in biotechnology are local in nature. Annex Graphs V.1 to V.5 provide a descriptive atlas of biotechnology regions in Europe.

• In the UK, British DBFs are clustered in East Anglia (Cambridge), south-east England (Oxfordshire, Greater London, Surrey), and Central Scotland – see Annex Graph V.2. In particular, most of the activities around the Oxford and Cambridge campuses as well as within the City of London are to be found within a radius of 10 kilometres. In addition to the university, Oxford includes other prestigious research organisations and hospitals (John Radcliffe Hospital, AEA Technology, MRC Radiobiology Institute, and Wellcome Trust Human Genetics Center). Also, a number of well-known Oxford spin–offs are located along the A34 corridor from Oxford to Didcot (i.e. Oxford GlycoSciences, Oxford Asymmetry, Powderject Pharmaceuticals).

• Around the university campus in Cambridge are located other leading institutes (Laboratory of Molecular Biology, the Babraham Institute, the Sanger Centre, and the European Bioinformatics Institute) as well as 27% of UK DBFs with a large variety of technological and business profiles.

• A large variety of actors – public research organisations (Imperial College, Medical Research Council, University College), research hospitals (Guy's and St Thomas' Hospital), venture capitalists, headquarters of the main pharmaceutical and chemical enterprises and new biotechnology firms – are located in London

• On 20 November 1996, the German Federal Ministry for Education, Science, Research and Technology announced the three winners of the BioRegio contest. Munich, Rhine/Neckar and Rhineland received an extra DM 50 million of federal funding over the next five years and at least the same amount from industry. Also as a consequence of this program, German DBFs tend to be located in Bayern, Baden–Württenberg, Rheinland-Pfalz, Nordrhein–Westfalen, and Berlin (see Annex Graph V.3). Many of the new DBFs benefited from the BioRegio program and located their activities close to leading institutes of research. The key Swiss clusters are Basel and Zurich. All these clusters emerged in the last five years, thanks to both strong public and private support and world–class local research institutes, particularly in small molecule discovery and computational chemistry.

• Annex Graph V.4 shows the high concentration of French biotechnology firms in Paris, the second largest cluster in terms of number of DBFs in Europe after Cambridge (Mytehlka, Pellegrin, 2001). According to BID data, about 30 % of French biotechnology firms are located in Paris trailed by a group of French regions (Alsace, Rhone–Alpes, Midi Pyrennees, Auvergne, Bretagne and Aquitaine) that have been catching up in the last five years (see France Biotech, 2000). Here again, in a 10 km2 area one can find a heterogeneous set of both public and private biotechnology organisations.

• Finally, Annex Graph V.5 shows two large Nordic clusters. The Novum Biopark in Stockholm is closely related to the Karolinska Institute Complex, which has a long tradition of excellence in medical and biological fields. The southern one is called Medicon Valley and grew up between Copenhagen and Lund–Malmö, especially after the construction of the bridge between Denmark and Sweden. Almost all biotechnology firms in Sweden are located in four major regions: Stockholm-Uppsala, Skåne - which is the southern region including Lund and Malmö-Gothenburg and Umeå (Vinnova, 2000), while in Denmark they are highly concentrated in the Sjælland Island.

• Other fast-growing clusters are in Finland (Helsinki, Turku, Tampere, Kuopio, Oulu), in the Netherlands (Zuid-Holland Region) and in Lombardia (Milan).

This data review suggests two remarks. First, clustering would seem to be strongly related to the presence of heterogeneous and interconnected prestigious research institutions. And, secondly, the main clusters are not simply characterised by dense internal or local relations, but also by the ability to establish strong and varied external ties with other clusters.

European clusters such as Cambridge, Oxford and Karolinska show a remarkable degree of organisational heterogeneity and internal interconnectivity, comparable to that which characterises the most important clusters in the US. The Swedish collaborative network presented in Annex Graph V.6 shows the central role of the Karolinska complex (Karolinska Institute and KaroBio) in the middle between the Astra and Pharmacia stars of international contacts. The most important cluster of Swedish biotechnology firms around Karolinska is brought into closer connection by diverse organisations located outside Sweden. The density of the Swedish national innovation network is greatly increased by the inclusion of diverse organisations from other geographical locations. Moreover, the Swedish picture emphasises the central role that small science–based firms can play in reaching out to other areas.
This model suggests that successful systems of innovation in biotechnology appear to grow from "old" regional clusters, developed around the strength of scientific expertise, the integrative capabilities of established pharmaceutical companies, and the dynamic role of small firms. These clusters have become over time both internally denser and much more outward–oriented.

In the second model of EU clusters (many French and Germans regions) networking is not yet developed to the same extent. They seem to lack interdisciplinary teams and the connections across stages of the R&D process that dense webs of local relations among hospitals, university labs and firms make possible. These difficulties, together with the centralisation and bureaucratisation of some of the relevant evaluation and selection processes, could constitute an inherent element of fragility for some of the younger clusters in continental Europe.

The tendency towards clustering is accompanied by a parallel process of increasing openness of the original clusters, a process also noted in the US. Recent trends suggest a combination of an increasing number of collaborations and a decreasing proportion of local connections (Owen-Smith, Riccaboni, Pammolli, Powell, 2001).

5.4. Institutional factors affecting Europe's industrial competitiveness in biotechnology

The commercial development of European biotechnology, as already indicated previously, is lagging significantly behind the US. Despite encouraging signs of dynamism – especially by the small Northern European countries – and a wave of entries of new DBFs – especially in Germany – innovative activities remain far below US levels. European companies make significant use of American research while US firms do not seem to make as much use of European research. The new European DBFs are much smaller than their American counterparts, much less active in the global network of collaborative relations and in the markets for technology, and mainly present in platform technologies.

One explanation for this may be that US firms enjoy first–mover advantages. In technologies where innovative activities are often characterised by increasing returns, first–mover advantages are an important phenomenon and are likely to provide long–lasting and difficult-to-erode leadership. European DBFs may have simply been pre-empted by their American counterparts, while the excellence of the American scientific research system has attracted financial and human resources from all parts of the world, further strengthening the US leadership in biotechnology. However, other variables have likely played a role. With biotechnology being fundamentally science–based and characterised by rapid innovation, it is possible that, at least partially, first–mover advantages may not be sustainable. Under these circumstances, catching–up and forging ahead – at the firm and country level – might be possible.

This section reviews some major institutional determinants of industrial competitiveness in biotechnology that might have hindered the development in Europe. In particular, the role of the following variables, known to contribute to competitiveness and growth in biotechnology and in the life sciences, will be examined:

- The size and the structure/organisation of the biomedical education and research systems;
- Basic institutions governing labour markets for skilled researchers and managers, as well as corporate governance and finance;

- Intellectual property rights and patent law, with particular reference to their role in the functioning of markets for technologies.

5.4.1. The structure of the research system

5.4.1.1. Funding

Biomedical research is expensive and public money always played an important role in supporting this field. With the advent of biotechnology the cost of research increased further, thus making a strong support even more necessary in maintaining high quality competitive research.

Molecular biology was developed predominantly in the US and in the UK, even though significant research groups were active in many other European countries. After World War II, US support for research in life sciences literally exploded. Public funding of biomedical research in the post–war period increased dramatically in Europe as well, but total spending remained significantly lower than in the US. The sheer size of resources devoted to biomedical research in the US in the post–war era explains much of the American leadership in life sciences.

Table V.12 provides an indication of the relative importance of public funding for biotechnology in OECD countries other than the US. In absolute PPP$ terms Germany spends the most on biotechnology, followed by the UK and France. The median contribution of government budgets dedicated to biotechnology is 3.5 %, with a considerable spread, ranging from 0.4 % in Italy to 13.8% in Belgium, 10.1% in Canada and 8.1 % in Finland.

In the US, the funding of human health research has been traditionally attributed to the National Institutes of Health in Bethesda, Maryland. Every year the NIH Grants Office deals with thousands of applications from all over the World, which are evaluated with a peer- review system. In 1998 the budget for funding extramural research (NIH has is own direct funding system for intramural research which is about 40 % of the extramural budget) was of $ 8 billion. President Clinton took the commitment to double this budget for the year 2003. Thus, for the fiscal year 2000, NIH invested about $ 13.5 billion to fund 50 000 research projects world-wide.

On the other hand, the total budget of the 5th EU Framework Programme (1998-2002) is of about € 15 billion, comparable to the NIH budget for one year. Of this total, the amount of money dedicated to the

Table V.12: Public funding of Research and Development in biotechnology (1997)

	Biotechnology R&D	Total Government Budget Appropriations or Outlays for R&D (GBOARD)	R&D Biotech/R&D Overall
	Million PPP$		%
Austria	16.8	1.146.5	1.5 %
Belgium	181.7	1.314.0	13.8 %
Canada	261.4	2.581.0	10.1 %
Denmark	45.2	945.6	4.8 %
Finland	94.5	1.165.0	8.1 %
France	560.0	12.683.1	4.4 %
Germany	1.048.2	15.595.7	6.7 %
Greece	6.5	430.9	1.5 %
Iceland	0.9	68.5	1.3 %
Ireland	15.0	229.9	6.5 %
Italy	32.1	7.329.6	0.4 %
Netherlands	78.0	3.069.9	2.5 %
Norway1	26.8 - 32.2	880.3	3 % - 3.7 %
Portugal	19.2	781.9	2.5 %
Spain	15.5	3.202.6	0.5 %
Sweden2	65.6	1.795.2	3.7 %
Switzerland2	16.4	1.379.7	1.2 %
United Kingdom	705.1	9.055.7	7.8 %

Notes
1. These data are national estimates, hence the range.
2. GBOARD has been estimated.

Source: OECD, based on data from the European Commission (Inventory of public biotechnology R&D programmes in Europe, 2000), Eurostat, Statistics Canada, and national sources.

Programme Quality of Life is € 2.4 billion. One must consider that this Programme is only partially devoted to biotechnology. The first prevision for the total budget of the 6th Framework Programme (2002-2006) is of € 17.5, i.e. exactly equal to the NIH budget for the year 2003 at the present exchange rate.

The total EU budget for research is only 4-5 % of the total research budget of all European nations together. The EU strategy has focused on supporting co-operative projects among EU Member States, the exchange of researchers, and the promotion of quality research in the most disadvantaged EU Member States. Recently, the European Commission introduced the new European Research Area concept and proposed a number of very large multi-centric projects for the next 6th Framework Programme, such as the Integrated Projects, the Centres of Excellence or the Clinical Trial Platform. This last project is aimed at supporting the development of new interventions against HIV/AIDS, malaria and tuberculosis in developing countries.

5.4.1.2. The institutional structure of research

The institutional structure of research – and of biomedical research in particular – evolved differently in continental Europe compared to the US (and partly to the UK).

• The structure of the funding system and the strategies of the funding agencies are crucially important. In the US, most of the funding is administered through the National Institute of Health (NIH).There is substantial integration between the production of biological knowledge concerning the nature and mechanisms of human diseases, clinical research, medical practice, and the discovery and development of new therapeutic treatments; and significant support towards fundamental science in universities and public research centres, widely disseminated through publication in the refereed literature. Moreover, the US system is characterised by a variety of sources of funding and selection mechanisms, which complement the role of the NIH and act according to different allocation principles (see Owen-Smith et al., 2001) Overall, the US research system achieves efficiency through competition among research units providing room, at the same time, for diversity and institutional flexibility.

• In Europe, funding tends to be administered mainly at national level, with strongly differentiated approaches and wide differences across countries. This is likely to have hindered the development of a critical mass, especially in smaller countries. In many cases, resources have either been spread over a large number of “small” laboratories, or they have been excessively concentrated in the few available centres of excellence. Funding from the various European programmes has only partially changed the situation. The absolute size and the higher degree of integration of the US research system, as opposed to the fragmented collection of national systems in Europe, amount to a fundamental difference.

5.4.1.3. The organisation and structure of universities

The US system is highly decentralised. Even public universities rely on diverse sources for funds, including state and national governments, foundations and corporate supporters, tuition revenues, and alumni gifts. Private universities, especially elite ones, are also supported by generous endowments.

The organisation of research and teaching has characteristics that facilitate flexibility and decentralisation but also integration of research. In the US and the UK, academic departments have long been the main organisational entities, while in Europe a single professor dominates. The departmental structure makes it easier to respond to the emergence of new disciplines, like computer sciences and biotechnology, both by integrating them into curricula in conventional programmes and/or by creating new departments and programmes.

It is possible to argue that the European model is characterised a high degrees of division of labour and specialisation between teaching and research institutions, whereas in the US the dominant model of post-graduate students being exposed to and trained to undertake scientific research within teams made up by students and professors within departments has been a more integrated one. In Europe, this separation might have had negative effects on both the quality of research and on the ability of academic institutions to interact with industry.

Despite national distinguishing characteristics, the structure of research systems in Europe is profoundly different from the Anglo–Saxon model.

• First, in Europe financing is considerably more centralised and, consequently, it entails more hierarchical control.

• Second, research institutions are far less interdisci-

plinary and flexible. In Germany, for example, a number of the highly prestigious Max Planck institutes are organised hierarchically around a single field, such as biochemistry, genetics, or immunology.

• Third, the integration of teaching with research has progressed far less than in the US (and, to some extent, the UK). Ph.D degrees are a relatively recent innovation in many continental European countries, and research has tended to be far more removed from teaching than in the US. Thus, for example, the diffusion of molecular biology into the general training in many European countries is a relatively recent phenomenon as compared to the US, and it has become only recently a standard part of the curricula of pharmacologists, pathologists and medical consultants, and plant biologists.

5.4.1.4. Diversity and integration among publicly-funded research organisations (PROs)

The research systems in the US and Europe are organised in qualitatively different ways and, hence, any comparison must be sensitive to differences in multiple dimensions.

Large and densely interconnected networks composed of tight, repeated interconnections among a diverse set of PROs characterise the US. Elite universities (Harvard, MIT), research institutes (the Dana-Farber Cancer Center), and hospitals (Brigham and Women's and Massachusetts General) play central roles in innovative collaborations both within Boston and across U.S. regions. In contrast, for example, the French and German national clusters show organisational homogeneity, do not include hospitals and have no identified universities[97]. The UK has a somewhat higher degree of organisational diversity, reflected in the presence of both government and non–profit research and funding agencies Closely–knit regional networks such as those found in Boston help account for the global centrality of American PROs. Connections across US regions linking geographically dispersed universities to the National Institutes of Health illustrate a public research system that also reaches across regions and organisational forms.

The evidence suggests that national specialisation in Europe falls along scientific lines. In the US, there is abundant regional clustering but, unlike in the European case, agglomeration is not driven by scientific specialisation. Points of excellence develop in both the US and European systems, but in Europe those clusters are limited to narrower specialities and specific nations. The U.S. represents a very different profile, characterised by diverse, substantively generalist research organisations connected both within and across key regional clusters[98] (see Owen-Smith et al. 2001).

This difference in the science base is critical, implying that increases in scale alone will not alter the focus of R&D efforts, because organisations typically engage in local searches, and would continue to patent in those areas in which they are most skilled. In essence, one reason for greater integration across and within US regions is the scientific overlap among generalist patentors. Alterations in the scale of patenting activity without corresponding shifts in this division of labour will not make the European system resemble its American counterpart. Instead, mere increases in scale might deepen specialisation and, perhaps, heighten fragmentation among European national research systems.

5.4.2. Industry–university relations

A further set of factors that explain the US advantage relate to the ability and willingness of the American academic system to interact with the industrial and commercial world. The key role acquired by scientific knowledge for technological innovation manifested itself in an unprecedented intensification of both industry–university ties and in the direct involvement of academic institutions and scientists in commercial activities. While both phenomena are not new, since the mid-1970s the drive towards an increasing commercialisation of the results of research accelerated dramatically, and patenting and licensing activities on the part of universities started to soar. The number of universities having established Offices for Technology Management also increased from 25 in 1980 to 200 in 1990 . The creation of spin-offs became a distinct and crucial phenomenon of the American academic system. Increasingly, universities were assuming and were asked to assume the role of direct engines of (local) economic growth.

The emergence of the entrepreneurial university and the specific forms this process took in the US depend strongly on some general characteristics of the social, institutional and legal context, including the attitudes towards intellectual property rights and the availability of venture capital. There is high mobility

97 Scientists at the CNRS or Max Plancks may well have university laboratories, but the government institute is identified as their primary affiliation on the patents.

98 For greater detail on the correspondence analysis used in this section, see the background study "Innovation and Competitiveness in Biotechnology: a European Perspective", op. cit.

between academia and the commercial world – and, more generally, there is an active labour market for scientists, technicians, and managerial experts – to a much more developed extent than in Europe. American university professors often participate in various ways in commercial activities, either retaining their academic affiliation or migrating back and forth between different affiliations. An alliance between scientific, organisational and entrepreneurial capabilities (together with a favourable attitude towards the establishment and enforcement of robust intellectual property rights) constitutes an essential pre–condition for growth in industry–university relations. It is possible to argue that a high degree of integration between research and teaching tends to favour further linkages, easier communication and more intense flows of knowledge and people between academia and the business world.

Conversely, the ties, bureaucracy, and hierarchies of its scientific institutions, at both the national and the European levels, strongly discourage labour mobility between academia and industry. As discussed by Soskice (1997), and Zucker, Darby and Brewer (1997), the organisation of labour and company law in Europe, combined with the organisational strategies of most large companies and with the structure of the academic labour market, constrains the development of US–style active labour markets, and makes it harder for companies to "hire and fire" personnel or rapidly cut non–performing assets. Moreover, though there is often some lateral movement between firms very early in a person's career, the vast majority of European employees build their careers within one firm and university.

Correspondingly, the structure of decision–making, remuneration, and career paths within firms and universities differ fundamentally from the US or UK model. Career paths, especially in universities, tend to be well-defined, incremental, and based on rank hierarchies. This structure works quite well in industries dependent on long–term investment strategies in relatively stable technologies, characterised by the diffusion of deep skills throughout the firm, but it creates fundamental obstacles to the creation of high–risk technology firms.

To the extent that innovation depends on the flow of knowledge between university labs, start–up research firms and large firms, joint research projects and strategic alliances facilitate this exchange of knowledge. Conversely, if the labour market does not support extensive lateral career mobility between academia and firms, these network externalities would be difficult to sustain (Soskice, 1997)[99].

In continental Europe, university–industry relationships have developed much more slowly[100] and even now – despite considerable progress – the situation remains unsatisfactory. Integration of research and teaching and collaboration with industry has been more frequent in the case of engineering schools and in selected disciplines in particular countries (chemistry in Germany). Unlike in the US, where universities have gradually extended their functions (an integrated model centred on universities), continental Europe has leaned towards the development of various types of specialised institutions for technology transfer which act as intermediaries between research and industry (the institutional specialisation model).

Thus, there have been a large number of initiatives all across Europe aimed at establishing stronger links between industry and universities and at encouraging a more entrepreneurial attitude by universities. In practice, policies have been targeted mainly towards the setting up of specific devices to manage technology transfer, like science and technology parks or other such agencies, but their performance has so far been mixed.

5.4.2.1. A European paradox?

Despite the presence of centres of absolute excellence, scientific research in Europe seems to lag behind the US. If this were the case, it could have created a vicious circle, with a significant drain of human and financial resources from Europe to the US that contributes to further strengthen the American advantage.

There is now significant qualitative and quantitative evidence indicating that the R&D productivity of large firms, as well as the rates of formation of new firms, are highly correlated with the strength of universities and other research institutions in the underlying sciences (Ward and Dranove, 1995; Cockburn and Henderson, 1996; Zucker, Darby and Brewer, 1997; Swann and Prevezer, 1996).

However, there is less agreement about the existen-

99 There is interesting evidence in this respect that mobility of researchers between different institutional settings enhances both scientific research and commercial performance, not only in the US but also in European countries (Gittelman, 2000).

100 More detailed information on the modalities and practices characterising industry-science relations in Europe can be found in the forthcoming report "Benchmarking Industry-Science relations – the role of framework conditions" cosponsored by the Austrian Federal Ministry of Economy and Labour and the European Commission.

ce of a direct link between the strength of the local science base and industrial and commercial performance. For example, the UK has been a leading location for a disproportionate share of the main research breakthroughs in biotechnology in the second half of 1900s, but much less so in the industrial application of such discoveries (Cooke, 2001). More generally, it is widely believed that scientific, but not industrial, research in Europe fares much better compared to the US – the so-called European paradox. In this view, competitive advantages cannot be explained by the strength of the local scientific base since academic science is rapidly published and thus rapidly available across the world. Differential performance in industrial biotechnology is more likely explained by different institutional mechanisms favouring the rapid translation of scientific research into industrial R&D.

There is little empirical evidence in favour of or against the European paradox. There is some evidence that the formation of university spin–offs and the emergence of biotechnology clusters seems to depend less on the existence of academic research, as such, than on the presence of "star scientists" and cutting-edge research (Zucker, Darby and Brewer, 1997). Similarly, there is substantial – albeit largely anecdotal – evidence suggesting that successful experiences in industry–university ties in Europe take place in areas where concentration of world-class research in different fields of biotechnology is available (and where the need for explicit supporting policies is, as a consequence, less severe).

These observations support the notion that the absolute quality and "quantity" of scientific research and the coupling of scientific and organisational capabilities are essential pre–conditions for subsequent developments in industry–university relations. Indeed, the development of an entrepreneurial function within universities in the US has not substituted their traditional functions. Rather, the entrepreneurial function appears to be strongly complementary to and integrated with the other functions, primarily teaching. The US experience would seem to suggest, in this respect, that linkages with industry simply cannot develop without the constant mediation of teaching, as a stimulator of demand for relationships and an important source of absorptive capabilities within firms. In Europe, the presence of intermediary institutions might in some cases have paradoxically increased the distance between university and industry, introducing an additional layer in the relationship instead of favouring the development of organisational and integrative capabilities within firms and within academic institutions.

5.4.3. Financial markets and venture capital

The availability of venture capital is commonly invoked as a fundamental ingredient of American leadership in biotechnology. Clearly, venture capital played an enormous role in fuelling the growth of the new biotechnology firms. Venture capital is a long–standing institution in the US financial and innovative system. It was already active at the beginning of the 20th century and emerged as a vibrant industry with the electronic revolution in the 1960s. By contrast, in many European countries, the lack of developed capital markets for technology firms creates important barriers for prospective venture capitalists. It is worth recalling how venture capital plays a crucial role in bridging and complementing different constituents and roles within the system of biotechnological innovation.

Venture capital provides first of all finance to prospective academic entrepreneurs. Second, venture capital not only provides finance but also-and perhaps more importantly-managerial advice, organisational capabilities and "signals" to prospective investors about the potential of the new company. Contrary to the conventional stereotype of American financial institutions, venture capitalists are characterised by an extremely strong "hands-on" and "long-run" approach towards the companies they are financing. A significant number of doctorate holders in biology end up working in venture capital firms, and venture capitalists have to be part of the same network of conferences, literature, scientists, etc. Thus, venture capital mixes technology, academia and finance.

Lack of a developed venture capital market has restricted the start–up of biotechnology firms outside the US. In Europe, and despite various forms of intervention at the national and even local level aiming at fostering its formation, venture capital has only very recently begun to develop.

Nevertheless, in Europe there have been many other sources of funds (usually through government programmes) available to prospective start–ups. Moreover, survey results suggest that financial constraints did not constitute the main obstacle to establishing new biotechnology firms in Europe (Senker, 1998). Although venture capital played a critical role in the founding of US biotechnology firms, collaborations between the new firms and the larger established firms provided a potentially even more important source of capital. This raises the question of why prospective European start–ups could not turn to established pharmaceutical firms as a source of

capital. A speculative but plausible answer could be that European companies tended to collaborate more with US biotechnology firms rather than European firms[101]. Even in the absence of other institutional barriers to entrepreneurial ventures, start–ups in Europe might have been crowded out by the large number of US–based firms anxious to trade non–US marketing rights for capital (Henderson, Orsenigo, Pisano, 1999). Given the number of American DBFs in search of capital, European firms interested in commercialising biotechnology had little incentive to invest in local biotechnology firms.

Finally, the slow development of European venture capital for biotechnology could reflect less the inability or unwillingness of European financial institutions to fund new ventures and more a scarcity of "good" projects on the part of the industry. In partial support for this interpretation, it is worth recalling that several initiatives by both domestic and foreign investors to launch venture capital funds were attempted in Europe during the 1990s. Many of these funds, if anything, ended up investing in new biotechnology companies outside Europe. Conversely, foreign venture capital firms have funded some of the few experiences of successful European DBFs. Thus, the delayed development of venture capital in Europe seems to depend less on the lack of investors and funds than on the paucity of supply of promising start–ups based on solid scientific research.

The role of venture capital markets in sustaining small, young high–tech firms that do not meet strict creditworthiness institution criteria for funding new projects remains crucial in Europe. Recent evidence suggests that European venture capital markets are increasingly active in supporting small biotechnology companies in their innovative efforts. Yet, some potential drawbacks still persist at the interface between public and private financial markets and institutions, which need to be better co-ordinated for defining coherent incentive schemes for risk–taking innovative entrepreneurs.

Table V.13 shows that, during the period of unprecedented expansion in the European biotechnology industry (1996-2000), venture capitalists did not change their capital allocation from less research–intensive sectors toward biotechnology. While total investment rose from about € 6 900 million to € 35 000 million, most of it is devoted to traditional sectors (industrial machinery and equipment, fashion, leisure products) and to expansion and leverage buyouts. The main recipient of higher early–stage investment (seed and start–up financing, about 12 % more in 1996-2000) has been the ICT sectors. US data (Science and Engineering Indicators, 2000) for 1996-1998 show that the share of venture capital devoted to US biotechnology has

101 Indeed, most DBFs' strategies emphasised licensing product rights outside the US to foreign partners. Thus, to an even greater extent than many established US pharmaceutical firms, European firms were well positioned as partners for US DBFs.

Table V.13: European venture Capital disbursements, by sector and financing stage, 1996–2000 (€ 1000)

	1996	1997	1998	1999	2000
By sector					
Biotech	182.355	250.348	346.354	643.838	1.017.185
	2.70 %	2.60 %	2.40 %	2.60 %	2.90 %
Hi-Tech	1.347.926	2.306.820	4.026.917	6.418.215	10.976.494
	19.60 %	23.90 %	27.80 %	25.60 %	31.40 %
Total	6.878.646	9.654.942	14.460.781	25.115.694	34.985.753
By stage					
Seed	68.992	85.137	169.271	467.536	819.680
	1.0 %	0.9 %	1.2 %	1.9 %	2.3 %
Start-up	375.430	625.953	1.468.511	2.771.872	5.843.723
	5.5 %	6.5 %	10.2 %	11.0 %	16.7 %
Expansion	2.712.015	3.375.956	4.334.539	7.432.678	12.986.306
	40.0 %	35.0 %	30.0 %	29.6 %	37.1 %
Replacement Capital	481.014	733.017	1.078.675	1.186.228	930.092
	7.1 %	7.6 %	7.5 %	4.7 %	2.7 %
Buyout	3.150.195	4.834.879	7.409.785	13.257.380	14.405.952
	46.4 %	50.1 %	51.2 %	52.8 %	41.2 %
Total	6.787.646	9.654.942	14.460.781	25.115.694	34.985.753

Source: EVCA, 2001

been more than double, ranging from 6.1 % to 8.1 % as has the share of seed investment, which varied between 3.8 % (1996) and 4.6 % (1997)[102]. Moreover, unlike in Europe, the period 1996-98 was one of stability for the US biotechnology industry, and the proportion of venture capital disbursements to DBFs was far from its historical 1992 peak. As a result, despite recent growth, European DBFs have continued to attract only $\frac{1}{4}$ of the global venture capital investments in biotechnology during the last five years (Ernst & Young, 2001).

The unique exception to this general trend within the EU appears to be Germany[103]. Germany's financial support has favoured biotechnology and start-up investments. France ranks second both in terms of total investment in biotechnology and of its share in early–stage financing, followed by the UK. French and German venture capitalists are playing an important role in supporting the rapid growth of their national systems of innovation in biotechnology. They are likely to start a phase of selection and buyouts among the vast population of new European biotechnology firms and to complement public start–up initiatives by providing financing to select growing biotechnology companies. However, the unbalanced distribution of venture capital investments towards American early–stage biotechnology companies could represent a structural weakness in Europe for a considerable length of time.

5.4.4. The regulation of intellectual property rights (IPR) in biotechnology

One important factor contributing to the growth of biotechnology in the US has been the recognition and enforcement of strong intellectual property rights. The establishment of clearly-defined property rights has played an important role in the explosion of new firms since, by definition, few firms had complementary assets that enabled them to appropriate returns from the new science in the absence of strong patent rights. In the early years of biotechnology, considerable confusion surrounded the conditions under which patents could be obtained. Research in genetic engineering was on the borderline between basic and applied science, conducted primarily in universities or otherwise publicly funded, and the degree to which it was appropriate to patent results of such research became almost immediately the subject of controversy[104].

5.4.4.1. IPRs in biotechnology in Europe

By adopting Directive 98/44/EC of the European Parliament and Council on the Legal Protection of Biotechnology Inventions[105], after intensive and lengthy discussions, the EU equipped itself with a common set of principles regarding the granting of biotechnology patents. However, in spite of this political commitment, only four of the fifteen Member States have adopted the necessary legislation so far.

Most European national legislation did not explicitly address some of the most controversial problems in the regulation of IPRs in biotech. The dominant situation was one in which national legislation did not include, in general, legal principles that prohibit the granting of patents on living matter, but at the same time it did not offer definitions and general principles, much less specific guidelines, to manage the most controversial problems. At the same time, biotechnological inventions were de facto patented in most countries.

According to an OECD study on patenting practices in 22 Member States[106] all reporting countries allowed patentability without exceptions for a large variety of objects. National differences concern the patentability of plants per se, parts of plants or vegetal varieties, and of animals per se, animal organs or animal varieties. All countries excluded the patentability of human beings, human organs or derived products of human origin, including cell lines, genes and sequences of nucleic acids or amino-acids. However, an isolated element of the human body, or one obtained through a technical process, including the sequence or partial sequence of a gene, might be patentable even though its structure may be identical to the naturally occurring one.

102 Original data provided by the Venture Economics Investor Service, Newark, NJ. Since data on US and European venture capital come from different sources, they are not strictly comparable (for a tentative comparison see National Science Foundation, 1998).

103 For greater detail on the correspondence analysis used in this section see the background study "Industrial Competitiveness in Biotechnology: a European Perspective" op. cit.

104 Millstein and Kohler's groundbreaking discovery -- hybridoma technology -- was never patented, while Stanford University filed a patent for Boyer and Cohen's process in 1974. Boyer and Cohen renounced their own rights to the patent but were nevertheless strongly criticised for having being instrumental in patenting what was considered to be a basic technology Similarly, growing tension emerged between publishing research results versus patenting them. Whilst the norms of the scientific community and the search for professional recognition had long stressed rapid publication, patent laws prohibited the granting of a patent to an already published discovery. In the second place, the law surrounding the possibility of patenting life-forms and procedures relating to the modification of life forms was not defined. This issue involved a variety of problems (see OTAF, 1984), but essentially boiled down, first, to whether living entities could be patented at all; and, second, to the scope of the claims that could be granted to such a patent (Merges and Nelson, 1994). The Bayh–Dole act of 1980 greatly facilitated university patenting and licensing, but the emergence of the industry–university connection depended very greatly on the revolutionary developments in micro–electronics and biotechnology in the second half of the 20th century.

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It is clear that national legislation does not include, in general, legal principles that prohibit the patentability of biotechnological inventions. At the same time, however, the implementation of patentability is subject to a number of specific norms that require explicit treatment by national legislators.

Directive 98/44 is based on the principle that biotechnological inventions can be patented, but there may be specific exclusions depending on the nature of the invention[107]. These exclusions clearly address the ethical concern expressed in the European Parliament and by the public about -the possibility of granting patents for processes that may modify human genetic identity or utilise human genetic materials in the organised form of embryos. However, the Directive is states clearly that an invention cannot be excluded for the sole reason that it concerns living matter.

The debate about IPRs in biotechnology is still highly controversial and problematic. The emergence of a regime where property rights can be precisely defined and appropriated has been favourable to the development of the biotechnology industry in the US, especially as an incentive for the creation of DBFs. At the same time, however, there is growing concern that permissive attitudes have gone too far and that the current US system might not be sustainable in the long run. In Europe, the IPR situation is much less extreme, and there is opposition to the Directive as well as problems of harmonisation across national legislation. The issues raised clearly go far beyond biotechnology and will continue to be controversial over the next decade(s). Within this environment, the key concerns raised at the frontier of science and technology can only be resolved through informed discussion, careful economic analysis, sound policy debate, and finally and most importantly, democratic consensus.

5.4.5. European biotechnology policies: France and Germany

It was suggested earlier that the slow pace of development of biotechnology in Europe has been due to lack of the basic preconditions for innovative activities in this field. These concern the scientific and industrial base, the organisational structures linking science to industry, venture capital and intellectual property rights.

However, in recent years European biotechnology appears to have found new dynamism. One possible reason for this might be that policies have begun to exert some impact. Many European countries began to initiate policies supporting biotechnology in the 1980s. These included measures to introduce some typical US institutional features that have been crucial to the development of new biotechnology start–ups (such as fostering venture capital, developing financial markets tailored for new high-risk companies, promoting the commercialisation of academic research and mobility between academia and commercial activities), but primarily aimed at strengthening technology transfer and the founding of new firms. Efforts were also directed towards supporting basic research in universities and national research laboratories and, in some countries, firms (France). Furthermore, in the UK and France, the government has been instrumental in the foundation of some of the oldest European biotechnology firms, namely Celltech in Britain and Transgene in France.

The effects of policies seem to have been widely different between countries and regions. The experience of France and of Germany, discussed below, suggests such different patterns[108]

5.4.5.1. France

Starting in the early 1980s with the “mobilisation (later “expansion”) programme”, public support in France has been directed towards stimulating both private and public sector research in biotechnology. A large part of basic research was actually conducted by public structures such as the Centre National de la Recherche Scientifique (CNRS) and the Institut National de la Recherche Médicale (INSERM). These institutes have also transferred funds to private institutions like the Institut Pasteur. Beyond supporting start–ups through venture capital and stimulating the creation of science and technology transfer centres within the major universities and research institutes, public funding was used to revitalise large established

106 These include Germany, Australia, Austria, Belgium, Canada, Korea, Denmark, Spain, the United States, Finland, France, Hungary, Italy, Japan, Norway, New Zealand, the Netherlands, the Czech Republic, the United Kingdom, Sweden, Switzerland and Turkey.

107 The following inventions are excluded from patenting:
- the human body and its elements in their natural form;
- new plant varieties and animal races and the essentially biological processes for the production of plants and animals;
- inventions that are contrary to public order and morality;
- processes for reproductive human cloning and for the utilisation of human embryos for industrial and commercial purposes;
- processes for the modification of the genetic identity of animals without evident utility for human health.

108 The experience of the United Kingdom has been well documented in several reports, such as the “Genome Valley” report of the Department of Trade and Industry and “Entrepreneurship in UK biotechnology: the role of public policy”, by G. Owen with J. Lemme; Diebold Institute Entrepreneurship and Public Policy Project. Consequently, it is not covered in a specific section in this report.

groups operating in the life sciences. In the 1990s, with the launch of the BioAvenir programme, this latter form of intervention became more pronounced, as suggested by the joint support to Rhône Poulenc and several public research centres, aimed at creating public–private partnerships.

The improvement of some indicators of biotechnology activity in France, and subsequently the creation of a more solid scientific and technological base, became evident during the implementation of a "latent" national champion policy, in which a large part of the public research system was made available to one private group. Such an approach has been thought to have retarded the birth of new firms in the early 1990s. However, this period was also one of little investor interest in biotechnology in general. In recent years, French policy has been characterised by new initiatives aimed at promoting knowledge transfer, the mobility of scientists, and more generally, increasing co–ordination between different agents and at improving the control of funded projects. Moreover, the opening of the "Nouveau Marché" is showing itself to be a relevant channel for collecting financial resources.

5.4.5.2. Germany

Publicly-funded research has been the primary source of biotechnology knowledge in Germany as well. The "Applied Biology and Biotechnology Programme", launched in 1986 by the Federal Ministry of Research and Technology, was intended to stimulate biotechnology research in universities (by the creation, for example, of "Gene Centres" at the universities of Munich, Cologne, Heidelberg and Berlin) and knowledge transfer to firms. Established chemical and pharmaceutical corporations were, in this phase, the main subjects of such interventions.

Characteristics of recent public policies in Germany have been the support for an environment encouraging new start–ups, and the "regional" focus in the development of some high–tech industries. Local labour markets, specialised inputs and knowledge spillovers are suggested as the main factors contributing to such phenomena. The Ministry of Research launched the BioRegio programme in 1996 to create a competition between 18 German regions, each of which was expected to define research projects based on biotechnology networks. Three of them (Munich, Rhineland and Rhine-Neckar) "won" the competition and received extra-funding, and one, Jena, received a special vote by the jury. This type of intervention is seen as one of the crucial factors contributing to growth in the number of new biotechnology firms, after a decade during which Germany had been losing its leading European position in life sciences.

It should be stressed, however, that such intervention has worked differently in different regions. In most of them, firm and job creation has been limited, both in terms of the number and size of new firms, and then of new jobs. A review of the leading regions shows that the new start–ups have been able to rely on a pre–existing, and quite diffused, knowledge base, as represented by universities, research institutes, and even the chemical and pharmaceutical industry. The case of Rhine-Neckar is characteristic. The majority of life science firms are located in the Heidelberg Technology Park (i.e., very close to university clinics and the German Cancer Research Centre), and, furthermore, chemical and pharmaceutical companies have long been present in the area. One can only speculate how the future will unfold once public support is over.

Clearly, it is difficult to evaluate the effectiveness of different policy approaches and arrive at one that might be preferable to others[109]. What emerges clearly, however, is that forward-oriented policies can have an impact, but that the presence of other factors-principally an established and developed knowledge and competence base – is necessary to attain a "critical mass" for the growth of the sector. Even if policies have played an important role in the recent dynamism of European biotechnology, it is not easy to isolate the contribution of any particular intervention. As already noted, the simultaneous presence of various factors appears to have played a determinant role. In many countries, indeed, policies have often been criticised for the lack of co–ordination between different measures and for the lack of a "strategic" vision.

5.4.6. Other institutional factors: public perceptions and overall regulatory stance

Public perceptions and attitudes can affect the economic and regulatory conditions under which an industry operates. Their impact can be felt through supply channels (attraction to young graduates and

109 Another interesting case is Denmark, where the development of biotechnology firms is in different ways linked, according to many observers, to their relationship with large and established companies like Novo Nordisk and Heineken. On the other hand, creating a favorable framework for foreign investment by providing fiscal incentives has been central to Ireland's biotechnology policy. The birth of new firms is mainly concentrated in areas such as Dublin where, again, a solid knowledge base and a scientific community were already present.

scientists, perceived social utility of related research, perceived risk factors with respect to financial conditions), the economics of production or the demand for the products and techniques that the industry puts on the market.
Regulation tends to be specific to the field of application and the technology. Generally, there cannot be any unequivocal judgement over its role as its short-term effects may differ from its longer term ones. However, there is little doubt that the regulatory framework can have a major impact on the competitiveness of biotechnology in Europe.

Available research (Gaskell et al., 2000) seems to suggest that the European public discriminates quite clearly among the fields of application of biotechnology. Europeans are neutral about agricultural biotechnology and opposed to both genetically modified food and the cloning of animals. By contrast, perceptions of medical and environmental biotechnology are very positive.

In the EU, no genetically modified organisms (GMOs) have been placed on the market for the past 3 years (since October 1998). Though the EU has one of the strictest pre-market risk assessment systems in the form of Directive 90/220/EEC, revised this year (see Directive 2001/18/EC), Member States have refused to authorise GMOs. As a consequence, genetically modified food products have not been authorised under the sector-based legislation and the entry of new genetically modified plant varieties onto the Common Catalogues was not possible, despite positive assessments from the EU's scientific bodies.

The above situation and the uncertainty as to when authorisation of GMOs and derived products may restart, has led the biotechnology industry to focus most of its investments – especially concerning R&D and the basis for new start-ups and SMEs, – in non-plant related areas, where mechanisms for product approval are in place and functioning.

This situation is in stark contrast with the one in the US where markets for all areas of biotechnology are in place.

5.5. Adoption of biotechnology among large European firms

An important aspect of the development of European biotechnology is the considerable lag, compared to American (and to some extent British) companies, in the adoption of new techniques, notably molecular biology, by many large established companies. The relevance of this factor is crucial. Given the low rate of creation of new firms, the development of biotechnology in Europe has rested on the activities of large companies. Moreover, in the absence of a vibrant research activity by large firms, prospective start-ups lacked an essential source of survival and growth through the establishment of collaborative agreements. As mentioned previously, in the absence of such skills, large companies would turn to the American scientific and technological base to tap and absorb the new requisite skills during their catching-up process. Thus, in Europe, a vicious circle between the relative backwardness of large firms and the low rate of formation of new start-ups has been created.

The rate of adoption of biotechnology by established companies varied widely across the world and between firms. Within Europe, some large British and Swiss firms were able to adopt the technology rather quickly. Other firms, with smaller research functions, more local in scope or more orientated towards the exploitation of established research, found the transition more difficult. Thus, almost all of the established French, Italian, German and Japanese companies appear to have been slow to adopt the new technologies. To be sure, some German companies (e.g. Hoechst) were among the first to establish connections with the American research base in biotechnology (as early as 1982 Hoechst signed a multimillion, ten-year agreement with Massachusetts General Hospital). Nevertheless, the actual absorption of the new technologies progresses on average more slowly in Europe than in the US.

What factors have possibly contributed to this?

• The relative strength of the local science base appears again to be relevant. American and UK science is arguably more advanced, leading to a slower diffusion of the new techniques to continental European pharmaceutical firms. However, many Swiss firms established strong connections with the US scientific system, suggesting that geographic proximity as such played a much less important role in the diffusion of molecular biology.

• Second, it is possible that the size and structure of the various national pharmaceutical industries determine diffusion. The existence of a strong national pharmaceutical industry, with some large internatio-

nalised companies, may have been a fundamental factor in the rapid adoption of biotechnology. In many European countries, the industry was highly fragmented into small companies engaged essentially in the marketing of licensed products and the development of minor products for the domestic markets. However, while size or global reach may have been a necessary condition, the delay of the largest German firms in adopting these techniques suggests that it was not sufficient. The largest German firms were undoubtedly among the most internationalised and largest companies in the world.

• Another important factor may be the degree of diversification. Most European firms have been large chemical firms, largely diversified into different technologies and markets, ranging from chemicals and pharmaceuticals to agricultural applications. US firms have been more specialised into narrowly defined areas. In other words, even if chemistry was the fundamental technological base for all firms, the European corporations have been essentially defined by their chemical culture, whereas US firms have been focused on more specific products and markets and, as a consequence, perhaps, more ready to explore new and alternative research. Moreover, in the early stage of development, biotechnology was often perceived as an opportunity for synergies. Over time, however, pharmaceutical, agri-food and chemical applications tended gradually to diverge and to progress along distinct paths.

• An additional factor is the stringency of the regulatory environment, especially as concerns pharmaceuticals. There is now widespread recognition that the introduction of the 1962 Kefauver - Harris Amendments had a significant impact in inducing a deep transformation of the US pharmaceutical industry. Similarly, it has been suggested that the European country whose leading firms did move more rapidly to adopt the new techniques - Britain – also appears to have actively encouraged a "harsher" competitive environment. This induced British firms to pursue strategies aimed less at fragmentation of innovative efforts into numerous minor products than at concentrating on a few important products that could be diffused widely into the global market. By the 1970s, the ensuing transformation of British firms had led to their increasing expansion in world markets.

The diffusion of the new technologies has varied also between firms. Most of the firms that rapidly adopted the new techniques have been large multinational or global companies, with a strong research presence in the US and in international markets. These firms had developed early a "taste" for science and were able to integrate the new knowledge into the firms. This, in turn, was accomplished through organisational changes directed towards building and sustaining close links with the public research community through the successful adoption of academic-like forms of organisation of research. Other institutional factors have also been necessary, albeit not sufficient.

• First, it is possible that the Anglo-Saxon forms of corporate governance made it easier for firms to “hire and fire” personnel or cut non-performing assets; continental companies seem to have hesitated to give long–term employment to biologists before biology was proven to be successful over the long run.

• Second, it is possible that the American advantage in the use of biotechnology within large corporations, as well as in new biotechnology companies, relates to the proximity and availability of first rate scientific research in universities and in the closer integration between industry and the academic community. One might also speculate that this has been the result of the strong scientific base of the American medical culture and of the adoption of strict scientific procedures in clinical trials. Through this mechanism, American companies might have to develop earlier and stronger relationships with the biomedical community, and with molecular biologists in particular.

5.6. Concluding comments

European biotechnology is still lagging significantly behind the US. Despite encouraging signals of dynamism – especially in the small Northern European countries – and a wave of entries of new DBFs – especially in Germany – innovative activities remain far below the American levels. European companies rely partially on American research while, more worryingly, US firms do not seem to consider European research equally attractive. The new European DBFs, furthermore, are much smaller than their American counterparts, much less active in the global network of collaborative relations and in the markets for technology, and are mainly present in platform technologies.

To some extent, the European performance deficit in biotechnology is the result of its late entry. Even in such a strongly science–based industry, innovative activities are characterised by various forms of

increasing returns, and early entrants acquire long-lasting leadership. This is a crucial point, since it implies that catching–up is inherently difficult. Yet, catching–up is possible, but it requires determined efforts to generate the appropriate skills, market signals and incentives.

Europe has had policies promoting biotechnology in place for several years, and some important results have already been achieved. Recent developments suggest that the policies might have begun to produce effects. Thus, it could be that European biotechnology might take-off suddenly and sooner than expected.
However, the results of this chapter suggest that late entry is only part of the problem and that the take–off of European biotechnology is still hindered by a variety of structural factors. This leads to some general implications.

5.6.1. A systemic approach seems necessary

First, it is important to recognise that the lagging behind of European biotechnology also has systemic causes, rather than being simply the result of specific market or institutional failures. Successful innovative and commercial activities in this industry depend on a delicate blend of skills and incentives and require the integration and co-ordination of several differentiated agents, capabilities and functions Focusing on some specific aspects of the puzzle is not likely to yield the desired outcomes and a co–ordinated strategy appears to be necessary.

Biotechnology involves the exploration of an enormous, imprecisely defined and rapidly changing space of unknown opportunities. This requires both decentralisation of efforts and a variety of approaches, as well as an ability to integrate and co-ordinate them. Clearly, this is a challenge to which no unique, optimal solution may exist but alternative strategies may in fact be appropriate. For example, in the de-coding of the human genome the Human Genome Project was achieved by extreme decentralisation of tasks and approaches among a large number of institutions, while Celera Genomics approached it through strong centralisation of resources and efforts. Both approaches have been partially successful and each benefited from the existence of the other.

US leadership in biotechnology derives from a unique blend of capabilities and institutional arrangements. These include a strong scientific, technological and industrial base; mechanisms that favour communication and transfer of knowledge between academia and industry; a financial system that promotes the start–up of new, risky ventures; strong intellectual property protection; and a favourable climate in terms of public perception and regulation that does not restrict genetic experimentation. European biotechnology need - and probably should not - necessarily take the US model as the one to follow. Some aspects of the development of biotechnology in the US cause concern, especially as regards IPRs. Moreover, Europe has different institutional set-ups, histories, traditions and skills. On them, it might be possible to develop a different, but equally successful, road to competitiveness. However, some basic lessons can be learned from the US case and serve as a source of inspiration for European policy.

5.6.2. Strengthening basic scientific research and building a European research system

Second, it is clear that the availability of leading–edge scientific capabilities is the fundamental precondition for successful development of biotechnology. Without a strong and integrated scientific research base, no technological take–off is possible. Nor can European industry simply tap the American scientific knowledge. At the very least, acquiring knowledge implies the ability to produce knowledge. Access to the scientific community requires direct and active participation in the networks of scientists. The dynamics (and the economics and sociology) of scientific research is characterised by strong path–dependence and first–mover advantages.

Europe is lagging behind in this respect too. While centres of excellence exist, Europe does not attract foreign resources, and European biotechnology in the large companies relies significantly on American research. Increased funding is certainly necessary, but it is only a part of the solution. An important finding is that the European research system is weak in terms of organisational diversity, it is specialised in rather narrow areas and is insufficiently interconnected across different research areas, types of organisations and stages of the research process. Thus, higher degrees of pluralism in funding sources, lower dependence on closed national systems, higher integration of research with teaching, clinical research and medical practice should become priorities of a European research policy in this area, allowing more efficient exploitation of available resources.

Finally, the European research systems may still be too rigid and bureaucratic and segregated. While

important advances have been made in recent years, further progress needs to be made in this respect

5.6.3. Integration of research and industry

The European research system may still be insufficiently integrated with industrial research. This is most likely a reflection of several factors, possibly that that European industry does not fully exploit the potential offered by European science, as well as institutional and organisational obstacles, which could be more directly relevant here, such as low mobility of researchers and bureaucratic obstacles to collaboration .

Policies in this area have focused on introducing incentives for academic researchers to become involved in industrial research and in building bridges between university and industry, as well as developing financial and infrastructure facilities like venture capital, science parks, etc. In practice, these measures, important as they are, appear to reflect an understanding of the innovation process based on the transfer of knowledge. However, because innovation is primarily an interactive process, more emphasis is necessary instead on how to integrate more directly different agents and fragments of knowledge. To a considerable extent, these difficulties derive from some long–standing characteristics of the European academic systems, particularly the integration of research and teaching and the structure of career paths in universities. In fact, universities often lack the necessary organisational capabilities to sustain intense interchange with industry. Again, considerable progress has been achieved in this area in recent years, but science and industry continue to encounter difficulties in their interactions. Thus, measures are necessary to favour the development of more direct linkages between universities and industry, through the integration of research and teaching and the development of markets for technology. These observations apply both to the creation of university spin–offs and to the relationships between universities and large corporations.

5.6.4. Sustaining the cr eation and develop - ment of dedicated biotechnology firms

The creation and development of a strong DBF sector is a crucial priority. DBFs constitute an important organisational device allowing exploration of the new opportunities. In Europe, this sector remains underdeveloped and too concentrated in a few areas. Moreover, the European DBFs are hardly comparable with the American biotechnology firms. They are far too small and too specialised in specific niches. Their ability to grow appears severely constrained.

Once again, interventions aiming at promoting the birth of DBFs have been at the centre of European biotechnology policies for more than a decade. The emphasis is still on strengthening industry–university relations, the creation of the “entrepreneurial university”, the development of venture capital and, to a lesser extent, on intellectual property rights. Although these are important, the main problem is an inadequate supply of cutting–edge scientific research and the difficulties that afflict the European research system. While venture capital remains an essential instrument for supporting the process of formation and the early growth of the new firms, it ought to be understood as one instrument within a wider array of sources of funding (including public research funding) and managerial capabilities.

Finally, it is important to recognise that DBFs exist in a relationship of strong complementarity with the large corporations. The latter are fundamental sources of demand for products and services of DBFs and provide crucial integration capabilities for transforming different fragments of knowledge into products. Large firms constitute reservoirs of technological and managerial competence. Especially in Europe, DBFs have been – and may increasingly become –spin–offs of large incumbents rather than of universities. Supporting the creation of DBFs may raise the competitiveness of “downstream” industries, mainly pharmaceuticals.

5.6.5. Intellectual property rights

Intellectual property rights constitute one of the most delicate and important issues for biotechnology. While problems of clarification and harmonisation of the legislation on these matters remain, the emerging European approach is on the whole balanced and flexible enough to accommodate diverging requirements. The creation of the Community Patent and the implementation of the Biotechnology Patent Directive will provide a useful addition in this area, by making EU-wide protection easier.

The problem concerning IPRs is also closely linked to issues pertaining to regulation and public perception. This question goes beyond biotechnology into the

wider issue of the social and political control of scientific progress. This is a difficult and important matter, where no clear solution can be proposed. In the end, the democratic process must decide what is morally acceptable. However, misinformation and emotional reaction might seriously hamper progress that provides enormous benefits to society.

It is useful to recall that rigorous regulation is not always an impediment to scientific and technological progress. On the contrary, it can be beneficial, both by providing reassurance to society and by forcing industry to adopt higher quality standards which, if combined with more streamlined administrative procedures, can lead it to become more competitive and efficient. In this respect, the example of the regulatory reforms concerning product approval in the pharmaceutical industry might be instructive. However, onerous regulation can severely undermine competitiveness by placing unnecessary constraints on innovation, thus encouraging individuals and companies to relocate.

References

Allansdottir, A., Bonaccorsi, A., Gambardella, A., Mariani, M., Pammolli, F. and Riccaboni, M. (2001), Innovation and Competitiveness in Biotechnology: A European Perspective, Background Reportprepared for the European Competitiveness Report 2001.

Arora, A., Fosfuri, A. and Gambardella, A. (2001), Markets for Technology, MIT Press, forthcoming.

Arora, A., Gambardella, A., Pammolli, F. and Riccaboni, M. (2001), The Nature and the Extent of the Market for Technology in Biopharmaceuticals, Paper Presented at the NBER Summer Institute, Cambridge, Ma.

Audretsch, D. B. and Stephan, P. (1996), Company-Scientist Locational Linkages: The Case of Biotechnology, American Economic Review, vol. 86, pp. 641-652.

BioWorld (2001), Biotechnology State of the Industry Report.

BVK (1994-2000), Venture Capital in Europe, BVK Nachrichten Special Report.

Cockburn, I. and Henderson, R. (1996), Public-Private Interaction in Pharmaceutical Research, Proceedings of the National Academy of Sciences, 93/23, November, pp.12725-12730.

Cooke, P. (2001), "Biotechnology Clusters in the U. K.: Lessons from Localisation in the Commercialisation of Science", Small Business Economics, vol. 17, pp. 43-59.

Deutsche Bank Research (1999), German Biotech: New Stars in the Universe, Deutsche Bank Research German Equities Biotechnology Group, April 27.

DTI (1999), Biotechnology Clusters, Department of Trade and Commerce, London, UK

DTI (1999), Genome Valley Report. The Economic Potential and Strategic Importance of Biotechnology in the UK. Department of Trade and Industry, London.

Eisenberg, R. (1996), Public Research and Private Development: Patents and Technology Transfer in Government-Sponsored Research, Virginia Law Review, vol. 82, pp. 1663-1727.

Ernst & Young (1993-2001), Biotech Reports, Ernst&Young, London.

European Commission, Panorama of the EU industry, various years, Brussels.

France Biotech (2000), Enquete 2000:400 PME de biotechnologie, 9 May 2001, (http://biotech.education.fr/web/fr/Panorama/pme2000/sld002.htm).

Fuchs, G. (2001), "Introduction. Biotechnology in Comparative Perspective: Regional Concentration and Industrial Dynamics", Small Business Economics, vol. 17, pp. 1-2.

Galambos, L. and Sturchio, J. (1996), The Pharmaceutical Industry in the Twentieth Century: a Reappraisal of the Sources of Innovation, History and Technology, 13, 2, pp. 83-100.

Gambardella, A. (1995), Science and innovation in the US Pharmaceutical Industry, Cambridge, Cambridge University Press.

Gambardella, A., Orsenigo, L. and Pammolli, F. (2001), Industrial Competitiveness in Pharmaceuticals. A European Perspective, DG Enterprise, European Commission, Working Paper n. 1, Brussels (http://dg3.eudra.org/pharmacos/com-doc_doc.htm).

Gaskell, G., Allum, N., Bauer, M., Durant, J., Allansdottir, A., Bonfadelli, H., Boy, D., de Cheveigné, S., Fjaestad, B., Gutteling, J. M., Hampel, J., Jelsøe, E., Correia Jesuino, J., Kohring, M., Kronberger, N., Midden, C., Nielsen, T.,H., Przestalski, A., Rusanen, T., Sakellaris, G., Torgersen, H., Twardowski, T. and Wagner, W. (2000), Biotechnology in the European Public. Nature Biotechnology, September.

Gieseke, S. (2000), The Contrasting Roles of Government In The Development of Biotechnology Industry in the US and Germany, Research Policy, n. 29, pp.205-223.

Gittelman, M. (2000), Mapping National Knowledge Networks: Scientists, Firms and Institutions in Biotechnology in the United States and France. Ph.D. Dissertation, New York University.

Gompers, P. and Lerner J. (1999), The Venture Capital Cycle, MIT Press, Cambridge, Ma.

Griliches, Z. (1990), Patent Statistics as Economic Indicators: A Survey, Journal of Economic Literature, vol. 28, pp. 1661-1707.

Hagedoorn, J. and Schakenraad, J. (1990), Strategic partnering and technological cooperation, in New explorations in the economics of technical change, Printer, London.

Heller, M. A. and Eisenberg, R. S. (1998), Can patents deter innovation? The Anticommons in biomedical research, Science, 280, 698-701.

Henderson, R., Orsenigo, L. and Pisano, G. (1999), The Pharmaceutical Industry and the Revolution in Molecular Biology, pp. 267-311 in Sources of Industrial Leadership, Mowery D., Nelson R.R., eds. New York: Cambridge University Press.

Jaffe, A., Trajtenberg, M. and Henderson, R. (1993), "Geographic Localisation of Knowledge Spillovers as Evidenced by Patent Citations", Quarterly Journal of Economics, n. 108, pp. 577-598.

Krauss, G. and Stahlecker, T. (2001), "New Biotechnology Firms in Germany: Heidelberg and the Bio Region Rhine-Neckar Triangle", Small Business Economics, vol. 17, pp. 143-153.

Lacetera, N. and Orsenigo, L. (2001), Political regimes, technological regimes and innovation in the evolution of the pharmaceutical industry in the US and in Europe, Paper prepared for the "Conference on Evolutionary Economics", Johns Hopkins University, Baltimore, March 30-31, 2001.

Lemarié, S., Mangematin, V. and Torre, A. (2001), "Is the Creation and Development of Biotech SMEs Localised? Conclusions Drawn from the French Case", Small Business Economics, vol. 17, pp. 61-76.

Lerner, J. and Merges, R. (1998), The Control of Technology Alliances: An Empirical Analysis of the Biotechnology Industry. J. Ind. Econ. 46 125-156.

March, J. (1991), Exploration and Exploitation in Organizational Learning, Organization Science, vol. 1, n. 2, pp. 71-87.

Medicon Valley (2000), The Bio-region of Europe.

Mowery, D. and Nelson, R. R. eds. (1999), Sources of Industrial Leadership. Studies of Seven Industries, New York, Cambridge University Press.

Mytelka, L. K. and Pellegrin, J. (2001), Can SME Survive? Static vs Dynamic Externalities in the French Biotechnology Industry, Paper to be presented at the DRUID Summer Conference, Aalborg June 12-15,2001.

Nilsson, A. (2001), Biotechnology Firms in Sweden, Small Business Economics, vol. 17, pp. 93-103.

OECD (2000), Economic Aspects of Biotechnologies related to Human Health, Parts I and II, OECD, Paris.

OECD (2001), Biotechnology Statistics in OECD Member Countries: Compendium of Existing National statistics, Second ad Hoc meeting on biotechnology statistics, OECD, Paris.

Orsenigo, L. (1989), The Emergence of Biotechnology, St. Martin Press, London.

Orsenigo, L., Pammolli, F. and Riccaboni, M. (2001), Technological Change and Network Dynamics, Research Policy, 30 pp. 485-508.Owen Smith J., M. Riccaboni, F. Pammolli, and W. Powell, A Comparison of US and European University-Industry Relations in the Life Sciences, Management Science, forthcoming.

Paci, R. and Usai, S. (1998), Technological enclaves and industrial districts: an analysis of the regional distribution of innovative activity in Europe, Regional Studies, vol. 34.2 pp.97-114.

Peterson, J. and Sharp, M. (1998), Technology Policy in the European Union. Basingstoke, MacMillan.

Prevezer, M. (1997), The Dynamics of Industrial Clustering in Biotechnology, Small Business Economics, n..9.

Prevezer, M. (2001), "Ingredients in the Early Development of the US Biotechnology Industry", Small Business Economics, vol. 17, pp. 17-29.

Saxenian, A. (1994), Regional Advantage, Harvard University Press, Cambridge, Ma.

Schienstock, G. and Tukki, P., "The Fourth Pillar? An Assessment of the Situation of the Finnish Biotechnology", Small Business Economics, vol. 17, pp.105-122.

Senker, J., Joly, P.B. and Reihnard, M. (1998), Biotechnology and Europe's chemi-cal/pharmaceutical multinationals. In Biotechnology and competitive advantage: Europe Firms and the US challenge. Cheltenham, Edgar.

Soskice, D. (1997), German Technology Policy, Innovation and National Institutional Frameworks, Industry and Innovation, 4, pp. 75-96.

Swann, P. and Prevezer, M. (1996), A Comparison of the Dynamics of Industrial Clustering in Computing and Biotechnology, Research Policy, vol. 25, pp. 1139-1157.

Thomas, L.,G. (1994), Implicit Industrial Policy: The Triumph of Britain and the Failure of France in Global Pharmaceuticals, Industrial and Corporate Change, Vol.3, n.2,

Trajtenberg, M. (1990), A Penny for your quotes: patent citations and the value of innovations, Rand Journal of Economics vol. 21.1 pp.172-187.

UK Department of Trade and Industry (1999), Genome Valley: The economic potential and strategic Importance of Biotechnology In the UK, DTI, London.

Van Beuzekom, B. (2001), Biotechnology Statistics in OECD Member Countries: Compendium of Existing National Statistics. Ad Hoc Meeting on Biotechnology Statistics, OECD, Paris, 3-4 May.

Vinnova (2000), The Swedish Biotechnology Innovation System, by Backlund A., Häggblad H., Markusson N., Norgren L., and Sandström A.

Zeller, C. (2001), “Clustering Biotech: A Recipe for Success? Spatial Patterns of Growth of Biotechnology in Munich, Rhineland and Hamburg” Small Business Economics, vol. 17, pp. 123-141.

Zucker, L., Darby, M. and Armstrong, J. (1998), Geographically localized knowledge: Spillovers or markets?, Economic Inquiry, 36, January, p 65-86.

Zuckerb L., Darbyb M. and Brewer, M. (1997), Intellectual Human Capital and the Birth of US Biotechnology Enterprises, American Economic Review, June 1997, v. 87, n. 3.