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Overseas Biotechnology Research by Europe's Chemical/Pharmaceuticals Multinationals: Rationale and Implications

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Europe provides the home base for many of the world's leading chemical and pharmaceutical multinational companies. The success of this industry has been built on mastery of its core technology, synthetic organic chemistry. Recognising the significance of developments in biotechnology to their continued competitive success, companies have taken steps to acquire new biotechnology capabilities. In an effort to access American knowledge and capabilities, many European-based companies have set up or extended their US laboratories, and negotiated contracts with US academic laboratories and/or dedicated biotechnology companies.

This project was designed to learn more about the organisation and management of biotechnology R&D by Europe's leading chemical/pharmaceutical multinational companies, and the relationship between their US and European research efforts. One of the aims of the study was to identify the needs of European chemical/pharmaceutical companies in relation to biotechnology in order to help the EU and its Member States to develop appropriate policies to support the continuing competitive success of this sector.

1 Background to Research

Within the last two decades, Europe's chemical/pharmaceutical industry has recognised that continued success demands that they build up in-house expertise in biotechnology. In particular they have recognised that biotechnology techniques are now an essential route to new product development in pharmaceuticals and agro-chemicals. Accordingly they have made considerable efforts to acquire the necessary capabilities. These efforts have been paralleled by national and EU policies to build up the science base in biotechnology, to encourage technology transfer, and to regulate biotechnology.

However, the leading edge of research in biotechnology has remained in the US where the emergence of a dynamic new sector based on small specialist research firms closely linked to academia has led to what can only be described as an 'explosion' of the inter-related science and technology base. As a result, many of the leading multi-national firms, including both British, French and German based companies, have found it necessary to find a means to access American knowledge and capabilities in this sector and have done so by a variety of methods including setting up (or extending existing) offshore laboratories, and negotiating contracts with both US academic laboratories and/or dedicated biotechnology companies. These same companies have simultaneously retained their established links with their indigenous science bases and forged new linkages in the area of the life sciences. Nevertheless, it is generally acknowledged that, with the exception of the UK, Europe has fallen behind US capabilities. In addition, Europe has signally failed to develop the dynamic small firm sector that is such a feature of the US scene (Sharp *et al*, 1993).

The overall result of these developments means that while European-owned multi-nationals have retained their competitive edge and built-up the necessary capabilities in this area, it is not clear that Europe itself (in a geographic sense) is acquiring the same skills and capabilities, nor even managing to retain the skills of the post-doctoral researchers trained in the European public research sector. How far this is happening (ie, how far Europe is acquiring the leading

edge skills) depends on the extent to which these multi-national companies are repatriating back to their domestic laboratories the knowledge, skills and capabilities built up in the US. The hypotheses of the project are that European multi-nationals are locating their leading edge biotechnology research in the US; are employing predominantly US nationals as scientists and engineers; are not transferring skills and capabilities back to their home laboratories and that, as a result, overall European skills and capabilities in this area are falling behind.

An ongoing debate over theory to explain multi-national companies' overseas R&D activities provides limited guidance only on the possible implications. The early literature stressed the role of home markets in determining firms' technological advantages. Successful export activities led on to the establishment of overseas production facilities and any associated R&D activity was mainly concerned with adapting products to meet local tastes (Vernon, 1966). Vernon (1979) later amended these views to suggest that in some high technology sectors firms engaged in programmes of almost simultaneous innovation in several major markets. Some argue that the process of globalisation of large multinational firms' technological activities has now accelerated and that the reasons underlying firms' decisions to locate R&D outside the home country have changed. Firms are now thought to assess the location of R&D in terms of the strength of the science and technology base and the availability of qualified scientists and engineers, with no special bias towards the home country. It is further suggested that advances in information and communications technology (ICT) will solve the problems of co-ordinating R&D activities in several locations (for a review see Patel, 1995). A recent analysis of the US patenting activity of the world's largest 539 firms (including 16% in chemicals and pharmaceuticals) indicates that, for the majority, technology production remains close to the home base (Patel, 1995). Moreover, when these firms locate R&D activities abroad, no systematic relationship is found between their presence in a technical field and the relative technological strength of the host country in that area (Patel, forthcoming); no evidence is presented on any relationship with the scientific strength of the host country in specific fields. However, the relevance of the analysis for the purposes of this study is doubtful since patent statistics do not satisfactorily measure capabilities in biotechnology.

2 Methodology

The methodology adopted for the study involved ten in-depth case studies of leading firms in the chemical/pharmaceutical sectors in each of Germany, France and the UK. This included three British, four German and three French[1] companies, of whom six are among the top ten spenders on R&D in the chemical and pharmaceutical industry world-wide (SCI, 1995). The results of the case studies are set in the context of European and national policies for biotechnology. Case studies are based on desk research and semi-structured interviews with senior managers responsible for biotechnology in the home country. It was intended to interview those responsible for biotechnology research in the companies' US facilities, as well as some bench scientists. In all we conducted 19 interviews in Europe and nine interviews in the US. Interviews in the US were restricted by some European companies' reluctance to provide access to their colleagues[2] (sometimes they had several US laboratories involved in biotechnology research, but only gave access to the main site). The number of US interviews was also limited by the availability of US managers during the period scheduled for this part of the research, because the people concerned made frequent visits to European HQ. Nor did it prove possible to meet any bench scientists in this part of the study. The US interviews demanded extensive travel, with interviews being conducted both on the East and West coasts, in North Carolina and in the Mid-West. Our interviews were concerned with the following broad issues:

i) the number of qualified R&D employees working on biotechnology issues in home and US laboratories, and how they were recruited;
ii) the nature, focus and type of biotechnology R&D company's home and overseas laboratories;

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[1]There are now two major French chemical/pharmaceutical multinationals only. The third company was, in fact, a Swiss-owned company, with significant French facilities and laboratories.
[2]One company allowed interviews only in Europe.

iii) their methods for building up and diffusing biotechnology capabilities in and between home and overseas laboratories, including collaborations with university research and dedicated biotechnology firms;

iv) the regulatory environment, scientific capabilities or other factors influencing the location of company biotechnology research in the US;

v) the effect of overseas research on European biotechnology capabilities.

For the sake of clarity, the results of our interviews treat all European sites as headquarters (HQ) and the US sites as subsidiaries, although this is not always a true representation of the status of the companies concerned.

3 European and National Policy Context

This section provides background information on policy for biotechnology at an EU level, and also in the home bases of the companies in the study: France, Germany and the UK.

a) *European Union*: European Union (EU) policies for R&D, patenting and regulation affect company decisions about their biotechnology activities. The earliest EU support for biotechnology research dates back to 1981, when the European Commission introduced the Biomolecular Engineering Programme (BEP), a small four-year programme which promoted post-doctoral training and exchange, and projects which linked academic research with industry. Biotechnology was declared a priority area for innovation in 1983 and a working party was set up to develop a joint EC R&D programme (Sharp, 1983). Over time, the EC's investment in biotechnology research increased and BEP was succeeded by various programmes. In some, such as FLAIR or SCIENCE, biotechnology was a subsidiary interest under broader themes. Programmes whose main thrust was biotechnology were the Biotechnology Action Programme (BAP) 1986-89, Biotechnology Research for Innovation, Development and Growth in Europe (BRIDGE) 1990-93 and BIOTECH 1992-98. The focus of most of these programmes has been basic research and, at first, most participants were

academic researchers (Malmborg *et al*, 1988). Growing industrial participation reflects EC efforts to increase involvement from this sector.

The EU has also been involved in developing policy for biotechnology patents and for the regulation of biotechnology. Policy making in both these areas is complicated by the fact that biotechnology is a new science and its application raises issues where there is a great deal of uncertainty. In addition, the EU had to seek harmonisation between the various Member States' approaches to these issues.

Patents in Western Europe can be obtained either under separate national laws of individual countries, or the law of the European Patent Convention (EPC). European patents fall under the jurisdiction of the designate states and are enforced in national courts. In 1988 the European Commission proposed a Directive to secure harmony between national regulations and the EPC, and to upgrade national patent laws in Europe to US and Japanese standards. The biotechnology industry reacted favourably to the Directive, because it indicated that the EC was interested in promoting the industry, but Member States had many objections to the Articles of the proposed Directive. An amended proposal was published in late 1992, which was agreed by the Council of Ministers in early 1994. However, the European Parliament voted down the final draft of the Council Directive on the Legal Protection of Biotechnological Inventions in Spring 1995. The chief problem with the proposed legislation was its treatment of transgenic plants and species and the ethical issue of whether the patenting of living things should be allowed. The failure of the European Parliament to approve the Directive is likely to have slight effect on industry only, since case law will continue to provide the basis for biotechnology patent protection (Crespi, 1993; Scott-Ram and Sheard, 1995).

In 1990, the European Council of Environment Ministers passed two Directives on the regulation of biotechnology - on the contained use of genetically modified organisms (GMOs) (90/219) and on their deliberate release (90/220). These Directives, responsibility for whose

implementation lies with Member States, allow national authorities to interpret and implement them in ways which conform with existing national practice. National differences in the way in which the Member States of the EU develop and implement regulations for biotechnology,[3] however, led to tensions between national authorities. The Danes, for instance, were unable to impose more stringent controls than those agreed in the Directives; France thought the controls too stringent (Shackley and Hodgson, 1991). The Directives have been much criticised. In the UK, for instance, a House of Lords Report on UK regulation of GMOs (based on the EC Directives) considers that "regulation of the new biotechnology of genetic modification is excessively precautionary, obsolescent, and unscientific." The Report calls for relaxation in the terms of both Directives and believes that product-based-regulation should largely replace the existing process-based laws. It states that "GMO-derived products should be regulated according to the same criteria as any other product" and thinks that process-based regulation should only be retained in work involving pathogenic organisms and deliberate release of GMOs outside the low-to-negligible risk category (House of Lords, 1993). The French accept taking a cautious approach to the regulation of GMOs. However they want a flexible regulatory system, able to respond to growing knowledge which may indicate that more simplified procedures are appropriate (personal communication). In June 1994, the EC put forward proposals to encourage the development of the European biotechnology industry. The proposals include amending the Directives so as to take account of the recognition that risks to human and environmental safety are lower than was thought when the Directives were adopted (Jones, 1994). However, as with the Patent Directive, there are mixed views across the Community, which makes it difficult to reach a clear-cut decision.

A unified European regulatory system for approving medicinal products has been developing over time. In the period to 1992, UK and France were the preferred regulatory authorities for handling applications with an EU-wide interest. Preference was based on their ability to

[3]There are high levels of public participation in decision-making in some Member States, such as Denmark and Germany; by comparison public participation is low in France, and secrecy surrounds the decision-making process (Shackley, 1993).

process applications expeditiously, and on having a high level of international credibility with regulatory authorities in other major markets. Since 1995, the EC approval process has come under the aegis of the European Medicines Evaluation Agency (EMEA). Procedures differ for non-biotechnology and biotechnology medicines. There are decentralised procedures for non-biotechnology medicine, under which approval in one member state is recognised by all the others. Any disputes are resolved by EMEA. Centralised procedures are mandatory for biotechnology products, and optional for other "high-tech" products. Applications from manufacturers for approval are made directly to EMEA. Product approvals by EMEA are valid in all member states (Griffin, 1995).

The Food and Drug Administration (FDA) is responsible for approving new drugs for the US market, including those which have been approved for use outside the US. Potential new drugs must, from the outset, be produced in facilities approved by the FDA. There are major differences between the role which the EMEA and the US Food and Drug Administration (FDA) have adopted towards regulatory approval for biopharmaceuticals. EMEA is concerned about product safety, and allows the market to decide whether the product is efficacious. The FDA is concerned both with a drug's safety and its efficacy. In consequence, clinical trials and their evaluation are considered to be quicker and cheaper in Europe than in the US (Ward, 1995). There are currently moves afoot in the US for legislation to reform the FDA, with hopes to bring US requirements into line with Europe (Holzman, 1995).

b) *France*: The majority of basic research in France is organised and funded by CNRS, a state-funded institution which funds biotechnology research in its own laboratories and in universities and other research institutes. Three other public research institutes are involved in biotechnology. INSERM focuses on health and medical research, INRA on agricultural research and the Commisariat á l'Energie Atomique has expertise in biophysics, structural and molecular biology and bio-informatics. In addition, the Institut Pasteur, a private institution, receives considerable income from CNRS and INSERM. Realisation that France's position was rather weak in biotechnology led, in 1982, to a Mobilisation Plan. The programme ran

for eleven years, with government funding of FF 1.8 billion and a similar amount of industrial investment. Its aim was to strengthen the R&D infrastructure and to encourage French companies to acquire genetic engineering technologies and know-how. A major achievement of the programme is considered to be the construction of new links between industry and universities. Prior to the programme, there was no tradition of technology transfer or collaborative links between industrial and public sector research (Dept of Commerce, 1991). In 1994, the Comité National d'Evaluation de la Recherche (CNER) published a report on the Programme Biotechnologie, however, which suggested that there could have been more efficiency in achieving these results. It criticised the Programme for a lack of strategic vision and coordination, and for failing to control and evaluate the projects which had been funded (CNER, 1994). Biotechnology has now been reintegrated into the general biology funding framework of the Ministry of Research and Technology (Hodgson, 1994).

France has a small but growing number of small biotechnology firms (Ramani, 1995).[4] Growth appears to have been supported by changes in venture capital availability and Government agencies such as ANVAR. Venture capital was almost non-existent in France until the late 1980s, but has subsequently become easier to obtain. Since 1983 ANVAR, originally established to transfer technology created in the public sector, has provided funds to support the commercialisation of public sector research. Such funds include seed capital for start-up firms (Walsh, Niosi and Mustar, 1995).

c) *Germany*: There are a multiplicity of sources of funding for biotechnology research in Germany. Biotechnology research is promoted and funded by several ministries including the Federal Ministries for Education, Science, Research and Technology (BMBF),[5] for Food, Agriculture and Forestry (BML) and for Health (BMG), and by the Länder (states). Basic

[4]More information on French biotechnology SMEs will be contained in a parallel study funded by the BIOTECH programme: P Saviotti and P-B Joly (1996).
[5]The former Federal Ministry for Research and Technology (BMFT).

research is carried out in universities, Max-Planck Institutes, National Research Centres, 'Blue List' institutions[6] and federal and state research laboratories (Irvine, Martin and Isard, 1990).

In the early 1980s biotechnology was not widely used in Germany and there was a lack of well qualified young scientists. Accordingly, in 1985 the BMFT set up a programme to help Germany catch up in biotechnology and to increase the numbers of scientists in the area. This 'Applied Biology and Biotechnology' programme, 1986-89, financed the Society for Biotechnology Research (a national research centre which receives 90% of its funds from BMBF), and provided support to four 'Gene Centres' set up by the universities at Munich, Cologne, Heidelberg and Berlin. The programme subsidised small and medium sized firms' involvement in biotechnology by providing grants for firms to purchase know-how and services from research laboratories. It also funded the cost of academic research in collaborative research projects between small firms and academics. The programme was judged to be a success and, from 1990, was continued and extended with the 'Biotechnology 2000' programme. With German reunification and Government policy to develop the biotechnology sector in the new Länder, four additional 'Blue List' institutes are being established in Jena, Magdeburg, Gatersleben and Halle, specialising in molecular biotechnology, neurobiology, plant genetics and plant biochemistry (BMFT, 1989 and 1993).

Campaigns by the Green Party against genetic manipulation in the early 1980s created a difficult regulatory and legal environment for companies wishing to commercialise biotechnology in Germany. The recommendations of a government commission on genetic engineering, published in 1987, led to a national debate on a proposed "gene law" to define the environment within which industry could conduct R&D. The commercialisation environment deteriorated when a Länder court blocked an application by the chemical company Hoechst to manufacture genetically engineered insulin. This decision and other considerations, such as catching up with leading-edge know-how, influenced several German companies to build

[6]A loose confederation of research institutes, whose functions vary between providing services (museums, libraries), carrying out basic or medical research and, in some cases, applied research.

manufacturing and research facilities in the US. There was growing realisation that lack of a reliable legal basis for genetic engineering R&D and manufacturing was leading to loss of German investment and jobs. Thus, in 1990 the first German Gene Technology Law was passed, but it resulted in little substantive change. The law was very stringent and placed most of the responsibility for implementation on the Länder, who had no experience in these matters. In late 1993 the Law was modified, removing many implementation barriers (Department of Commerce, 1991; Edgington, 1995).

Germany has approximately 75 small biopharmaceutical companies (Ernst & Young, 1995).[7] Most provide support services (contract research, research reagents or diagnostics). Modifying the gene law may remove one barrier to the establishment of these firms, but significant barriers still remain. These include poor public acceptance of biotechnology, the lack of an entrepreneurial culture amongst academic scientists and the dearth of German venture capital firms able to evaluate plans for biotechnology start-ups (Kirk, 1993; Edgington, 1995).

d) *UK*: British policy for biotechnology was stimulated by the Spinks Report, published in 1980, which highlighted the importance of the technology. There was a fragmented response from the various agencies responsible for university, agricultural and food, and medical research. The most targeted efforts developed in the academic sector, with the establishment of the Biotechnology Directorate in 1982. The Biotechnology Directorate was successful in its aims to foster a programme of strategic university research in biotechnology, and to forge links between that research and industry. At about the same time, the Department of Trade and Industry set up the Biotechnology Unit, to raise industrial awareness of opportunities in biotechnology and to encourage more R&D in industry. The Biotechnology Directorate and the Biotechnology Unit developed close links, including shared funding of several programmes of collaborative university/industry research (Senker and Sharp, 1988).

[7]In a 1994 study, ifo identified 78 companies in Germany, of whom 48 were doing "new biotechnology".

A major reorganisation of British research funding agencies took place in 1994, which was expressly designed to make public sector research more industrially relevant and to build stronger links with industry. A significant feature of this reorganisation was creation of a Biotechnology and Biological Sciences Research Council (BBSRC), which integrated responsibilities for funding academic and agricultural and food research in these disciplines. The results of a Technology Foresight Programme now informs the direction, balance and content of the BBSRC's funding allocations (Cabinet Office, 1992).

Britain has the largest population of small biotechnology firms in Europe. Two dedicated biotechnology firms were founded in the early 1980s, on the initiative of the Government, to commercialise results of publicly funded research. The Government also intervened in the capital market to increase the availability of venture capital (Walsh, Niosi and Mustar, 1995). Growth of the British small firms sector accelerated in the 1990s. Relaxation of the rules for listing by the British Stock Exchange now permits developing biotechnology companies to raise investment funds.

This review of biotechnology policy in the EU, France, Germany and the UK has common themes: policy has been directed towards building up the competence of the science base, and creating links with industrial and academic research. Developing policy for biotechnology regulation and patents has not been easy, but this brief summary of the major events of recent years tends to suggest that workable solutions are slowly being found.

We turn now to the biotechnology activities of large chemical/pharmaceutical companies, both in Europe and the US. These companies influence policy to the extent that their top managers sit on government advisory committees, and the slow development of European policy for biotechnology is, in part, a reflection of their tardy recognition of the significance of biotechnology. Subsequently, the development of biotechnology in Europe has been significantly influenced by the substantial investments these companies make in in-house and

external biotechnology research, both in public sector research and in dedicated biotechnology firms. The nature of these investments, and their location, are presented in the following sections.

4 Location of Biotechnology Activities

Of our ten case-study companies, half apply biotechnology to a broad range of chemical and pharmaceutical businesses; the other half are either involved only in pharmaceuticals or apply biotechnology mainly to their pharmaceutical business. As shown in Table 1, the major application of biotechnology is to the health and diagnostics areas. All our European interviews provided information about companies' use of biotechnology in health; companies were rather guarded about their application of biotechnology to seeds and plant protection. We have information on these two areas from three companies only and none of these provided access to their US R&D facilities. Thus our US interviews were mainly with the Health Divisions of the companies concerned and our results are biased towards this application.

Of the six companies involved in both pharmaceuticals and diagnostics, we found only one where there was close integration between diagnostics and pharmaceuticals research, and strategic thinking about how diagnostics could help to support development. This company has a strategy to move from "diagnose and cure" to "predict and prevent".

Table 1: Focus of Companies' Biotechnology Activities

Company	Health	Diagnostics	Food/Seeds	Plant Protection	Other*
A	X	X	X	X	X
B	X	X	X	X	-
C	X	-	X	X	X
D	X	-	-	X	-
E	X	X	-	X	X
F	X	-	-	-	-
G	X	X	-	-	X
H	X	X	-	-	-
I	X	X	-	-	-
J	X	-	-	-	-

* Businesses such as fine chemicals or animal health

All the companies involved in our study apply biotechnology to their research activities in Europe, and their first explorations of the potential applications of biotechnology were at their home laboratories in Europe. These explorations date back to the late 1970s or early 1980s and, in one or two instances, even earlier.

Most of the companies have now extended the application of biotechnology to their US laboratories, with two exceptions. Company G has decided to concentrate its biotechnology efforts at home in Europe. Company H also goes against the trend by applying biotechnology only to its diagnostics business in the US. It has made a strategic decision not to get involved in pharmaceutical biotechnology in the US, because the use of traditional techniques to identify new molecules has been so successful that they have more than enough new drugs in the development pipeline.

Two of the companies in our study have long established US subsidiaries, one dating back to the last century. Seven of the companies had acquired US companies during the period 1972-1990, but few of these acquisitions carried out R&D and only one had pre-existing biotechnology expertise. However, two acquired companies had production capabilities in

second generation biotechnology. The application of biotechnology to US research efforts began in the early 1980s. Companies introduced or expanded the application of biotechnology in their existing laboratories and in six newly established laboratories. In the late 1980s, the tenth company merged with a US company; both had similar competencies in biotechnology.

Two companies increased their US research efforts deliberately to tap into strong US biotechnology research, both in the universities and in DBFs. One German company set up both biotechnology research and production in the US as a direct result of the restrictive implementation of gene law by local Länder officials. In agriculture, biotechnology research in the US is partly explained by the need to carry out field trials near the main market, primarily for climatic reasons. But one company's facilities were created to access scientific competencies which, at the time, were available only in the US. These two companies, however, do not represent the norm.

The majority of companies in pharmaceuticals increased their US R&D in order to enter or reinforce their position in the US market, the largest pharmaceutical market in the world. It is necessary for companies which regard themselves as global players to undertake R&D in all their major markets. Nonetheless, the establishment of US facilities also had another effect. Some European HQ were late in taking the genetic engineering revolution seriously. Inertia resulted from 'old guard' pharmacologists driving the research agenda. New US laboratories were set up at about the time that biotechnology began to be exploited in pharmaceutical research, and biotechnology often diffused through the new laboratories more quickly than in Europe. Sometimes, the US laboratories demonstrated the power of the technology to such good effect that biotechnology became more fully integrated into European research efforts.

5 Employment of Biotechnology QSEs

Companies were asked how many R&D employees they had in their laboratories with doctoral or post-doctoral qualifications who were working on issues which fall into the category of biotechnology. Companies differed in their interpretation of what was meant by 'biotechnology' expertise, and who to count as 'QSEs'; some included technicians and other excluded them. Difficulty was also created when companies did not think of their researchers in a 'biotechnology' category, with some suggesting that there was now such widespread diffusion of biotechnology techniques throughout their laboratories that it was difficult to give a meaningful answer. We have analysed the data given us to make it comparable between companies, by calculating the percentage of companies' biotechnology QSEs in various locations throughout the world. Given the difficulties in data collection, and the bias which may have been introduced by the sample of companies selected for our study, our results must be interpreted with caution. Table 2 shows that on average HQ laboratories have 59% of biotechnology research staff, US laboratories 35% and the remaining 6% are in laboratories in the Rest of the World (the major concentrations being about 2% in Latin America for field trials of crops, 2% in Japan for screening and 1% in Australia for pharmaceutical research).

Table 2: Percentage of Companies' Biotechnology Research by Location (by Numbers of Research Staff)

Country/Region	Overall %	Pharms %	Plants/Seeds %
Europe	59	42	16
US	35	21	14
Rest of World	6	3	3

There is some difference between regions when these percentages are disaggregated between pharmaceuticals and plants/seeds. In pharmaceuticals, the US proportion of total biotechnology QSEs is half the proportion of that in European laboratories. In plants/seeds the proportions in both locations are very similar.

Within Europe, UK companies have the highest proportion of these biotechnology QSEs (35%), followed by France (29%), Germany (22%) and Switzerland (12%); there are also small groups in Belgium, Italy and Spain.

6 Recruitment

Each laboratory recruits researchers from the locally available pool of recruits. The main criteria affecting recruitment is the competence of the people concerned. Two British companies mentioned that the competition for skilled biotechnology researchers is greater in the UK than in the US, and the former has a smaller pool of expertise in specific areas. Lack of specialists in the UK may lead to more of certain types of work being carried out in the US, for instance bio-informatics.

One company reported that biotechnology research in the US laboratory might be increased at the expense of European facilities, because it is easier to attract high calibre people from the US training system, both in terms of the numbers available, and of the expertise available. Microbial and viral areas used to be the responsibility of the European laboratory but they have been moved to the US because the company has only been able to attract good people in these areas in the US. Microbiology training is an example of an area which has been reduced world-wide, so research in that area is also being moved from Europe to the US.

The US laboratories reported that they had few problems in recruiting biotechnology staff and mainly relied on personal networks for all but the most senior positions. A couple of companies had recruitment problems when they were first set up; as foreign companies, they

were unknown, and this made it more difficult to recruit high quality people. One published a lot of academic papers to build up the company's reputation and another adopted a policy of recruiting some US research 'stars'. Often good scientists make decisions about where to work on the basis of the people they will be working with, and 'stars' attract other good scientists through their personal reputations and contacts. The general lack of recruitment problems in the US was ascribed to the 'rich' US research environment. "All a scientist looks for is good peers and resources to do research and that was available [here]." However, it was apparent that companies away from mainstream areas for biotechnology research (East and West coasts of US) suffered from recruitment problems from time to time.

A few subsidiaries have recruited a tiny proportion of senior managers from Europe, but most research staff are US-born or trained. 'US-trained' reflects the fact that a great many post-doctoral researchers in the US come from Asia and Europe, and the QSEs recruited reflect this trend. Research staff who are European by origin had all done post-docs in US universities and often these European researchers are better than their US peers, because "they were top of their class [in Europe] and therefore got into the top labs in the US." In the words of one of the senior managers interviewed, "the difference that this US training gives is to make researchers more driven, more aggressive than their European-trained counterparts."

There was a divergence of views on the relative advantages of post-graduate training in various countries. A senior manager at a European HQ thought that one of the major problems with the European system of education was the advanced age when studies were completed. He had the impression that Americans get their first post-doc experience when three to four years younger than their European counterparts. In reflection of the lack of uniformity in the European training system, we were also told (by a European senior manager in a US laboratory) that US researchers have longer post-graduate and broader undergraduate training than in the UK. He considers that US students to be both properly trained and mature; they complete their PhDs around the age of 27, while some UK doctoral studies may be only 24 years of age. Another European manager contrasted US, French and German

training. In the US and France doctoral programmes are completed by the time students are 24 or 25 years of age; in Germany this training takes much longer. He also considered that the quality of French doctorate did not correspond to an American PhD.

7 What Research Done and Where

There were several common themes in companies' answers to the question of how they applied biotechnology, and the variation in such applications between Europe and the US. Both the European and US laboratories apply biotechnology as a set of research tools and techniques to pharmaceutical research. These techniques can help improve understanding of the origin and development of disease and assist better identification of targets for conventional drugs. The majority of pharmaceuticals companies also told us that biotechnology is now part of the entire discovery process, from basic research right through to clinical trials.

In seeds, biotechnology supplies the basic underpinning research. In agro-chemicals biotechnology techniques are used to help identify targets for plant protection products. Two of the three companies we interviewed in this area carried out the majority of their molecular biology research in Europe, with field trials taking place abroad, close to their major markets.

A second common theme to emerge in pharmaceuticals and diagnostics was that much of the work in US laboratories is concerned with the clinical development processes required to get FDA approval for products and getting them to the market**.** Companies told us that world regulatory standards are set by the FDA and companies which pass US regulatory hurdles and US clinical trials gain world-wide acceptance of their products. Thus, US laboratories are often used to develop compounds which emerge from research anywhere in the world and to carry out clinical trials according to FDA regulations. Alternatively, clinical development is carried out in countries where clinical research standards are acceptable to the FDA. One company told us that its clinical trials are conducted only to the standards of the FDA, which

is the most restrictive, but that development sometimes has to take place in parallel in the US and Europe for regulatory reasons. Another company duplicates some European efforts in the US, because FDA development requirements in infectious diseases are stricter than elsewhere. A third company focuses its regulatory efforts on the US FDA. Once FDA approval has been gained, the results are sent to other countries, who may tweak these or do whatever local trials are necessary to meet local needs.

Several companies mentioned the significant advantages that had accrued to them from having a long-term relationship with the FDA regarding approval of manufacturing plant for second generation biotechnology products (plasma products, vaccines, etc). It was relatively easy for them to have facilities approved for biotechnology products. For companies which lacked such facilities, there were complicated regulatory issues concerning manufacturing approvals for recombinant proteins, especially if manufacturing is out-sourced from a DBF.

Although the majority of companies are using biotechnology to develop a range of *in-vitro* pre-clinical tests, for instance toxicology or safety tests, the FDA was considered a barrier to these tests replacing *in vivo* tests. The FDA is not ready to accept surrogate markers and still want drugs to be tested in people.

No clear pattern emerged for the location of development efforts targeted towards biotechnology products or processes. One company had no biotechnology products and none in the pipeline. A few companies carried out development in Europe only and one company was involved in development at the US site only. The majority, however, were using biotechnology for their product and process development in both locations. Seven companies have decided to invest in gene therapy and five in genomics and these activities usually involve collaborations, investments or acquisitions of external partners.

Before discussing these external collaborations in more detail, it is relevant to mention the response of two companies to the restrictive German genetic laws passed in the mid 1980s.

As mentioned in Section 3, these genetic laws were implemented locally by the Länder and involved discretionary decisions which were based on political views for or against genetic engineering. The first company carries out its biotechnology research only in Germany, and also manufactures therapeutic proteins there. It has never found the regulatory environment a problem, but its plant is located in a pro-industry Länder which appears to have implemented gene law in a loose fashion. The second company was just about to build a production plant for protein therapeutics in Germany at the time the gene law was passed. The local Länder did not give approval for this facility. This led to setting up US research and production facilities.[8] Although German gene law has now been amended and there is no longer a barrier to German production, the availability of spare capacity in the US rules out that possibility in the short term.

8 External Research

All the companies involved in our study use collaborations with university or public sector research (PSR) and with dedicated biotechnology firms (DBFs) to build up in-house competencies. Some links with PSR have been crucial to companies' initial competence building in biotechnology, and several companies have current large collaborations designed to bring genomics and gene therapy knowledge in-house.

It was difficult to get a clear picture of the proportion of in-house R&D budgets being spent on external collaborations in biotechnology. Some companies either could not or would not provide this information. Some companies control external R&D expenditure tightly and are aware of the proportion involved; others delegate it to individual laboratories or make investments in strategic collaborations on a case-by case basis, allocating additional funds from corporate budgets as necessary. The spend on external alliances is also complicated in companies which have a corporate investment division. Given these limitations Table 3, which

[8]Some people think that the US operation was caused because biotechnology production was not allowed in Germany. A group of senior researchers used the rejection as a means of mobilising top management support for the US facility (interview information).

is based both on our interviews and on press reports, sets out a rough indication of the percentage of total R&D expenditure allocated to external biotechnology research.

Table 3: Cost of External Research as a Proportion of Total R&D

Company	
A	3% on university research. Additional allocations for strategic alliances
B	10% - sometimes more
C	Over 10%
D	5% on university research. Additional allocations for strategic alliances
E	Over 5%
F	3-5% with plans to increase to 10%
G	3% on university research. Additional allocations for strategic alliances
H	Very low. University links to be increased
I	10% on university links and strategic alliances. Additional funds for equity investments in DBFs
J	4% on university research and 15% for strategic alliances

As is indicated by Company J, strategic alliances are generally more expensive than university collaborations, and may be funded from general corporate budgets rather than from R&D budgets. For instance, one US laboratory spends 1% of its research budget on university research. The European HQ has topped up the total US research budget by 15% to finance one DBF alliance. The larger scale expenditure on strategic alliances than university collaborations reflects the fact that companies anticipate getting much more out of the former, for example appropriating technologies which they wish to bring in-house. Alliances with DBFs enable firms to move quickly into new areas of research and gain critical expertise. PSR is slower to produce things of immediate relevance, but it is important in searching for new ideas, techniques, for specific bits of contract research and for recruitment. The main advantage of external links is that they provide a lot of flexibility in getting in and out of activities and in sharing the risk with someone else.

In addition to collaborations with university research and DBFs, we were also surprised to learn that six of the ten companies involved in this study are involved in research collaborations (or joint ventures) with other medium to large sized companies; some partners are in the same sector and others are potential users of the technology being developed. We were told about at least ten collaborations in pharmaceuticals, diagnostics and seeds, and the partners are in the US, Europe and Japan. One company, which had been involved in unsuccessful discussions about a possible collaboration with another medium/large sized company thought such collaborations would be a growing trend.

a) *Collaborations with University Research*: The majority of European HQs have many more collaborations with European than with US PSR, and tend to have arrangements with universities in the same country as their HQ. French companies, for instance, collaborate with CNRS or Institut Pasteur, German companies with Max Planck Institutes and British companies with British universities. One UK company commented that they had tried to link with Max Planck Institutes in Germany and INRA in France, but had been given the impression that these public research organisations were not prepared to do a deal with a foreign company; they saw it as their duty to give first preference to national firms. Only one company mentioned Framework programmes as a means to build links with PSR around Europe; this company had recently submitted its first proposal to the EU.

Two HQs had no US university links at all. But there is one HQ whose only academic collaboration is in the US, and this is a very large, long-term commitment. Another HQ said that an increasing proportion of its university links are in the US. In order to find the best academic partners in one specific area, it had recently set up a formal process to select the best academic people in European and North American universities. This had led to collaboration with a US university, selected from a short-list which was composed predominantly of North American universities. We were reminded that collaborations with US academics may differ from their European counterparts, since many of those in US PSR with industrial contracts are trying to turn themselves into DBFs!

The majority of the US laboratories' PSR collaborations are local to the US and four laboratories have links only with US PSR. The remaining subsidiaries have a small number of collaborations with European PSR, usually in the same country as HQ.

b) *Strategic Alliances with DBFs*: The companies involved in the study had a range of different arrangements for linking up with DBFs which ranged from acquisitions to investments, strategic alliances and licensing. The majority of strategic alliances are in the health area. Companies mentioned a small number of current agreements with US DBFs in the seeds/plant protection area, but are of the opinion that these will decrease in the future, because the number of independent companies in plant biotechnology is shrinking.

The European sites of the companies involved in our study are involved in 20-30 significant strategic alliances with US DBFs (with multi-million annual budgets), including some very large investments and some acquisitions. These expensive arrangements in the US tend to be funded from European HQ, with the US laboratories acting as licensing agents/talent spotters. There are also examples where the European HQ fail to use its US laboratories in this way. Some companies are currently increasing their portfolios of strategic alliances in the US; others have terminated such arrangements or are cutting back on the scale of their arrangements.

Strategic alliances between European companies and EU DBFs are rare; those which exist are mainly with UK and French DBFs. The US laboratories appear to be less involved in strategic alliances than their European HQ. The majority are with US and Canadian DBFs, with a few alliances in the UK and one in Denmark.

The majority of knowledge flowing through these strategic alliances is from the US DBF to the European HQ. Though one or two companies are trying to encourage their US laboratories to make direct contact with US DBF partners where this might be relevant, the main way for the US laboratories to acquire knowledge generated through the European

laboratories' strategic alliances is through formal, international Research Committee meetings. One US facility reported that it is barred from making contact with HQ's strategic partner in the US, although the work in progress is considered to be more relevant to the US than the European laboratory.

9 Technology Transfer Between Laboratories

Answers given to our questions about how companies shared knowledge developed in one laboratory with company scientists in other locations revealed that few companies have yet developed satisfactory methods. Some have not even thought about intra-company technology transfer. Every company organised regular meetings of senior Research Directors from their various laboratories. These meetings are used to discuss a wide variety of issues such as research programmes, strategy, regulation or alliances with DBFs, but they are also used to present research reports. Research Directors, in theory, are the means by which knowledge about what is happening in overseas laboratories permeates down to appropriate research groups. Companies also have systems for exchanging research reports; in the best examples all types of research reports - on exploratory ideas, progress reports and final reports - are widely available to all levels of staff throughout the company. Other companies exchange reports infrequently and restrict circulation to libraries and specific individuals such as Research Directors. One US laboratory complained that it was not sent research reports of European collaborations, a problem compounded because these reports are not written in English. Most companies hold corporate scientific meetings, but often these are not company-wide or lack bench scientist involvement. Short-term exchanges of staff between laboratories - for a few weeks - are quite common. Staff usually go to another company laboratory to learn new techniques, or to train colleagues. Only six companies had arrangements for longer term placements abroad, and this happened rather infrequently. The aim of these long-term placements abroad is to support the career development of outstanding young scientists. The general experience, except for one British company, is that these scientists return to Europe at

the end of their placements. Only five companies second their staff to the laboratories where they place research contracts.

We found little evidence to suggest that the use of ICT is facilitating international communication between laboratories. Four companies use e-mail and three companies teleconference. One company reported that US-European e-mail interaction (at a high level) is easier than intra-company e-mail in Europe (because so few European staff have been placed on the internet.) Another company, which has recently introduced e-mail internationally, has found that this facility is underused by bench scientists; the lack of personal contacts at other sites is a barrier to interaction. Teleconferencing is used to replace some face-to-face meetings by high level managers and one company uses it for presenting research results. Teleconferencing saves the time and cost involved in transporting people around the world, but companies have not yet worked out the best way to exploit the new facility. Problems are caused by gaps between talking and hearing, not being able to jump into a conversation to make a point, and the lack of eye contact around the table. Although it does have it uses, it is thought unlikely ever to substitute fully for face-to-face meetings.

We end this section with a report of the company which seems furthest down the road in terms of building mechanisms to encourage knowledge flow between its UK and US laboratories. The company recognises the importance of integrating the work of its US and UK laboratories, and the organisation of research on a matrix system is a means to this end.[9] It is trying to encourage links between the US and European laboratories, with each other's partners and vice versa. In addition to frequent meetings between senior R&D staff at the two sites, there are a variety of other mechanisms. There has been a major investment in electronically networking the entire company, from top management to bench scientists. They have 24-hour a day computer communication throughout the company and use highly advanced computer technology so people in the US can be in frequent communication with

[9]Research is organised by disease areas; there are also departments responsible for various disciplines (e.g. biotechnology, cell biology) and methods for relevant skills to diffuse into every research group as needed.

people in Europe. Every single US scientist is computer linked to every European scientist. There is also a company rule that any time any US scientist travels to Europe - for a conference, for example - (or a European scientist travels to the US), they have to spend two-three additional days at the sister laboratory, in order to get to know their colleagues and the work they are doing. This forms the basis upon which e-mail works. There are also several other methods for exchanging research results between laboratories:

a) A research database (access to which is determined by seniority). Every research programme is reviewed annually and review documents are placed in the database. The database also contains summaries of all research programmes and quarterly up-dates on progress.

b) There are a whole variety of scientific company meetings. Company scientists publish a lot and attend and speak at general scientific conferences. Every department runs a seminar programme where people are invited from other parts of the company to speak about their research; they also invite external speakers.

c) There are many short-term exchanges of scientists. Staff at every level, including technicians, go on short-term exchanges to the sister laboratory. These exchanges last anywhere from two-three weeks up to several months. Some people have had longer periods of work in each other's environments. When they return, they give talks about what they have learned at the other site and the research carried out there.

Despite all these efforts, distance and the differing cultures at the two laboratories remain major barriers to the intra-company flow of knowledge. The company thinks it very important, however, to retain some element of cultural identity in the two laboratories. They do operate differently, but the cultural tensions which result are very creative.

10 Comparison of US and European Research Environment

a) *Public Sector Research*: Those we interviewed all agree that the main characteristic which distinguishes US from European public sector research is its scale. The US biotechnology science base is described as having "ten times more universities than Europe", "more science", and "critical mass because of the sheer numbers involved"; it is "strong and dominant", "very progressive and innovative" and "avid for novelty". Within the US, Boston is identified as having the world's largest concentration of biotechnology research, which means it is possible to find an expert in almost any speciality. The greater pool of scientific talent provides companies with choice because

> in any scientific area there will be three or four laboratories, with good top 'young lions' as well as key investigators. You can select the people you want to work with rather than being stuck with a single option.

High levels of funding for PSR also result in very good laboratories, equipment and research, and attract the world's best scientists, including many European professors and post-docs. We also heard that there are so many laboratories in the US that they are able to negotiate better prices from vendors of scientific equipment. For example, we were told that one US laboratory paid 40% less than French HQ for a piece of equipment bought from a European company.

There were also negative comments. The ready availability of research funds is thought to make it more difficult for companies to direct the work of top academic researchers into new areas; the ease with which top researchers can secure public funds to pursue their own ideas makes them very independent. Moreover, collaborations with US universities are thought to be more expensive than in the UK.

We were also told that molecular biology has diffused more rapidly into general training in the US than in the UK. For instance in the US molecular biology is now part of courses for

pharmacologists, pathologists and medical consultants, and there are good educational programmes in areas unknown to UK universities, eg, molecular pathology and molecular neurology.

> US medical registration authorities have changed the rules of what they expect a consultant doctor to do. Top class consultants in the US work in molecular biology labs, but that is unheard of in the UK where consultants are still trained in time-honoured fashion, with surgical experience, but the idea that consultants should do molecular biology research is unheard of.

Very few people had any overview of European PSR in biotechnology. One British research director had wide knowledge of European science; he thought French PSR was the best in Europe, closely followed by the UK and Germany. Spain was improving fast, and thought capable of overtaking Italy, but that still left these two countries far behind the leaders. By contrast, although French companies considered French PSR to be of high quality, they criticised its lack of critical mass and the institutional inertia which affected its capacity to focus on strategic areas, particularly in plant biotechnology. Apart from a few areas like nitrogen fixation and male sterility, French PSR was characterised as a "good follower".

The majority of people, however, were generally aware only of the science base in the country of company HQ, reflecting the fact that European PSR is very fragmented, and not viewed as a single entity in the same way as US PSR. There were many comments that the quality of science in France, Britain or Germany is comparable to the US; the main difference is in the quantity. A few think that European science is more solid and systematic than in the US, and more creative. However, European academic scientists differ from their American counterparts in lacking an understanding of industry and its perspective and in being poor at translating their work into products. We also heard concerns about the UK as an academic environment.

> There are still some centres of excellence, like Cambridge and Oxford. But outside those centres of excellence, the UK has been in relative decline in terms of the physical

> and equipment infra-structure and all the modern machines, which has implications for the training of the next generation of scientists to do research. The UK was a world leader in sequencing technology, but it has lost that lead.

European competence is highly praised in plant biotechnology, molecular biology, structural sequencing and in the human genome programme; there are perceived to be gaps in microbial and mammalian areas and in combinatorial chemistry. Another major concern is that European biotechnology training is concentrated in areas like cell biology, molecular biology and immunology, but there needs to be more breadth. Research training is quite capital-intensive, but academic research is under-capitalised and that has affected academic research in the biotechnology area.

There were also anxieties about wider trends in biotechnology research, with implications for both US and European policy. In the words of one of those interviewed:

> Such a heavy emphasis in biotechnology has been put on identifying initial targets (for drugs) that down-stream efforts may have difficulty in finding relevant compounds for drugs. There has been so much focus on molecular biology that clinical pharmacology and chemistry capabilities have been neglected. There are not enough good people out there in these fields. Combinatorial chemistry will drive up the need for chemists and good pharmacologists will become more important. But there is too much focus and concern on the front end of all this. Perhaps there will be some re-emphasis. It is very much needed in relation to antibiotics. The last new antibiotic class discovered was in 1976 and antibiotic-resistant bacteria are on the rise, but nobody understands microbial pathology or does research in that area anymore.

b) *DBFs*: The higher number of DBFs in the US than Europe is explained by the general environment. The US in general is just more risk-accepting and interested in novelty. Academics are very entrepreneurial and well supported by venture capital which makes it easy for scientists to get investments for their companies by 'hyping' the potential applications of their knowledge. Moreover, scientists regard working in DBFs as an attractive career option. US DBFs are thought to be especially good in genomics and gene therapy; European DBFs are not thought to offer expertise in these two areas, although some praised genomics work in

France, Germany and the UK. Overall US DBFs are considered less strong in agricultural than pharmaceutical applications. Indeed one HQ in agricultural biotechnology had originally found it unavoidable to link with US DBFs in plant biotechnology; now they get relevant knowledge from national PSR.

By contrast, the DBF sector in Europe is considered small and underdeveloped. The main problems are considered to be lack of venture capital and poor capability (or interest) of academics in commercialising their work. Those with knowledge of UK DBFs consider them to be "real businesses doing science", whilst a lot of US DBFs are venture capital investment vehicles only, which are trying to raise money to finance their operations. One Research Director in a US subsidiary was completely unaware of any European DBFs. He attributes this to the fact that European DBFs do not publish in the scientific journals. He believes that this is how US DBFs sell themselves for stock market purposes.

c) *Other*: There is a consensus among all those we interviewed that the US is a far more favourable climate for commercialising biotechnology than Europe. There is more public acceptance of biotechnology in the US and people seem readier to accept the use of genetic manipulation; Europeans are too prone to enter into moral debates about such uses, creating a difficult environment for gene therapy approaches. One of those interviewed identified Northern European countries with an Anglo-Saxon culture as having a particularly hostile attitude to biotechnology. Green Party activities were thought to be largely responsible for this anti-science and development climate, which is very trying for the companies involved in biotechnology, and has led to a decline in creativity.

The US also benefits from having a very pro-industry policy environment, with the Government providing tax credits for companies which do R&D and Congress exerting great pressure for FDA regulations to be softened. We were also told that Europe lacked a tradition of picking up families of people with genetic disorders and working with them, as is possible in the US. The UK National Health Service used to track family histories in gene

disorders, providing a background resource to support gene disorder research. The break-up of the NHS means this resource no longer is there and has made it very difficult to do population pedigree analysis. In the US these analyses have been commercialised.

A very large number of those interviewed, however, identified the regulatory and patenting environments as the most significant differences affecting commercialisation in the two regions. In plants, Europe was unlike the US in having no defined system for risk assessment on environmental releases; this created a difficult environment for biotechnology in agriculture and food in Europe. Another area where the US has a better regulatory environment is the genetic manipulation of organisms (GMOs) in the laboratory setting; while regulation is very professional and tight in the US, it is considered much less restrictive than in Europe. In Europe, for instance, some types of biotechnology research require a P3 laboratory; the US might require only a P1 or a P2.

In comparing regulation in various European countries, British companies described the UK as recognising the balance which is needed between risk assessment and management in the laboratory, and the competitive development of products. We were told that the UK had taken an active role in trying to influence the EU regulatory environment by pressing for a legal framework which is product rather than process oriented. This view is reported in the House of Lords Report on the Regulation of GMOs.[10] It considers that the balance of risk and benefit should be driven by the risks in the final product rather than any risks inherent in some of the processes leading up to the product. Europe seems to be driven more by the latter (process) view. The former would lead to a less restrictive environment for regulating biotechnology, and would be closer to what is the norm in the US. If the latter view becomes the basis for European regulation, it could lead to more biotechnology being undertaken in the US. Another regulatory problem aired by one company is the delay and lack of transparency in EC procedures for approving products. In building up applications for product approval, they found it almost impossible to foresee what would cause delays.

[10]House of Lords (1993)

When it came to clinical trials for diagnostic products, however, we were told that some countries in Europe have a much easier regulatory system than the US (especially related to HIV). In the US, some diagnostic products required two years of clinical trials followed by two years for regulatory approval in the US; following successful clinical trials in Europe, the same product may take six months only for regulatory approval. For some products clinical trials in Europe only take one month. Therefore, it is usual for biotechnology firms to launch diagnostics products in Europe[11] before the US.

In Europe, regulatory efforts by the EC are seen to support harmonisation, and those responsible in the Commission are regarded as being well-disposed to the development of biotechnology, unlike the EC Parliament. The European Commission has been trying to produce an overall Directive on patenting for the last seven years, as mentioned in Section 3, They finally produced a Directive which industry supported, but it was not voted through by the European Parliament; this was the first time the European Parliament voted out a Directive. There will be intense pressure to have a new Directive, but its terms may bow to socialist/Green pressure and that would change the environment for biotechnology in Europe. Companies would still patent in the normal way, but symbolically it is not promising. Though companies would still wish to conduct biotechnology R&D in Europe, this activity may be a pawn in the game which companies choose to use if biotechnology patents are disallowed.

11 Conclusions

This study had five major research questions about companies' European and US research activities: the relative numbers of biotechnology researchers in each; differences in the nature of biotechnology R&D in each; methods for acquiring and transferring biotechnology capabilities in and between home and overseas laboratories; the factors influencing the

[11]Particularly in France and Spain. Italy and Germany are beginning to be more difficult and the UK has never been an easy environment (interview information).

location of company biotechnology research in the US; and the effect of overseas research on European biotechnology capabilities.

We found that European HQ employ roughly twice as many biotechnology researchers as their US subsidiaries, but that US laboratories often recruit European-born researchers from among post-docs at leading universities. European researchers seconded to the US laboratories are few in number and normally return home at the end of their placements. There is no great difference in the type of biotechnology research carried out in Europe and the US in pharmaceuticals, except for the emphasis on clinical development in the US demanded by FDA regulations. In agricultural biotechnology, however, the majority of molecular biology research is carried out in Europe, with the US mainly involved in field trials and plant breeding.

Companies build in-house competencies through external collaborations with PSR, and with strategic alliances with DBFs. The majority of university alliances are local to each laboratory. The majority of strategic alliances are in pharmaceuticals and with US-based DBFs. European HQ control the majority of these arrangements, and the majority of knowledge flowing through these strategic alliances is from the US DBF to the European HQ. We were also surprised to discover that more than half the companies in our study are involved in research collaborations with other medium to large sized firms. The major reason for the location of laboratories in the US is the size of the market, the need to comply with FDA regulations and to tap into US science. However, companies have found that the general environment for commercialising biotechnology is more friendly in the US than Europe, especially in terms of regulation and patenting, but also general public acceptance for biotechnology.

The results of our study indicate that the US activities of European chemical/pharmaceutical multinationals are helping to increase their biotechnology capabilities in Europe in areas where Europe has weaknesses, for instance in gene therapy, genomics and combinatorial chemistry.

In some areas where European PSR is weak, such as microbial physiology and virology, the shift of corporate activities to the US is exacerbating existing weaknesses.

The study also produced other findings which have implications for multinational corporate strategy and for European science, training and regulatory policy. The results of the study show that companies have not yet adequately addressed the problem of how to diffuse and integrate the scientific and technological knowledge being accumulated in globally dispersed R&D laboratories. We found little evidence to suggest that ICT will support such knowledge flow. The few companies experimenting with ICT found it useful, but not a complete replacement for face-to-face contact.

In relation to EU policy we found, first, that in comparison to the US, Europe's science base lacks critical mass due to its fragmented and somewhat chauvinistic character. National PSR for its part, appears to be more supportive of national than other European companies. Companies, for their part, appear to have little knowledge of overall European PSR expertise in biotechnology. In part this may reflect the historic focus of Framework programmes in biotechnology on basic, academic research rather than on strategic research involving collaborations with industry. This focus has given little opportunity for companies to build relationships with PSR competence around the EU as it has in other technologies. Support for university-industry links in biotechnology in the UK have been a important method for companies to explore university expertise in biotechnology (Senker and Sharp, 1987). Recent EU attempts to increase industrial involvement in its biotechnology programmes may remedy this problem, especially if programmes promote intra-community university/industry research collaborations.

We were told that companies were moving some areas of research to the US because of gaps in European expertise - namely in microbial and mammalian areas, bio-informatics and combinatorial chemistry. Companies expressed concern about the lack of breadth in European research, with over-concentration on cell biology, molecular biology and immunology.

Europe also lacks background resource to support gene disorder research. The US, however, shares Europe's weakness in failing to direct research towards the discovery of new classes of antibiotics.

Secondly, our results indicate big gaps in European research and training which need to be addressed. The main loss of talent from Europe to the US appears to be at post-doctoral level. We do not know whether scientists are attracted to work in the US by the science, or whether limited opportunities and conditions for post-doctoral work in Europe drive them abroad. For instance, we were told that academic biotechnology research in Europe is adversely affected by under-capitalisation. This perception is supported by perceptions that European PSR is less well equipped than US. Post-doctoral training abroad is advantageous to all concerned but there may be cause for concern if a large proportion of European post-docs are subsequently recruited to work in the US. There appears to be a need to review the opportunities and conditions for post-doctoral research in Europe.

Moreover, it appears that in the UK and perhaps in other European countries, molecular biology is not diffusing into general medical training in a way which supports the commercialisation of biotechnology. There may be a need to modernise training for pharmacologists, pathologists and medical consultants, incorporating new courses such as molecular pathology or neurology

Finally, we found that FDA regulations are a significant influence on the establishment of R&D laboratories in the US. It is not clear how acceptable FDA regulations would be to Member States which have more or less stringent requirements, but this problem has not yet been solved by EU Directives. Moreover, the duplication of clinical trials in Europe and the US appears unnecessarily expensive and time-consuming. While not minimising the political difficulties involved, it would appear beneficial for negotiations between the FDA and EU regulatory authorities to attempt to harmonise regulations and begin to work out the basis upon which mutual recognition of clinical trials might be achieved.

The results of the study indicate that the hypotheses of this project (see page 2) are not proven. The evidence shows that leading edge biotechnology R&D by multinationals is not leaving Europe for the US, and thus not affecting European research capabilities. The study is reassuring in indicating that Europe is maintaining its capabilities in the mainstream areas of biotechnology. However, US outsourcing of R&D in specialist areas suggests that, if it is to retain its position, Europe needs to nurture centres of expertise in areas such as combinatorial chemistry and bio-informatics.

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