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European Biotechnology Innovation Systems

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Abstract

The European Biotechnology Innovation System (EBIS) project aimed to identify whether the development of biotechnology in Europe is mainly influenced by national or sectoral factors, and to consider the implications for biotechnology policy both at a European and national level. It also aimed to increase theoretical understanding and empirical knowledge about 'national systems of innovation' (NSI).

Case studies were prepared of biotechnology developments in Austria, France, Germany, Greece, Ireland, The Netherlands, Spain and the UK. They focused on three sectors of biotechnology: bio-pharmaceuticals, agro-food and research equipment and supplies. The national case studies contain a review of four networks relating to each sector - knowledge and skills, industry and supply, demand and social acceptability, and finance and industrial development - and the links between them. The results of the project draw on the national case studies, sectoral overviews and analysis of a database of firms active in biotechnology in the eight countries. They also consider US and European competitiveness in the three sectors, and take account of EC and US policy for the science base, patenting and SMEs.

The national case studies show great differences in innovation patterns between the eight countries studied. Partial explanations for these differences are provided by NSI, confirming that the R&D system, the role of the public sector including public policy, interfirm relationships, the financial system, and the national education and training system are important elements of a NSI. Using a systems approach to consider the relationships between these elements also helps to explain national innovation performance. The major impact on innovation identified by the study, however, is demand, the nature of the market and public attitudes to applications of biotechnology. These findings do not challenge the relevance of the NSI approach, but suggest that it does not go far enough. Demand, the nature of the market and public acceptance differ greatly between sectors and also have a major influence on sectoral innovation activity. These differences, and in particular the varying effect on innovation of sectors with domestic and global markets suggests that the development of biotechnology in Europe takes place mainly at the sectoral level.

The great difference between countries suggests that each country has its own pattern of innovation in biotechnology. Countries with large home markets appear to have the best opportunities to exploit the development of new market niches. We found some evidence of synergy between sectors at a national level. We could find little evidence of integration of European markets for these sectors. The equipment and supplies market is fragmented by a plethora of standards and the biopharmaceuticals market by different pricing regimes in each country.

The study has four main policy conclusions. Firstly, there is need for EC Member States to agree a common definition for biotechnology and a common approach to providing statistical data to resolve current difficulties in collecting comparable data. Secondly, despite public hostility, there are many reasons for continued national and EC funding of public sector research in plant biotechnology. Thirdly, it is timely for the European Committee for Standardisation to consider whether it is opportune to introduce common standards in some areas of the equipment and supplies market. Finally, consideration should to be given to the adoption of similar pricing regimes for innovative new biopharmaceutical products across the EC, although we recognise that this is a very sensitive issue for national governments.

1. Executive Summary

1.1 Objectives and Approach to the Project

The main aims of the European Biotechnology Innovation System (EBIS) project were to discover whether the development of biotechnology in Europe is mainly influenced by national or sectoral factors, and to consider the implications for biotechnology policy both at a European and national level. It also aimed to increase theoretical understanding and empirical knowledge about 'national systems of innovation'.

To meet these aims, the approach to studying the development of biotechnology encompassed scientific, industrial, technical, economic and regulatory changes and trends, both past and present, as well as attempting to predict future patterns. The aim was to contribute to a wider understanding of the processes underlying the development of new technologies in general and the evolution of biotechnology in particular.

Eight national case studies were prepared of biotechnology commercialisation in three sectors of biotechnology: bio-pharmaceuticals, agro-food (including applications to both agriculture and food)¹ and equipment and supplies. Case studies were conducted in Austria, France, Germany, Greece, Ireland, The Netherlands, Spain and the UK. These case study countries differ in terms of size, economic and industrial strengths, public attitudes to biotechnology and public policy. Some constitute the core of the European biotechnology industry and in others the exploitation of biotechnology is less well developed. It was thought that comparing case studies of countries with these national differences would help to identify the processes underlying the commercial exploitation of biotechnology.

The common framework for the national case studies was based on three main bodies of literature: national systems of innovation, technological systems and socio-technical systems. It also drew on controversy literature. The framework consisted of four networks - knowledge and skills; industry and supply; demand and social acceptability; and finance and industrial development - and the links between them. This framework is more comprehensive than that provided individually by the three underlying bodies of literature.

The eight national reports have a general introduction to the characteristics of each country which might have affected the development of biotechnology, including industrial policy since 1990. Chapters on each sector review the science base, industrial structure, the nature of the market including consumer attitudes and the prospects for the sector. The national reports conclude by comparing the three sectors. Data gathered about the companies in each country was consolidated in a single database which, together with the national case studies, contribute to cross-sectoral overviews for each of the biopharmaceuticals, agro-food and equipment and supplies sectors. The results of the project draw on the national case studies, the cross-sectoral overviews and analysis of the database of firms active in

¹ Throughout this report we use the term agro-food biotechnology to refer to the application of biotechnology both to agriculture (seed and agrochemical firms), and to food production (for control processes or diagnostics).

biotechnology in the eight countries. They also consider US and European competitiveness in the three sectors, and take account of EC and US policy for the science base, patenting and SMEs.

1.2 Main Results

1.2.1 Commercial Activity

The comparison of commercial activity in biotechnology in the three sectors and its distribution between the eight countries shows that the countries with the highest overall number of biotechnology firms are France, Germany and the UK. The Netherlands also has a significant number of firms. These countries are all home to domestic multinational chemical and/or pharmaceutical companies. Austria, Greece and Spain have few biotechnology firms (but these include a high proportion of subsidiary companies in Austria and Greece) and most were created 30-40 years ago, indicating that the majority have diversified into biotechnology. The average date of foundation of Irish, French, German and UK firms is more recent, suggesting that the majority were created specifically to exploit biotechnology. Most firms were independently founded and university spin-offs are rare, except for Germany, Ireland and the UK where they account for 20% of biotechnology firms.

There are biopharmaceutical companies in every country in our study, with the highest numbers in France, Germany and the UK. Every country also has some firms in the agro-food sector, but the number is small except in France, Germany, The Netherlands and Spain. Equipment and supplies firm are not so well distributed. They are mainly located in Germany, The Netherlands and the UK.

Of the 723 firms for which we have data, the largest number are in the biopharmaceuticals sector (337). They are younger than firms in the other two sectors, suggesting that they were set up specifically to exploit biotechnology. More than two-thirds of these firms have under 50 employees, but over one-fifth have more than 100 employees. Total turnover accounted for by biotechnology is the highest of the three sectors, but median turnover is the lowest. The majority of firms are involved in R&D collaborations, focusing mainly on domestic and European public sector partners. US firms are the most frequent choice of private sector partners.

In contrast, the agro-food sector is the smallest sector (162 firms), with the oldest and largest firms and the highest proportion of subsidiaries. These subsidiaries may act principally as suppliers to their parent companies. Aggregate turnover for firms in this sector is reasonable, in view of the lower number of firms involved. Almost every firm is involved in R&D collaborations, mainly with domestic and European partners. Collaborations with the public sector partners predominate over those with other firms.

The equipment and supplies sector has a relatively large number of companies (224). The average age of the firms in the sector suggests that many have diversified into biotechnology. The sector consists of many small firms, showing a high level of commercial activity and a high share of turnover generated in biotechnology. Most of the firms have less than 50 employees, but the median biotechnology turnover for all equipment and supplies firms is the highest of the three sectors.

1.2.2 Factors Influencing Biopharmaceutical Innovation

An examination of national strengths and weaknesses in the key factors influencing innovation found that France, Germany and the UK far outstrip the other countries in terms of funds allocated to public sector research, the number of university departments and Research Institutes carrying out research, and in the numbers of post-graduate students being trained in relevant areas. The Netherlands and Spain have broadly comparable, but more modest achievements. The difference in population size between these two countries suggests that per capita expenditure on biotechnology research is probably higher in The Netherlands than in Spain. The other countries invest far less funds in relevant research and research training.

The vast majority of biotechnology SMEs are in France, Germany and the UK. These countries are home to multinational pharmaceutical companies and, together with The Netherlands, have attracted foreign pharmaceutical multinationals to establish research-active subsidiaries; these countries also have strong sectoral business interest non government organisations (BINGOs) to represent the interests of the business community. Subsidiaries of multinational pharmaceutical companies involved in R&D can also boost national activity, and they account for most industrial biotechnology research in Austria and Spain.

The size of the market and the regimes followed for procuring pharmaceuticals by national healthcare systems clearly influence the activities of companies in the larger countries. Countries with a procurement regime which favours low priced products, particularly The Netherlands, Spain and Greece, seem to have had a negative impact on the development of national biopharmaceutical companies. Among the smaller countries Austria seems to have attracted inward investment by a previous policy of providing an agreed margin for products manufactured inside Austria. Austria, like Ireland, has a rather strong pharmaceutical sector based around the activities of foreign subsidiaries. Both countries serve as good entry points to larger markets: Ireland to the EU and Austria to Central and Eastern Europe.

Public attitudes to biopharmaceuticals are positive in all countries. There is also a common regulatory regime for biopharmaceuticals, which mainly follows EC regulations. There has been long-standing and strong technology policy to support the development of biotechnology firms in the UK, Germany and Ireland, including mechanisms to encourage technology transfer. Until recently, policy to promote biotechnology innovation or technology transfer was weak in France, The Netherlands, Austria, Greece and Spain. France and The Netherlands are now doing more to support the creation of small firms. With the exception of Greece, technology policy has also improved in the other countries. Availability of finance capital can affect the creation of start-up firms. Conditions are favourable in the UK, Germany, France and The Netherlands but poor in Austria, Ireland, Greece and Spain.

To sum up: the UK and Germany have an environment where most factors are supportive or strongly supportive of innovation in biopharmaceuticals and none impede the development of the sector. Most factors in France provide some support to the sector, but there are also several areas which have so far acted as a brake on innovation, although recent policy is now attempting to address these handicaps.

The Netherlands has a mixture of both positive and negative influences on innovation. The negative effect of the small market size is compounded by low expenditure on pharmaceutical products but this seems to outweigh many positive factors which could encourage pharmaceutical innovation. Austria and Ireland, by contrast, have only a few positive factors. Demand-side factors, particularly the opportunity to provide a launch-pad for access to adjacent markets, however, seems to allow these two countries to play a bigger role in biopharmaceutical innovation than might otherwise be expected. Spain has certain strengths in knowledge and skills and engages in public-private R&D cooperation. However, the potential for biopharmaceuticals innovation is limited by widespread weaknesses, especially strong control of pharmaceutical prices. Greece invests in scientific education, but most of the other factors affecting innovation suffer from weakness and impede national innovation. This analysis appears to suggest that though all the factors may have a role to play in contributing to innovation, their significance in the process varies.

1.2.3 Factors Affecting Agro-Food Biotechnology Innovation

Public sector biotechnology research related to agriculture and agro-food receives much lower funding than that in the biopharmaceuticals area. However, much of European investment in relevant research comes from public (national or the EC) sources, not private investment.

Germany, France and The Netherlands make the largest investment in public sector research and mainly focus on plant biotechnology. The UK and Ireland also invest in plant biotechnology and plant science but these investments do not generate commercial activity. Austria, Spain and Greece are building a scientific base, which may or may not be dedicated to agro-food biotechnology. Spanish agro-food biotechnology research is growing in strength.

Industrial activity is strongest in Germany, France and The Netherlands, partly due to the activities of large, domestic multinational companies and their subsidiaries. These countries neglected technology transfer and small business creation until recently, but public policy now emphasises these activities. In terms of small biotechnology firms, the leading countries are France, The Netherlands and Spain, with Germany in fourth place. Agro-food SMEs dominate Greece's very small number of biotechnology firms, but there are only a tiny number in the UK. Technology policy is little different from that for biopharmaceuticals. However, there is now a tendency for European agro-chemical multinational companies (MNCs) to locate their biotechnology R&D facilities in the US.

The main focus of commercialisation in this sector has been by MNCs, and they have concentrated on six or seven important crops (maize, cotton, rapeseed, soybeans etc.), and on applications connected with herbicide resistance. There is low demand or public acceptance for these applications of GM (genetically modified) crops and food, although the strength of public opposition varies from country to country. Concentrated food retailers and manufacturers have played a major role in eliminating these products from the products they stock. Despite the EC providing a common background regulatory framework, national agencies have sometimes adopted a more stringent approach at the detailed level. Thus there is fragmented regulation and competition between European and national agencies to promote the

precautionary principle or other ethical standards. In addition, food retailers and manufacturing have introduced *de facto* regulation by introducing "zero-tolerance" to GM ingredients.

It is very difficult to interpret data on field trials for GM crops, especially since they date back to 1991, when public opposition to GM crops scarcely existed. The concentration of field trials in France is difficult to interpret. France is a large country with a strong agricultural sector. Public opposition may count for less than agricultural interests, be less organised than elsewhere or government agencies may choose to disregard public hostility to GMOs. There may also be less extreme public opposition to GMOs in Spain and The Netherlands since a significant percentage of trials also take place in these two countries. The presence of several major, influential companies may partly explain this activity in The Netherlands. France, The Netherlands and Spain also have the most small biotechnology firms in the sector. This could be due to the strong agricultural traditions of these countries, together with muted public opposition.

The results for the UK are difficult to understand. It has a strong science base in the area and there is a national emphasis on commercialising that science base. Although there have been a significant number of field trials, there are very few small biotechnology firms. The campaigns of public interest groups, reinforced by media coverage and the response of concentrated food retailers appear to have created an environment where venture capital is loath to invest in these firms. Alternatively those companies which are involved may not be prepared to admit that they are active in the area. Another possible explanation is related to the importance of subsidiaries in this sector. Multinationals may choose to locate subsidiaries in countries where public acceptance is higher than in the UK. This hypothesis is partly borne out by data about the countries which appear to have the highest number of field trials for GM crops.

To sum up, the development of the agro-food biotechnology sector faces considerable barriers. The countries best placed to develop their competences in the area are France and The Netherlands, based on their science base, their multinational companies and muted public opposition to GMOs. Spain's fast-growing science base and relative lack of public opposition to GMOs gives it the potential to develop national strength. The main brake on the development of agro-food biotechnology, however, is the weakness of private investment in R&D, together with non-availability of venture capital to support the formation of small firms. Germany has a large number of domestic agrochemical multinationals; they may choose to use the knowledge developed in the public sector for applications and field trials in other parts of the world where there is less public hostility.

North America has given the majority of approvals to commercialisation of GM crops and, in 1999, had almost three-quarters of world-wide acreage planted with transgenic crops. Reasons for the predominant activity in the US include the size of the market and the suitability to US climatic conditions of some of the crops first modified. Differences in regulation and in public acceptance between the US and Europe appear to be far more significant. It is not clear whether BSE and other crises connected with food production have aroused European public concern about the risks of GMOs. Fears about GMOs may have spread rapidly throughout Europe

because the process of developing common regulations, and disagreements between countries on those regulations, provided a platform for public interest groups to draw attention to potential risks.

1.2.4 Factors Affecting Equipment and Supplies Innovation

Germany, The Netherlands and UK have a well-developed biotechnology equipment and supplies sector. These countries maintain numerous institutions devoted to scientific research and education. The number of scientists per capita and the pool of academics engaged in advanced scientific research in these countries are high. The scope of basic research funding may also serve as an important demand factor for the equipment and supplies industry. There is also considerable investment in research by various multinational chemical and pharmaceutical companies in these countries, as well as a growing population of new biotechnology firms. National research activity provides both a market for equipment and supplies and may also stimulate the development of new generations of products. The domestic market in Germany and UK is large enough to induce further growth of the sector. The businesses in The Netherlands have strong links to firms in other countries which may compensate for the relatively small domestic market. The strong venture capital markets in these countries nurture the foundation and growth of small start-up companies.

Public research funding in Austria, Greece, Ireland and Spain is low compared to other countries, thus hampering demand and the development of a large pool of creative scientists. In addition, Austria, Spain, Greece and Ireland have few biotechnology firms in the equipment and supplies sector, and though Austria and Spain host R&D-performing subsidiaries of multinational pharmaceutical and/or chemical companies, these companies may source equipment and supplies from their home countries. In France, academic and industrial research communities are healthy but they are poorly linked, and institutional mechanisms have failed to exploit these strengths. The cluster of countries with little or no industrial activity in equipment and supplies does not have much of a tradition in engineering or in the development of instrumentation; its academic researchers have a low commercial orientation, and availability of venture capital is poor.

The market for the equipment and supplies sector is stable and robust because its products are used in a number of industries and by a wide range of public sector research (PSR) organisations and institutions. Unlike other sectors, companies do not appear to have to cope with negative public attitudes to their work. However, the proliferation of standards throughout Europe caused by national and cultural differences may hinder the long-term development of the sector. The US does not suffer from this proliferation of standards.

1.3 Conclusions

The central aim of this study was to identify the extent to which the development of biotechnology in Europe takes place at the sectoral level or, in contrast, is mainly determined by the institutional features of particular 'national systems of innovation' (NSI). Our findings reveal great differences in innovation patterns between the eight countries studied. Partial explanations for these differences are provided by the NSI conceptual framework. National case studies confirm that the R&D system, the role of the public sector including public policy, interfirm relationships, the financial

system, and the national education and training system are important elements of a NSI. They also show the relevance of taking a systems approach to understanding innovation performance which considers the relationships between these elements. For instance, although some of the difference in national innovation performance in biotechnology is related to public policy for developing the science base, it also depends on whether such policy was associated with mechanisms to link the science base with industry or to overcome cultural traditions in universities which acted as a barrier to small firm creation. NSI is also correct in suggesting that the existing national structure of production will influence innovation patterns. ("Path-dependence" could be another way to describe this phenomenon.) The strength of France, Germany and the UK in biopharmaceuticals is partly related to existing national strength in the pharmaceuticals sector. Moreover, the strength of Germany, The Netherlands and the UK in the equipment and supplies sector appears to be related to R&D activities in domestic and foreign-owned chemical/pharmaceuticals MNCs, as well as substantial investment in public sector research. The findings may also be related to the fact that emerging technologies often demand the development of new markets. It could be that only countries with large markets are able to exploit these opportunities at the early stages of development. Despite the usefulness of NSI in explaining the findings, however, it does not fully capture all the significant factors explaining variation in innovation between countries. In particular, NSI does not pay sufficient attention to demand or the nature of the market, and ignores public attitudes.

These three factors are also important in explaining differences in innovation activity between sectors. Again, however, partial explanations can be drawn from differences in the other framework conditions for innovation in the three sectors. The results show that research knowledge and skills for bio-pharmaceuticals are the focus of public sector investment in every country. Agro-food biotechnology knowledge and skills are also present in every country, but are only given priority in a few of them and receive a small fraction of the funds dedicated to biopharmaceuticals. There is no specific science base for equipment and supplies (if we ignore the fact that the materials and techniques developed during the course of any biotechnology research may be relevant for the sector). Industrial activity concentrates on the biopharmaceutical sector, is significant in equipment and supplies, but is least evident in the agro-food sector.

It is possible to gain insight into the different innovation patterns in the three sectors by considering how investment in public sector research and the nature of the market affect the opportunities and the risks faced by entrepreneurs. High potential demand and public acceptance for biopharmaceuticals allied with heavy investment in public sector research create a plethora of opportunities for business creation. The promise of rewards seems to compensate for the risks involved. The agro-food sector faces public hostility, lack of demand and relatively low investment in public sector research. Thus innovation faces high risks, and limited opportunities for new business creation. There is high actual and potential demand for research equipment and supplies, especially in countries with large public and private research communities. Research activity may also generate ideas for new products. The sector appears to be unaffected by public opinion and there are therefore low risks and high opportunities for new business creation.

The nature of demand and the market appear to play a very significant role in explaining different patterns of innovation activity both by country and by sector. In agro-food biotechnology the market is characterised by close links between producers, distributors and final consumers (the food chain). Demand has been negatively affected by a combination of public opposition to GMOs, media coverage and the response of concentrated food manufacturers and retailers, and led to relatively low innovation activity by firms. The market for GM seeds is more global than the food sector, and European MNCs in the agrochemical/seeds sector are pursuing their activities overseas. Demand and innovation activity in the equipment and supplies sector concentrate in those countries where a healthy market is guaranteed by high investment in public and private sector research. National demand for biopharmaceuticals is affected by the size of the country, per capita expenditure on pharmaceutical products and the public procurement regime. Innovation clusters in countries with large markets and procurement policies which guarantee certain profits or in smaller countries which give access to adjacent markets. However, this sector operates at the global level and though innovation may be supported by national demand characteristics, it is also driven by the potential of the global market.

The comparison of the differences in demand for the three sectors highlights the distinction between sectors which are shaped by national or global demand. Global markets are mainly exploited by MNCs, rather than new biotechnology firms. As suggested by NSI, the existing national production structure, including the existence of domestic MNCs, has an influence on national patterns of innovation. Our study shows that benefits can also flow from the innovation activities of foreign subsidiaries. However, public policy to exploit biotechnology must address both new firm creation and the needs of MNCs.

The significance of public acceptance and demand in shaping innovation in biotechnology, the difference of these characteristics between sectors, and the differential effect on innovation of sectors with domestic and global markets suggests that the development of biotechnology in Europe takes place mainly at the sectoral level across clusters of countries with similar conditions for industrial innovation. We therefore conclude, in answer to one of the underlying questions of the project, that each sector has its own system of innovation, but that its specific shaping is determined by national characteristics. The institutional features of particular NSIs do affect biotechnology innovation because sectoral innovation occurs in specific national locations and is dependent on history and the trajectory of innovation. National factors, however, appear to be of secondary importance to sectoral characteristics in explaining patterns of commercialisation in biotechnology. These findings confirm the views of Malerba (1999) that the development of appropriate public policy requires the description of "the working, structure and dynamics of a sector in ... developing, producing and selling products and services to a demand composed by users and consumers and the way a sector changes over time."

A second objective of the study was to add to theoretical understanding and empirical knowledge of 'national systems of innovation'. Our findings reinforce some aspects of NSI, but it is considered to be more useful as a heuristic than as a theory, because it does not provide any clear indicators that would allow analysis to

concentrate on similarities and differences between countries. The findings do not challenge the relevance of the NSI approach, but suggest that it does not go far enough. It ignores both demand and social acceptance in explaining national innovation performance. Public acceptance can affect demand significantly and may be crucial in new technologies which are potentially risky or raise ethical issues. In addition, although policymakers may be concerned with understanding how firms react to public policy, our study shows that any analysis must be considered in the context of sectoral demand.

A third objective of the project was to examine the implications of taking a systemic approach to the formation of national and EU policy aimed at promoting the social management of biotechnology, industrial innovation, and the harmonisation and integration of European markets. The study falls short of meeting this very ambitious objective, but it does throw some light on the issues raised. Regarding the social management of biotechnology, there has been some experience of the effects of organised public debates in The Netherlands. The Dutch government has carried out a number of initiatives since the 1980s to assess the social and ethical effects of biotechnology, to disseminate information to the public and to organise public debates. The Dutch attitude to biotechnology is above the European average, and it is one of the few countries with significant numbers of agro-food biotechnology firms. A few other countries also have firms in the sector and muted public opposition to GMOs, but they have not organised such initiatives. Therefore it is difficult to know what drives social acceptance and whether it can be influenced by government intervention. We could find little evidence of harmonisation or integration of European markets for these sectors. The equipment and supplies sector, in particular, is fragmented by a plethora of standards, even at the national level, and there is a relative lack of attention to the European market. The market for biopharmaceuticals is fragmented by different pricing regimes in each country and that for agro-food by fragmented regulation for GMOs between European and national agencies. The European Commission is currently giving close attention to the latter factor and it may be resolved soon.

Finally, we reflect on whether each country has its own system of innovation in biotechnology and the nature of any relationship between biotechnology sectors at a national and European level. The great differences between countries suggest that each country does have its own pattern of innovation in biotechnology. The results appear to indicate that countries with large home markets appear to have greater ability than smaller ones to exploit the development of new market niches for emerging technologies. We also found some evidence of synergy between sectors at a national level, particularly for the equipment and supplies sector, where major activity takes place in countries with significant R&D activity in the pharmaceutical and chemicals sectors, as well as in PSR.

Several characteristics of biotechnology firms in the eight countries differentiate them from their US counterparts. First is the high proportion of independently established firms and dearth of university spin-offs. Secondly, we found a significant number of European firms which had diversified into biotechnology, especially in the agro-food and equipment and supplies sectors. We do not know whether this shows better diffusion or the benefits of late entry. These characteristics, however, do not indicate the existence of a European biotechnology innovation system. The US

appears to be closer to having a national biotechnology innovation system because, in general, there have been similar regulations for each sector, with the United States Department of Agriculture (USDA) and the Food and Drug Administration (FDA) working closely together. In Europe the great fragmentation between social actors prevents the operation of a single market in any of the sectors. This is particularly marked in the agro-food sector, where there are both national and cultural differences in food preferences and the implementation of EC policy, suggesting that common European regulation and patents may be a necessary, but not sufficient condition for creating a single market.

Before turning to the policy implications of these results, the methodology employed for the study merits attention. The decision to select research equipment and supplies as one of the sectors to be studied has been completely vindicated. To date this sector has received very little attention but the results of the study show that it covers a large number of profitable firms in Europe.

However, there was difficulty in getting comparable data on the public biotechnology science base, either for research funding or for the training and production of PhDs. Some countries do not differentiate between various elements of "life sciences" in their statistics. Moreover, it is unclear what definition of biotechnology is being used by countries which do provide data for the field. The problem of definition is complicated both because of the dynamic nature of the field and because of the emergence of new non-biotechnology areas which are closely linked to biotechnology (e.g. combinatorial chemistry and bio-informatics).

Secondly, it was often difficult to identify firms, or to get useful data about them. Small companies often did not have the time to complete questionnaires, or were unready to provide information which they regarded as confidential. Those, which had diversified into biotechnology, were sometimes unable to differentiate between their biotechnology and non-biotechnology activities. Our approach to defining sectors by a list of technologies was largely successful. However, the technology is rather dynamic and over time a company's products may become generic in the sense that they become applicable to more than one sector. There is a risk that the "list of technologies" approach to identifying sectors could fail to identify firms with generic products which might be used in several sectors.

Finally, although NSI focuses on the systemic character of the whole system, our study has not captured sufficiently the links within or between the four networks used as the basis for data collection. This was partly related to the design of the project. Links are possibly better captured by in-depth, case studies with a small number of companies rather than with extensive industrial surveys. However, a larger part of the problem was related to the vagueness of NSI concepts – it was very difficult to work out how to operationalise identification of the detailed working of network links in a consistent manner. However, this project was not designed to improve methodology, it was an applied project. Future research projects could focus on how to apply the NSI conceptual framework in a consistent manner.

1.4 Policy Implications

The results of the study suggest several implications for policy. The first concerns the lack of comparative biotechnology data, particularly about the science base.

There is need for EC Member States to agree on a common definition for biotechnology and on a common approach to providing statistical data.

A number of policy implications are connected to current widespread public hostility to biotechnology applied to the food chain. The project team considers that there should be continued national and EC funding of public sector research in plant biotechnology. This is required to encourage strong European MNCs in the sector to maintain R&D facilities in Europe. In addition, continuing world-wide activity in the area, especially in North America, demands that Europe continues to have the expertise to operate in international networks, for instance to assess the risks associated with these developments, and to participate in international negotiations – as well as capturing spillovers from external knowledge.

Public resistance to agro-food biotechnology has mainly been provoked by the initial commercial activities of the MNCs. Their focus on herbicide resistance connected to a few major crops have been unacceptable to the public, but there is enormous unexplored potential for developing knowledge about more acceptable applications. For instance, plant biotechnology can be used to develop raw materials for industry or for the production of biopharmaceuticals. Biotechnology can also be used as a tool in plant breeding. Moreover, GM crops designed to reduce levels of pesticide use could benefit rather than harm the environment. To ensure public confidence, however, it is not sufficient to build up research capabilities, it is also necessary to invest in systematic EC bio-safety research and testing capabilities, i.e. field trials, to provide a framework which makes this option possible. This will provide a framework for communicating to the public about safe and beneficial application of biotechnology to agriculture. The example of The Netherlands suggests communication should be associated with public debate and efforts to seek public views.

Bearing in mind the many small seeds producers in the southern Mediterranean, it also seems relevant for collective research to be funded into horticultural crops relevant to southern countries. This would allow southern Mediterranean countries to capture niche markets and strengthen their competitive advantage. An example might be to decode the melon genome as the basis for improving disease resistance, flavour, or keeping qualities etc.

One of the positive outcomes of the study was identifying the active and profitable European equipment and supplies sector, even though this mainly concentrates in three countries. The flexibility of European firms to respond to user needs and the variety of products offered could be a strength. However, we believe that these firms should be encouraged to do more to exploit the European market as a whole, and that the European Committee for Standardisation needs to look at the plethora of standards affecting this market and consider whether it is opportune to introduce common standards in any areas.

Widely varying procurement regimes for pharmaceuticals across EC Member States are another area of concern. The introduction of the Euro will do much to make these differences transparent and it may be appropriate for consideration to be given to the adoption of similar pricing regimes for innovative new products across the EC, although we recognise that this is a very sensitive issue for national governments.

2. Background and objectives of the project

The development of biotechnology in Europe faces a number of major problems, including a lack of international competitiveness and consumer resistance to new products. The emphasis of EU policy on harmonisation and the formation of the single market appeared to have resulted in too little attention being given to the national, sectoral and cultural differences between member states which may partly explain these difficulties. This project was designed to examine how far barriers to development are rooted at either the national or the sectoral level. It also aimed to provide a systemic analysis which linked economic change to broader cultural and social processes.

The three main objectives of the project were:

- to assess the extent to which the development of biotechnology in Europe takes place at the sectoral level or, in contrast, is mainly determined by the institutional features of particular 'national systems of innovation';
- to add to theoretical understanding and empirical knowledge of 'national systems of innovation' by examining the adequacy of this concept in an analysis of three different sectors of biotechnology;
- to examine the implications of taking a systemic approach to the formation of national and EU policy aimed at promoting the social management of biotechnology, industrial innovation, and the harmonisation and integration of European markets.

In this study the development of biotechnology encompassed scientific, industrial, technical, economic and regulatory changes and trends, both past and present, as well as an attempt to predict future patterns. It took this approach with the intention of contributing to a wider understanding of the processes underlying the development of new technologies in general and the evolution of biotechnology in particular.

A number of important questions arose from the systemic view of innovation used in this study:

- How do different countries vary in their ability to develop, and adapt to, the creation of new biotechnology-based innovations? Does each European country have its own national system of innovation in biotechnology?
- To what extent is innovation specific to a given sector of biotechnology (e.g. biopharmaceuticals)? Does each sector have its own system of innovation? What is the relationship between biotechnology sectors at a national and European level?
- Are national or sectoral differences based on a particular pattern of social, cultural and economic institutions? What are the structural, institutional and organisational bases of specific national competencies?

The study's central aim - to identify whether the national or sectoral system of innovation is dominant in biotechnology - has important policy implications. If biotechnology is characterised by strong sectoral systems, then it may be easy to create a single integrated European market. In this case, policy formation would be appropriate at the European level, with programmes tailored to the specific character of each sector. However, it may be that economic integration is proceeding at different rates in different sectors, and that in some sectors it will be relatively easy to construct a single market, whilst in others it will be extremely difficult. If national systems of innovation are dominant in some sectors, there may be nationally based institutional limits to the process of harmonisation and integration. The project concluded by exploring if a new policy agenda, based on an acceptance of diversity, might be more effective in promoting both the competitive and acceptable development of biotechnology throughout Europe.

3. Scientific description of the project results and methodology

This section first describes the methodology used to achieve the objectives outlined above. It then presents the main findings of the project by comparing commercial activity in biotechnology in the three sectors studied: pharmaceuticals, agro-foods and equipment and supplies. It also discusses how that activity is distributed between the eight case study countries: Austria, France, Germany, Greece, Ireland, The Netherlands, Spain and the U.K. The section concludes by considering the key factors influencing innovation, and the differences between sectors and countries which may be responsible for producing these results.

3.1 Project Methodology

In order to reach the objectives outlined in section 2, the project was designed so as to be able to make comparisons of the innovation system both within countries by sector and between sectors in the eight countries involved. Two components of the methodology directly addressed this task. The first was the preparation of eight national case studies of developments in three sectors: bio-pharmaceuticals, agro-food and equipment and supplies. The second was the use of the national case studies to prepare three cross-sectoral analyses of developments in the three sectors of interest. The selection of case study countries includes those which differ in terms of many characteristics including size, economic and industrial strengths, public attitudes to biotechnology and public policy. Another major difference between the case study countries is that some constitute the core of the European biotechnology industry and in others the exploitation of biotechnology is less well developed. It was thought that comparing case studies of countries with these national differences would help to identify the processes underlying the commercial exploitation of biotechnology. The results presented in this report draw on both the national and cross-sectoral analyses. The following paragraphs outline in detail these and other supporting components of the methodology.

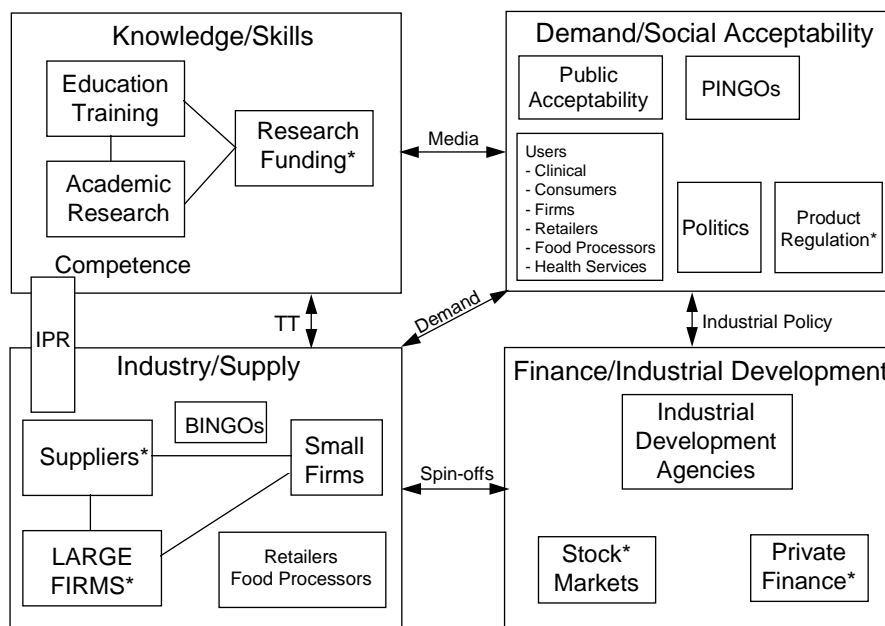
A common framework was developed for the national case studies. It drew on literature reviews² and workshop discussions to identify the central elements and relationships between three main bodies of literature: national systems of innovation, technological systems and socio-technical systems. These literatures are extensive and have significant overlaps, but also serve to complement each other in identifying important additional features which may affect the process of technological change. The NSI approach is a macro-level concept, whereas technological systems focus on specific techno-industrial areas. The socio-technical approach emphasises public or private social actors and intermediaries in innovation networks. These three literatures had limited usefulness, however, in terms of mapping the "social or public acceptability" of new technologies, or the public actors involved in decisions connected with new technologies. To fill this gap, a fourth literature review was undertaken on controversies, and in particular the constructivist approach within it.

Figure 1 provides a simplified overview of the factors identified as significant to innovation, the networks within which these institutions and organisations are embedded and their inter-relationships. As shown, the main components of the

² J. Senker et al (1999)

framework are networks of knowledge and skills; industry and supply; demand and social acceptability; and finance and industrial development. This framework is more comprehensive than that provided by the three underlying bodies of literature. The national case studies aimed to provide information about these networks and about the elements which linked them together.

Figure 1: Networks of Key Factors Influencing Innovation



*International influence

TT = technology transfer IPR = Intellectual Property Rights PINGOs = Public interest non-government organisations BINGOs = Business interest non-government organisations

Workshop discussions about the design of the national case studies focused on making decisions about

- the questions to be answered about the networks and elements in Figure 1.
- the key factors for which data was to be collected. Decisions on this were informed by partners' knowledge about the limitations and/or costs and time involved in using specific data-sources.³
- the common data sources to be used.
- the approach to be adopted for the collection of data.
- the definition to identify firms involved in each sector. This was based on specified product areas and sub-fields of biotechnology.
- the controversy that would help to assess the social acceptability of biotechnology for each sector. These were xenotransplantation for the bio-pharmaceuticals sector, GM foods or crops for the agro-food sector and genome sequencing equipment for equipment and supplies.

³ For instance, it was agreed that for the knowledge/skills network we would concentrate mainly on input and not performance data. This was because performance data such as bibliometrics, patents, the number of molecular biology PhDs awarded, or industrial revenue received by universities were available in aggregate form only and not disaggregated to a level to match the sectors in the study.

A common reporting structure was also agreed for the national reports. This included a general introduction to the characteristics of each country which might affect the development of biotechnology such as strong national economic sectors, critical historical events, elements of the culture or political style, industrial policy since 1990 and any recent changes in direction in terms of the four networks being considered. Chapters on each sector also followed a common framework and reviewed the science base, the industrial structure, the nature of the market including consumer attitudes and the prospects for the sector. The national reports concluded by comparing the three sectors.

Secondary sources were used for collecting background national and sectoral information. Model questionnaires were designed for collecting information about new biotechnology firms, or other firms which had diversified into biotechnology. They were for optional use only, and partners were free to collect required information by other means. The agreed approach for all the issues was detailed in a "Methodological Guidebook" which was distributed to all partners. The guidebook was an attempt to ensure that the national case studies were as comparable as possible through employing a common framework and definitions for the phenomena being studied, by using the same indicators and similar data sources to represent the factors under study and by reporting the findings in reports which were to conform to a common structure.

Two workshops were held during this phase of the project. They reviewed progress on the national case studies, and resolved difficulties experienced in following the Guidebook. In particular it was decided that it was not appropriate to include a controversy on the equipment and supplies sector. The literature review indicated that public controversies are characterised by the involvement of actors who do not belong exclusively to the scientific community, but these were the only participants in the controversy about genome sequencing. To facilitate the preparation of cross-sectoral analyses for each of the pharmaceuticals, agro-food and equipment and supplies sectors it was also decided to develop a common database to hold the data produced by the industry surveys in each country. This was an addition to the work content originally agreed for the project.

An assessment of European policy for biotechnology was prepared to provide contextual background for the cross-sectoral analyses. It discussed EC policy for the science base, for regulation, for patenting, as well as policy to support small firms. These policies were contrasted with US conditions, where appropriate. This policy overview, the national studies and relevant secondary sources were used to prepare the three cross-sectoral analyses.

3.2 Commercial Exploitation of Biotechnology

This section provides background information about the general characteristics of the three sectors studied before presenting the main results of the industry survey.

3.2.1 General characteristics of the sectors

i) Pharmaceuticals: The European pharmaceutical industry competes in a global market place and in 1998 it accounted for 40% of world output. It is a net exporter of pharmaceuticals and with the exception of Austria and Spain, the countries in this study have a positive pharmaceuticals balance of trade. Multinational companies dominate the sector and invest in intensive R&D to bring new products to market, to move into competitors' markets and to meet health and safety regulations. The long time (typically 12 years) and high cost of bringing new drugs to market has been a major barrier to entry, and provided an excuse to maintain high profit margins on new drugs (Sharp & Senker, 1999).

The costs of innovation have been increased substantially by advances in biotechnology which are being applied both as research tools in the drug discovery process and in the discovery of new drugs (Henderson et al, 1999). The growth of mergers between large multinational companies in recent years has been driven by the need to reduce innovation and sales costs (Hodgson, 1999).

Domestic multinational pharmaceutical companies are significant players in three of the countries in our study: France, Germany and the UK. These three countries are also home to subsidiaries of other European and US multinationals which are active in R&D. France, for instance, is home to several laboratories of Swiss pharmaceutical firms. The Netherlands has major multinational chemical companies (but none in pharmaceuticals) and these appear to have had some influence on industrial biotechnology activities.

The research activities of foreign-owned subsidiaries are a significant part of the biotechnology R&D effort throughout Europe. There are subsidiaries of major European multinationals in every country except Ireland and Greece. US subsidiaries are mainly located in Germany (8) the UK (6) and Ireland (4) with 2 each in Spain and France. Irish pharmaceutical subsidiaries are mainly involved in manufacturing in state-of-the-art facilities. They have had limited research activities but a trend is now developing for them to undertake biopharmaceutical research in Ireland. Subsidiaries undertake significant biotechnology activities in The Netherlands and Austria; they also make some contribution in Spain. Foreign subsidiaries in Spain and Austria are included in the general analysis of the activities of small and medium sized companies, in 3.2.1 below because they are almost the only significant industrial performers of biotechnology research in these countries.

Pharmaceutical business interest non government organisations (BINGOs) are active in every country except Greece, and play a minimal role in Austria and Spain. They are extremely strong in Germany and significant in France, The Netherlands and the UK.

ii) The agro-food sector: The agro-food sector involves a wide variety of diverse actors: on the one hand there is agriculture, with farmers, seed firms and agrochemical firms producing pesticides and fertilisers; on the other, there are agro-

food firms that supply products directly to consumers, essentially through mass distribution. In both cases, the implications of the use of biotechnology are different. For agriculture, biotechnology allows seeds to be improved and this can be linked to reduced application of agrochemicals. In agro-food, biotechnology is used to control processes and for diagnostics. In all cases, agricultural and agro-food biotechnology is rarely integrated into final products; it is used for production or control.

Since the late 1970s, the sector has been shaped by the activities of agrochemical firms. They faced increasingly saturated markets and biotechnology offered the potential to develop new, profitable products to wipe out competition from low-cost products no longer in patent protection. Biotechnology can speed up the screening process for new agrochemicals and improve their efficiency. Initially the agrochemicals firms were extremely active in acquiring seeds companies; more recently, as the sector became more mature there have been mergers between agrochemical companies (Tait et al, 2001). The main characteristics of the two sectors are:

- important to national and the European economies;
- large number of firms and concentration of research in a small number of large firms, mainly multinationals in agriculture (seed and agrochemical companies); the seed multinationals are oriented to the European market and agrochemical multinationals towards the international market. Food manufacturing is also highly concentrated but, with a high volume, low value-added market, companies have a low propensity to invest in R&D.
- national specificities in food consumption.
- limited use of patents. In agriculture, plant varieties are protected by plant certificates. Patent protection is used mainly by biotech firms for specific genes or specific techniques. Agrochemical firms protect innovation by producing complementary products, especially plants with genes resistant to specific herbicides. In the agro-food sector firms have a low propensity to patent because much innovation is in the production process which is difficult to imitate. Secondly, there are low margins for agro-food and firms base competition more on marketing, than on intellectual property.

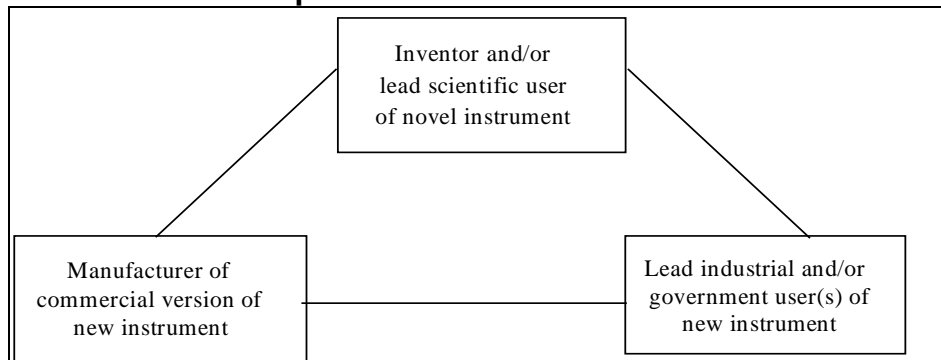
Germany, UK, France and the Netherlands are countries in which technological progress in agriculture is important. They all have a strong industrial base in agriculture and agro-food, and large domestic multinationals. In Austria, Ireland, Spain and Greece the farming system is less intensive and the agro-food sector is less developed.

Apart from The Netherlands, where the interests of agro-food firms are represented by a BINGO for the biotechnology industry, there do not seem to be any specific biotech associations for the agriculture or agro-food sectors. Nor are BINGOs in the agriculture and agro-food sectors visible or powerful. One of their main handicaps is the segmentation of markets (milk, beer, yeast, etc.) and relationships with other professional associations.

iii) The equipment and supplies sector: There is no statistical sector for the equipment and supplies, or publicly available information about market size and growth rates. The sector was defined solely according to specified product areas

and sub-fields of biotechnology. The overlap between traditional research areas like immunology, molecular biology and biochemistry is one reason why it is so difficult to delimit a clear market segment for this sector. It has been assumed that innovation in the sector is similar to that in the scientific instruments sector. Irvine (1991) suggests that successful development of scientific instruments depends on integrating potential (scientific) users into the testing and commercialisation process, as shown in Figure 2. The involvement of lead-users from industry or

Figure 2: The Golden Triangle of Relationships in Successful Development of Scientific Instruments



Source: Irvine, 1991

government ensures that market needs are taken into account during the innovation process, and guarantees important initial sales. Technically sophisticated, high-status lead-users can promote the rapid diffusion of new scientific instruments. This analysis suggests that the strength of the biotech instruments and supplies sector may be intimately linked to the strength of the science base and industrial research in any country.

3.2.2 Strategies for Biotechnology in the Three Sectors

Small biopharmaceutical firms have been formed to exploit new scientific breakthroughs in biotechnology, especially their potential to revolutionise the innovation process. There appear to be two possible paths which new biotechnology firms may follow. They may seek to provide "platform" technologies or other specialised knowledge to large pharmaceutical and small biotechnology firms. Alternatively they may attempt to become integrated pharmaceutical companies and compete with the incumbents. Both strategies are likely to lead to increased concentration. Firms following the former strategy may become vulnerable to take-over by multinational companies in the long term. However, initial platform technologies were unidisciplinary (based on molecular biology or biology). Current platform technologies are multidisciplinary or interdisciplinary (DNA chips, DNA/RNA arrays, proteomic analysis combining electrophoresis and NMR, genome sequencing or mapping single nucleotide polymorphisms). In this orientation, referred to as the "omics", the blend of hardware and reagents provides the basis for firms to enter the equipment and supplies sector and achieve high levels of profitability.

Firms following the latter strategy may seek to acquire or merge with other small biotechnology firms so as to expand their product pipeline, increase company valuation, provide access to complementary expertise or technologies, increase

"critical mass" and capabilities so as to create a new, strong entity in which the whole is greater than the sum of the individual parts.

The agriculture and agro-food sectors are characterised by strong concentration around a few multinationals. In this context of strong concentration, biotech SMEs developed in close contact with industrial groups, especially in the 1980s and 90s. This explains why biotechnology SMEs linked to agriculture have a higher turnover and number of employees than the average. They are also older, on average, and the parent companies provide a market that enables them to economically valorise their technological developments.

While SMEs in the agriculture and agro-food sectors that developed during the 1980s and 90s from major industrial groups were able to generate high turnovers compared to firms in the bio-pharmaceutical sector, the late 1990s witnessed a new wave of start-ups based on more recent technologies (genomics, gene function). This new generation of firms relies on research that highlights the unity of living matter, and uses specific plants as model species. Technical progress has enabled them to develop diagnostic kits to resolve questions relevant to the public: content of vitamins, fats, lipids, etc., presence of listeria, or GMOs, etc. This movement is now strengthening, with the development of diagnostic kits for environmental applications and for the detection of transmissible animal diseases such as foot and mouth disease and BSE.

Zipkin (2000) suggests that the equipment and supplies market is segregating into

- supermarket companies providing a broad range of reagents and consumables. Growth is a prerequisite for such firms to stay competitive. Consolidation is most likely in this arena.
- players combining instrumentation and reagents in several well-defined application niches, and
- small companies occupying a single niche, concentrating on product branding.

Suppliers of biotech reagents and instruments have to keep up with their increasingly sophisticated customers. Both in the US and Europe, small firms trying to exploit experimental niches have shown impressive growth. At the same time, larger companies in the life science supply chain are trying to increase their market share and brand name recognition. In the past, many of the big firms have been built around platform technologies like molecular biology or immunology. This pattern is vanishing in the face of customers' demands for systems solutions, designed to solve problems of a particular experimental technique. Maintaining the link between instrument platform technologies and corresponding reagents may well be a key to ensure market share and profitability because the cross-selling potential is high. Customers like to buy both from the same supplier in order to maintain compatibility. Margins are often higher in reagents than in hardware.

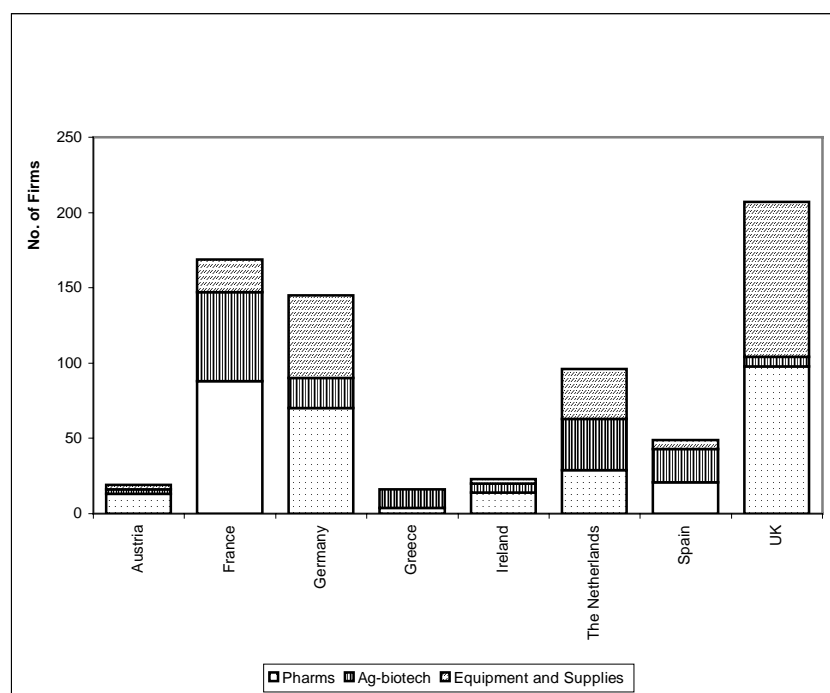
3.2.3 Results of the industry survey

The industry survey collected information on 724 small firms involved in biotechnology. It included subsidiaries of MNCs. Details of each company were

entered on the common database.⁴ A small number of firms (14) are involved in more than one sector. An analysis of the main results of the survey, presented below, found that the commercial exploitation of biotechnology differs markedly between the three sectors and eight countries.

The greatest number of firms (337) were involved in pharmaceutical applications of biotechnology, followed by equipment and supplies firms (224). Only 162 firms involved in agro-food biotech applications were identified, less than half the number active in the pharmaceutical area. Figure 3 shows the distribution of firms by sector and country. This shows that France, Germany and the UK are the major biotechnology players, with The Netherlands not far behind. Every country has firms involved in innovation in biopharmaceuticals and in agro-food biotech, but the focus on the latter activity is very limited in some countries. Equipment and supplies firms tend to concentrate their activities in the countries that are the major players, and scarcely exist in the other countries.

Figure 3: No. of Biotech Firms by Sector and Country



The industrial structure of firms in each country can also be analysed in terms of their age. Table 1 gives the median date for the creation of biotech firms in each country. In Austria, Greece and Spain, the number of biotech firms is small and a median creation date in the first half of the 1970s suggests that the majority have diversified into biotech. The median foundation year for firms in Germany, France, UK, The Netherlands and Ireland is after 1989, suggesting that the majority have been created specifically to exploit biotechnology. The median date of creation of

⁴ Data on some aspects is poor. For instance some firms did not provide information on turnover. We do not know whether this reflects lack of turnover or commercial confidentiality. Some gave the amount of turnover, but not the proportion contributed by biotechnology. Others told us the proportion of turnover contributed by biotechnology, but not the amount. Primary information on sector, date of establishment, origin of firm is more comprehensive than other details. The results of the analysis of the database should therefore be regarded as indicative only, and treated with caution.

firms also differs by sector, with agro-food firms having the oldest median age (1987), equipment and supplies firms slightly more recent (1989) and biopharmaceutical firms the youngest (1993). Moreover, it seems that some of the older firms (those founded before 1980) mainly diversified into biotechnology, rather than being established to exploit the technology. One third of agro-food and 22% of equipment and supplies firms are long established, but only a minority of biopharmaceutical firms (13%) were founded before 1980.

Table 1: Median foundation date of biotech firms, by country

	A	DE	FR	GR	IRL	NL	SP	UK
Median date of foundation of biotech firms	1974	1994	1992	1973	1993	1989	1974	1990

Figure 4 shows the number of firms created each year since 1980 for each sector. The late 1980s were a period of rapid growth in the creation of biotechnology firms in all sectors. Since then growth in new agro-food firms has first levelled off and then slowed down. Biopharmaceutical firms entered a second period of dynamic growth since 1995. Creation of firms in the equipment and supplies sectors has shown steady growth overall, with fluctuations from year to year.

Figure 4: No. of Firms Created by Sector and Year

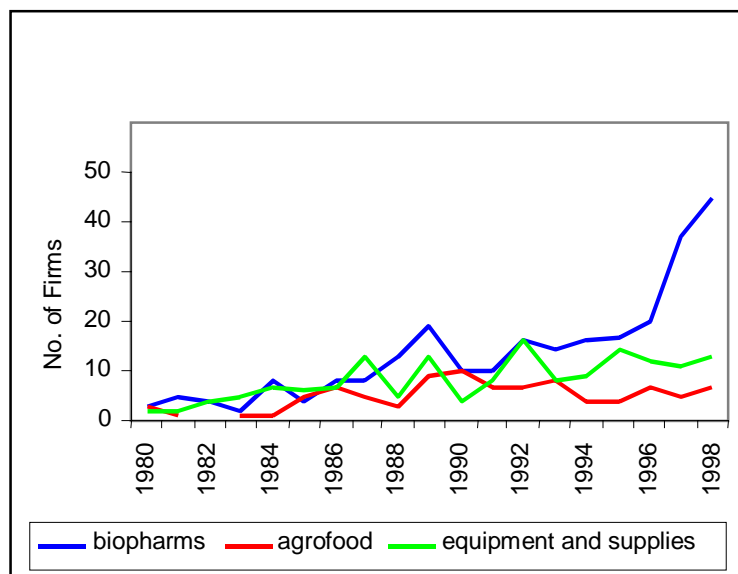


Figure 5, the distribution of firms by the number of employees and sector, shows that agro-food biotech firms have the highest proportion of large firms (>100 employees). Equipment and supplies firms have the highest proportion of firms with less than 20 employees and over 80% have less than 50 employees. Over two-thirds of biopharms firms have less than 50 employees, but some of the new firms now appear to have grown; over 20% have more than 100 employees.

Figure 5: Distribution of Firms by Size and Sector

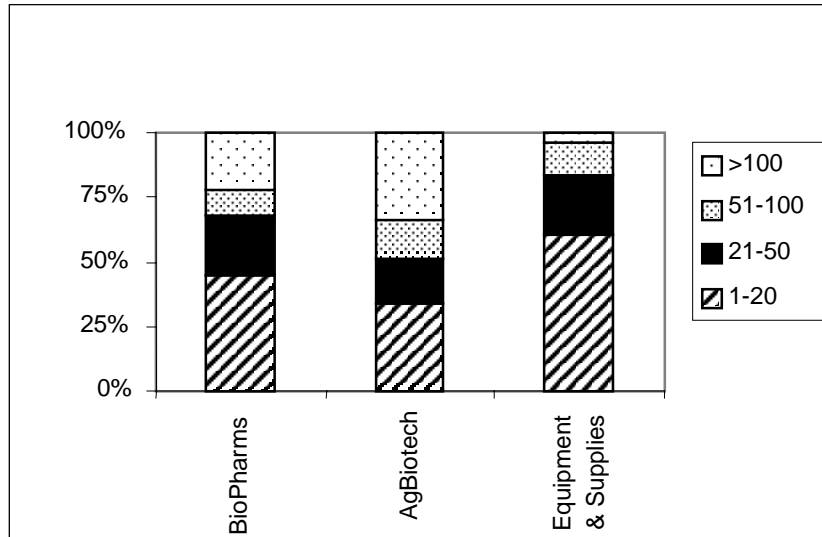
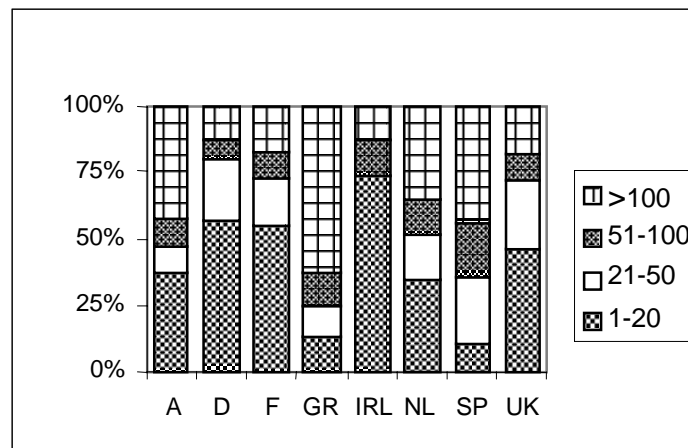


Figure 6 shows how firms of different sizes are distributed between countries. The countries in which the number of employees concentrate in firms with over 100 employees are also those whose firms are the oldest - Austria, Greece and Spain, suggesting that exploitation of biotechnology is mainly by diversification, not the creation of new firms. By contrast, it appears that in countries with younger firms on average, and a high proportion of small and very small firms (UK, DE, F and Ireland), commercial activity is led by dedicated biotechnology firms.

Figure 6: Proportion of Firms by Size and Country



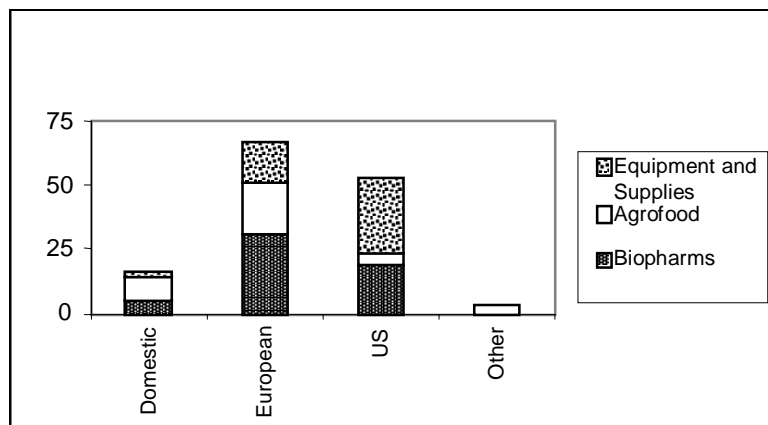
Information on the amount and proportion of turnover attributable to biotechnology was not provided by all firms (see footnote 4). The highest total turnover (€3.989M) came from the biopharmaceuticals sector, followed by agro-food biotech (€1.478M) with equipment and supplies firms slightly behind (€1.281M). Median turnover for each sector provides a different ranking. The highest median turnover is €1.87M (equipment and supplies), followed by agro-food biotech (€1.199M) with biopharmaceuticals firms in third place (€1.134M).⁵

⁵ The results are based on 70% of agro-food biotech firms, 60% of equipment and supplies firms and 58% of biopharms firms.

Only one third of the biopharmaceuticals companies are involved in selling biotechnology products but over 50% (175 firms) are offering a wide variety of specialized services including contract research, contract manufacturing, custom synthesis, development, sequencing, testing, software design and so on. There is patchy data only on companies' sales activities in the agro-food biotech sector. We have information on the main product markets of 61 firms only:⁶ almost 60% of these regard the domestic market as most important. Fewer than 20% treat Europe as their main product market and the remainder focus on markets outside Europe and the US. The majority of firms in the equipment and supplies sector sell biotechnology products (86%) and the domestic market is particularly important for German and British firms. Dutch firms focused more on Europe and other countries (outside Europe and the US). In general, the domestic market was most important for 36% of the firms and Europe was the main market for 32%; only 16% of the firms see their main product market in the US. Since most of the patents (55%) held by firms have national claims only, it is reasonable to assume that the majority of the equipment and supply firms focus mainly on the domestic market.

The sample of biotechnology firms included 139 subsidiaries (19% of total) who provided information about the location of their parent company. As shown in Figure 7, a small number were subsidiaries of a parent company in the same country (16), but the majority were subsidiaries of firms in other European companies (67). There were 53 subsidiaries of US companies; 56% of these were in the equipment and supplies sector, but very few (4) in agro-food. The majority of subsidiaries were located in France (29%) and Germany (28%); in terms of their share of all national companies, subsidiaries were most significant in Austria (32%) and Greece (31%).

Figure 7: No. of Subsidiaries by Location of Parent and Sector



The highest proportion of subsidiaries was in the agro-food (23%) and equipment and supplies (21%) sectors. They only represented 16% of firms in biopharms. Seventy per cent of firms in the agro-food sector with >€150M turnover were subsidiaries. It is suggested that the high turnover may be explained by the parent company acting as a market for its subsidiaries.

⁶ It appears that approximately 26% of the remaining firms are not yet selling products and we have no information about the remainder.

In terms of their origins, the majority of firms were independently established, as shown in Figure 8. Industry spin-offs are negligible, and the highest proportion of university spin-offs are in the biopharms sector.

Figure 8: Origin of Companies by Sector

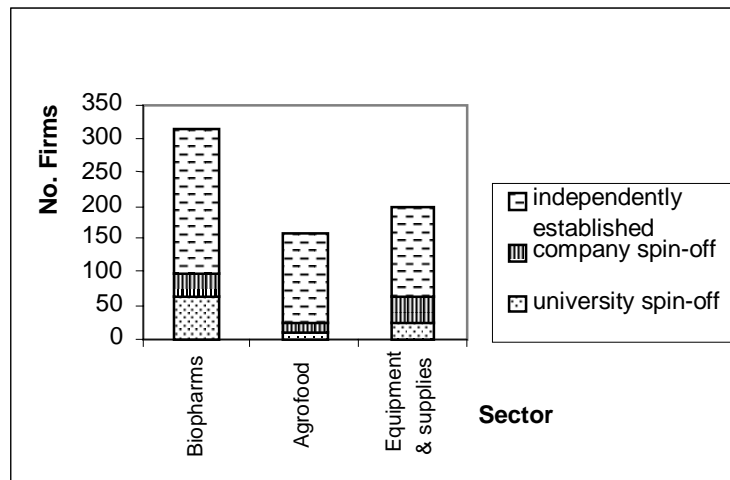
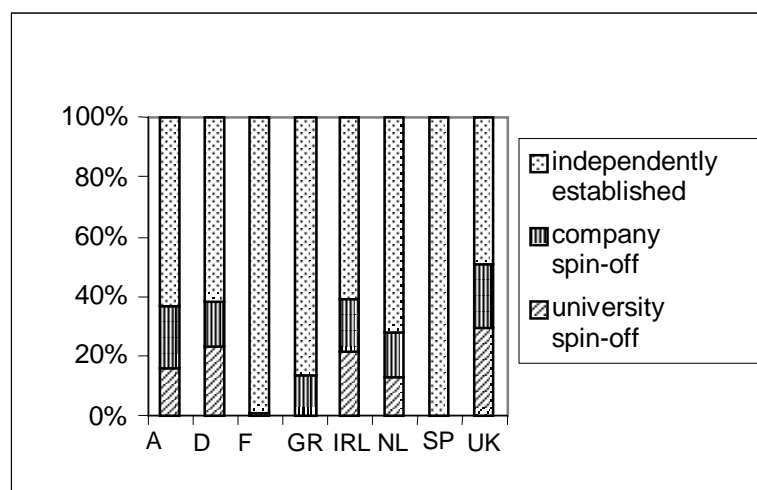


Figure 9 shows the origins of companies by country. The countries with the greatest proportion of university spin-offs (just over 20%) are Germany, Ireland and the UK. In Spain there are only independently established companies and, with a small number of exceptions, the same is true of France.

Figure 9: Origin of Companies by Country



The majority of agro-food (96%) and biopharms (83%) companies are involved in R&D collaborations; the proportion of equipment and supplies firms involved in R&D collaborations is much lower (44%). In biopharms and agro-food, collaborative partners in PSR are more frequent than those with other firms. PSR partners are mainly domestic and European. In biopharms, firms in the US formed the highest number of collaborative partners in industry, with domestic firms lagging slightly behind. In agro-food, R&D collaboration with the private sector focused on domestic and European partners. In equipment and supplies, we have data on R&D collaborations for Germany, The Netherlands and the UK (the countries where the

sector is most developed). Firms in this sector tend to collaborate with domestic PSR. On average, British and Dutch firms tend to team up more with other European firms than the German firms, which have a greater propensity to partner domestic firms.

3.2.4 Summarising the Industry/Supply Network in the 3 Sectors

The largest number of firms are in the biopharmaceuticals sector (337) and, on average, they are much younger than firms in the other two sectors. This suggests that the firms were set up specifically to exploit the potential of biotechnology. More than two-thirds of these firms have under 50 employees, but over one-fifth of all firms have more than 100 employees. This sector has the highest total turnover, but lowest median turnover. Only one third of the companies are involved in selling biotechnology products but over 50% (175 firms) are offering a wide variety of specialized services. Only 16% of these companies are subsidiaries of other firms. Although few European biotechnology firms began life as university spin-offs, the highest proportion occurs in the biopharmaceuticals sector. The majority of firms are involved in R&D collaborations, focusing mainly on domestic and European public sector partners. US firms are the most frequent choice of private sector partners. There are firms in this sector in every country in the study.

In contrast, the agro-food sector is the smallest sector (162 firms), with the oldest and largest firms and the highest proportion of subsidiaries. The relatively small number of firms explains the relatively low aggregate turnover. These subsidiaries may act principally as suppliers to their parent companies. Almost every firm is involved in R&D collaborations, mainly with domestic and European partners. Collaborations with the public sector partners predominate over those with other firms.

The equipment and supplies sector has a relatively large number of companies (224), and these concentrate in a few countries. The average age of the firms in the sector suggests that many have diversified into biotechnology. Most of the firms have less than 50 employees but firms in this sector have the highest median turnover of the three sectors. The proportion of subsidiaries is similar to agro-food but, unlike the agro-food sector, the majority of these (almost one quarter) have US parents. Some of these act as distribution outlets for the parent company.

The majority of the firms in this sector are selling biotechnology products (86%), and their main focus is domestic and European markets. In those countries where the sector is more developed (in Germany, the Netherlands and the UK), the sector consists of many small firms, showing a high level of commercial activity and a high share of turnover generated in biotechnology. Obviously, the time to market is considerably shorter than in the pharmaceuticals sector. The size structure suggests that the sector may provide many business opportunities for suppliers of niche market products, but that the scope for growth may not be as great as that in the pharmaceuticals sector. On average, the British and the Dutch firms collaborate with other European firms more often than the German companies. The latter tend to have R&D collaborations with domestic enterprises. However, companies' R&D collaborations are predominantly with public sector partners.

3.2.4 Summarising the Industry/Supply Network in the Eight Countries

The countries with the highest number of biotechnology firms are France, Germany and the UK. With the exception of Spain, these are the largest countries in terms of population. The Netherlands, one of the smaller countries, also has a significant number of firms. Austria, Greece and Spain have few firms and most were created 30-40 years ago, indicating that the majority have diversified into biotechnology. In contrast, a more recent average year of foundation for Irish, French, German and UK firms suggests that the majority were created specifically to exploit biotechnology. These countries also have a high proportion of firms with less than 50 employees. France and Germany have the most subsidiary companies, but they constitute the highest proportion of all biotechnology firms in Austria and Greece. University spin-off firms are rare, but they are most frequent in Germany, Ireland and the UK where they account for approximately 20% of all biotechnology firms.

Biopharmaceuticals companies exist in every country in our study, with the highest numbers in France, Germany and the UK. Every country also has some firms in the agro-food sector, but the number is small except in France, Germany, The Netherlands and Spain. It is especially surprising to find only a tiny number of firms in this sector in the UK, since it is the country with the highest number of biotechnology companies overall. There are substantial numbers of equipment and supplies firms only in Germany, The Netherlands and the UK; the number in France is rather low.

3.3 Key Factors affecting innovation

In an attempt to understand the results of the industry survey, this section will review the key factors affecting innovation in the knowledge/skills, finance/industrial development and demand/social acceptability networks and how they differ between countries. Some of the national differences in the interfaces between these networks (intellectual property, technology transfer etc.) are also discussed. Some of the key factors discussed do not differ by sector (e.g. technology transfer mechanisms), but where evidence of differences exist, these are mentioned.

3.3.1 The Knowledge/Skills Network

This section considers the government policies for the science base relevant to innovation. These include the investment in public sector research and postgraduate training, instruments to promote technology transfer and intellectual property regimes for public sector research. Barriers to achieving the aims of these policies are also discussed.

The current skills and knowledge base in each country depends in part at the date at which national policy first focused on its development. The countries in our study can be roughly divided into two groups: the first group commissioned reports about biotechnology during the 1970s and began to introduce policies to enhance or provide a biotechnology research infrastructure around 1980 (France, Greece, The Netherlands and the UK). France and the UK also took steps to raise industrial awareness about the potential of biotechnology, to promote academic links with industry and to encourage the commercialisation of academic research; this also occurred in The Netherlands from the mid 1990s. France, the UK and Greece also intervened in the formation of dedicated biotechnology firms. Two of the French start-ups (founded in 1979 and 1982) and one of the British start-ups (founded in 1980) focused on medical applications. The Greek start-up (which no longer exists)

was intended to act as an intermediary between academic research and industrial application.

The second group of countries (Austria, Germany, Ireland and Spain) did not introduce policies for biotechnology until the second half of the 1980s. Germany commissioned a report about biotechnology in the early 1970s and started funding biotechnology projects at that time. The first infrastructural measure to build up the science base was the establishment of Gene Centres in Cologne, Heidelberg and Munich in 1982. The first programme for promoting "applied biology and biotechnology", however, commenced only in 1985. A 1980 report about biotechnology in Austria was intended to guide strategy for biotechnology. The first initiative, in 1984, aimed to transfer knowledge from research institutions to industry and no steps were taken to build up the research infrastructure until 1985. Spain became aware in 1984 that it lacked both the industrial infrastructure and skilled scientists to launch a research programme in biotechnology. It therefore introduced a programme to remedy this deficit and by 1988 its National Plans were able to include a special programme for biotechnology. The Irish biotechnology programme did not commence until 1987. It aimed to develop commercially-oriented research in Irish universities.

Collecting truly comparable data about investment in public sector research, national research manpower and postgraduate training in biotechnology, especially for the three sectors in our study, proved almost impossible. Each country has a different system for organising public sector research, and uses a different basis for assembling data on expenditure, research manpower,⁷ and postgraduate degrees. The data collected indicates that the large countries have numerous public sector institutes and university departments involved in research as well as numbering their public sector researchers and PhD awards in the thousands. This contrasts with lower activity in the smaller countries, which is compensated for by students who undertake post-graduate training abroad.

Even where figures are available for public research expenditure, these are probably under-estimates as significant allocations of funds are omitted, including those allocated by regional authorities (especially in France, Spain and Germany), and the block grant provided for university faculty to conduct research in countries such as France, Germany and Spain.

Expenditure on public biopharmaceuticals related research is only available for some of the countries in our study.⁸ The data that is available suggests that this field commands a high proportion of the public biotechnology research budget. Non-profit organisations also make a significant contribution to this area in France, The Netherlands and the UK. A rough comparison of per capita public expenditure on biopharmaceuticals research shows Spain spends around half of the amount in the leading countries: France, Germany and the UK. Austrian and Greek expenditure is negligible.

⁷ Note for instance that France collects information for "life sciences" only and does not separately gather statistics on biotechnology. Germany made one attempt only, in 1992, to gather official biotechnology statistics.

⁸ For instance, expenditure on public sector research in The Netherlands is not classified in a manner that allows the identification of the amount allocated to biopharmaceuticals related research.

Expenditure on agro-biotech research is only a small fraction of that allocated to the biopharmaceuticals area. The countries spending the most are France, Germany, The Netherlands and the UK. Greece, Austria and Ireland spend the least on the science base. However, Ireland has a specific position because of the weight of agriculture and agro-food in gross domestic product and because of the priority ascribed to the biotechnology science base in general. However, support for this area is concentrated into a few fields only. Spain has an intermediate position with a fast growing science base, especially in terms of the number of trained researchers. Research seems to be more relevant to agricultural biotech than to agro-food. In the latter area research focuses on technological issues such as improved efficiency in fermentation and on the control of food safety.

Almost all universities in Europe with science or engineering faculties undertake some research with relevance for the equipment and supplies sector. Underpinning knowledge for this sector may arise during the course of almost any research which employs biotechnology techniques or concentrates on specific aspects of biotechnology. Thus it may be appropriate to suggest that almost the whole of the biotechnology science base in any country supports the equipment and supply sector. It is difficult, however, to estimate the number of skilled researchers or students in this area with any accuracy. Limited data and qualitative assessments in national case studies suggest that there is a specific science base for the equipment and supplies sector only in Germany and the UK. No specific science base could be identified in Austria, France, Greece, Ireland, the Netherlands or Spain. Some of these countries (France, Greece, The Netherlands and Spain) have recently developed expertise in bioinformatics.

3.3.2 Technology transfer and IPR

Technology transfer mechanisms for public sector research are very strong in the UK, quite good, but improving in Germany, and strong in Ireland. Patterns of technology transfer in France and The Netherlands formerly favoured large firms. In recent years the focus has shifted to encouraging the creation of new firms to exploit research results. Austria, Greece and Spain are characterised by poor links between academic research and industry. Moreover academic entrepreneurship is inhibited by academic job security and/or rules for academic intellectual property in every country except the UK. Some countries, notably France, are now changing some of these rules to stimulate technology transfer and small firm creation.

Germany and the UK have a wide range of mechanisms which support the public-private collaborative research links of relevance to large companies, stimulate the creation of small start-up companies and encourage existing small firms to appreciate the benefits of applying biotechnology tools and techniques. Ireland has benefited from the activities of BioResearch Ireland, a Programme in Advanced Technology which focuses on biotechnology. It was set up in 1988 as a partnership between government and the universities to promote the commercialisation of university research. Some countries, like France and The Netherlands, have only belatedly recognised the importance of policies directed towards small firm creation. Previously efforts concentrated on links with large firms only. Poor technology transfer in Austria may be related to the lack of any specific research programmes

targeted at biotechnology or the lack of any technology transfer mechanisms until 1998.

There are a variety of policies for dealing with the intellectual property (IP) which arises from academic research. There are two main approaches that vary both between and within countries. The main difference between the approaches is whether IP belongs to the inventor or to the institution within which the inventor works. Policy for academic patents is perceived as having a relationship to technology transfer but there is lack of knowledge about which arrangement works better at promoting the application of results by industry, or the conditions affecting such application. Academics are generally perceived as having neither the knowledge nor the resources to take out patents. Where IP rests with the inventor, policies focus on overcoming academic reluctance to apply for patents. Where IP belongs to the institution, policy focuses on establishing agencies to handle IP. It is usual for special arrangements to be agreed for the IP rights arising from collaborative research between academics and industry.

3.3.4 The Finance/Industrial Development Network

Most countries have a range of policies to support industrial innovation in general; sometimes these policies focus on biotechnology in general. Industrial policy in Greece and Austria, however, lacks any special focus on biotechnology and this was also true of Dutch industrial policy during some periods in the last twenty years.

Dutch industrial policy in the early 1980s focused on promoting companies' in-house research. In the 1990s it has focused on grants for collaborative research programmes between industry and public sector research and on stimulating the commercialisation of public sector research. This mainly focused on large existing firms. From 2000 initiatives were put in place to promote the creation of new start-up firms. Loans are available to companies for the development phase of innovative products and processes, and the government funds 40% of total costs up to a maximum level. Tax credits are also available which provide 40% of the costs of R&D employees. Greek industrial policy is largely connected to its technology transfer initiatives. It also funds industrial research projects undertaken by a consortium of firms or a single firm. Since 1998 Austrian industrial policy has also focused on initiatives including those to commercialise the results of public sector research, to promote knowledge transfer between public and private sector research and the creation of start-up companies.

Industrial policy in the other countries gives some emphasis to biotechnology. BioResearch Ireland funds research in universities, supports the transfer of research results to existing industry, or to new university-based start-up companies. German industrial policy includes programmes to encourage firms to adopt new technologies and to raise industrial awareness about biotechnology. It also promotes applications-oriented research by distributing funds for collaborative research through the Association of Industrial Research Organisations. French industrial policy provides tax credits for companies conducting in-house research. UK industrial policy takes the form of a wide range of schemes to promote and fund university-industry research links with firms of all sizes, as well as encouraging the creation of new start-ups. Spanish industrial policy funds joint research by firms and public research groups, development projects to take new products to the market and projects to

help companies adopt new technology. Firms' costs are funded by credits at low (or zero) rates of interest. Although biotechnology is one of its action areas it received only a tiny proportion of available funds.

The views of multinational pharmaceutical companies contribute to shaping research programmes in France, Germany and the UK and there are several programmes with a focus on topics of direct interest to biopharmaceuticals. In these countries some aspects of industrial policy focus on the biopharmaceuticals areas. France, for instance, has created a 'genopole' for genomics and gene therapy which brings together public research institutes, university teaching and small firms. The 'genopole' is intended to be a "pole" of excellence which serves as a technological platform and promotes the creation of start-up companies. Biopharmaceutical companies in Germany are encouraged to participate in research collaborations with public researchers involved in the Human Genome Research project and with some Gene Centres/centres of excellence.

For many years Europe had very poor availability of venture capital compared with the US.⁹ In 1979, for instance, there were 250 US venture capital firms, but very few in Europe, except for a handful in the UK (Rothwell and Zegveld 1982, pp. 37 and 89). The situation has changed rapidly in recent years, but in some countries it is still difficult for new biotechnology firms to find initial financing.

For instance, although private equity investment in Spain is increasing, the majority goes to large Spanish companies involved in industrial products and services. New start-ups received only 5%, there was even less for seed capital (1%), and less than .02% was directed towards biotechnology. The first Greek investment capital fund was set up in 1991, but it mainly invested in mature companies or those able to produce high profits quickly. A new law was passed in 1995 to encourage private equity to increase the amount of investment in seed and start-up companies. Since the venture capital firms lack expertise in biotechnology and are risk averse, they have not invested in biotech start-ups. There is also low availability of venture capital in Austria. Two venture capital firms are active in biotechnology but only a tiny proportion of available funds has been allocated to this sector. Irish venture capital firms are also reluctant to invest in the biotechnology sector because most companies are "early stage" and cannot meet venture capital firms' investment criteria. Some biopharmaceutical companies have received investment from international venture capital firms with life science/ biotechnology sections.

The situation is rather better in the UK, Germany, France and The Netherlands. The UK has one of the most favourable legal and fiscal environments for private equity in Europe with the Alternative Investment Market and other stock exchanges providing the equity firms with a number of exit opportunities. Biotechnology receives a small proportion of available venture capital, but the share has risen over time. Tax relief is also available for private investors (business angels) who buy shares in some unquoted trading companies. However, agro-food biotechnology companies have not generated enthusiasm within the investment community. Compared to other biotechnology sectors, agro-food biotechnology is perceived as high risk and with less potential premiums for its products (Crowther et al, 1999). There is an

⁹ Venture capital companies supply risk capital to new companies set up to exploit scientific research.

abundance of venture capital seeking investment opportunities in Germany, and a high interest in biopharmaceutical firms because of the potential for a high return, especially when a company is launched on the stock exchange. The *Neuer Markt* in Frankfurt encourages biopharmaceutical firms to list their stocks. Dutch venture capital is well developed and one firm specializes in biotechnology investment. However, many applications for venture capital fail because start-up firms lack the management capabilities demanded by venture capital firms. There are also many business angels and an agency for introducing Dutch entrepreneurs to these informal investors. The agency has also established a "circle" of investors with a specific interest in biotechnology and pharmaceuticals. Most start-up firms use their own resources or rely on business angels. France has created the *Nouveau Marché*, a stock exchange for high tech and rapidly growing firms. There has also been rapid growth of venture capital firms who only invest in companies in the health sector. At the regional level venture capital firms work together with local government agencies. The recent collapse of new, high tech market segments (especially in information and communications technologies) suggest that exit conditions for venture capital are becoming more difficult. Although new life science companies have not been so badly affected it is presently unclear how venture capital financing for this sector will develop.

3.3.5 Demand/Social Acceptability Network

This section discusses the demand factors which affect the innovation process in the three sectors. Each sector is discussed separately because these factors vary by sector. Public procurement, for instance, is important in pharmaceuticals and standards have significance for equipment and supplies. The analysis of controversies undertaken in the three sectors to identify "public acceptance" of the new technology, and the public actors involved in decisions about them found that there was no public debate in the equipment and supplies sector. Although there was public debate in both the agro/agro-food and biopharmaceuticals sectors, the influence of public interest non-government organisations (PINGOs), and public acceptance of the application of biotechnology was very different in these two sectors. Regulation is relevant to all three sectors, but its impact also varies by sector.

3.3.5.1 Biopharmaceuticals

The potential market for pharmaceutical products is affected by the size of the country, per capita expenditure on pharmaceutical products and the public procurement regime. The largest markets for pharmaceutical products are in France and Germany. Per capita expenditure¹⁰ is highest in France, with Austria and Germany not far behind. The Netherlands, Spain and the UK are in an intermediate position, but per capita expenditure in Greece and Ireland trails far behind. The size of the market for some small countries, notably Ireland and Austria, is much larger than the domestic market. Global pharmaceutical companies from the US locate in Ireland, mainly for manufacturing purposes, so as to access the European market. Similarly, one of the advantages of locating in Austria is the closeness to the expanding markets of Central and Eastern Europe.

¹⁰ Based on sales of pharmaceuticals to "end-consumers" (i.e. patients through pharmacies or other distribution channels) in each country. The data is drawn from a variety of sources, which are not strictly comparable and should be regarded as indicative only.

Every European country uses public procurement policies to control pharmaceutical prices, because the state is largely responsible for the costs of healthcare. There is hard bargaining between companies and health ministries and considerable price variation between countries, because each country bargains in isolation and has its own regime for regulating prices. Thus, the market for pharmaceutical products in the EC is highly fragmented.

Germany and the UK promote innovation by pharmaceutical companies, with Germany allowing companies freedom in setting prices for new products and the UK regulating profits, but rewarding R&D activity. Austria used to provide companies with a certain margin on their production costs for products produced inside the country, whereas international reference prices were used to regulate the price of imports. New procedures were introduced in 1999. Prices are highly regulated in the other countries; France requires approval of the manufacturer's price before a product is authorised for reimbursement. Price increases are rarely allowed and decreases may be introduced (Danzon & Chao, 2000). The Netherlands, Greece, Ireland and Spain use international comparisons for setting pharmaceutical prices. Spain pays much lower prices for pharmaceutical products than other European countries and pricing policies in Greece have disadvantaged domestic companies and favoured imports.

Regulation in every country mainly follows EC Directives and, since 1995, the approval of new bio-pharmaceuticals has rested with the European Medicines Evaluation Agency (EMA).

Surveys in many countries have assessed public acceptance of various applications of biotechnology, as well as general knowledge about biotechnology. The Dutch have the highest level of knowledge about biotechnology in the EC and also have a positive attitude to medical applications. These attitudes have developed in an environment in which there have been many studies on the social effects of biotechnology and several public campaigns to raise public awareness of the technology. After wide ranging debates in the early 1990s it was generally acknowledged that acceptable exploitation of biotechnology depended on a constructive dialogue between all those concerned, including the general public, producers and consumers. Surveys in Spain and Greece have shown a low level of knowledge about biotechnology but high acceptance of medical applications of biotechnology. The Germans and the British also accept most medical applications of biotechnology. The Austrian public is the most negative towards biotechnology of all the countries in this study. However, medical applications of biotechnology have greater acceptance. Broad representation of the general public in committees which advise the government on the safety and wider impacts of biotechnology in the UK and consultation of the public by advisory committees in The Netherlands, may tend to strengthen public acceptance of biotechnology, when compared to countries such as Spain which have a policy to keep such advice confidential.

There are many different types of Public Interest Non-Government Organisations (PINGOs) which can affect the activities of the pharmaceutical industry. The UK and The Netherlands have several organisations which review the implications of new treatments, or play a part in public debates on their wider implications. In Britain,

there are two PINGOs which focus specifically on biotechnology, but the Dutch PINGOs involved are general consumers associations or a technology assessment institute. Germany's largest consumer association is concerned about transparency over genetic engineering. Patients' associations, supported by the families of patients suffering from specific conditions, are another type of PINGO. Their influence on the pharmaceutical industry differs between countries. They have very little influence on the pharmaceutical industry in Spain and Austria, which bases its R&D decisions on international considerations. Both the UK and France have several medical charities which are significant in funding research into specific areas of disease and promoting the development of new treatments; the French charities focus specifically on genetic disorders. There are also patients associations in Greece. The third type of PINGO which may affect the activities of the pharmaceutical industry are animal welfare organisations. They are concerned with the rights of animals and in reducing the number of animal trials and conditions for the animals involved. They are very active in the UK, The Netherlands and Germany. There are also animal rights groups in Greece and Austria; the former has very little influence on Greek society.

3.3.5.2 Agro -food biotech

The market of seeds, pesticides and other agrochemicals on the one hand and of agro-food products on the other is not controlled *per se*, nor is there any regulation of prices. However, in each country, and at the European level, various agencies control field trials and are concerned with the impact of products on health, the environment and food security. Pesticide regulation is seen as having the potential to create markets for new pesticides, particularly as replacements for older products which are thought to damage to the environment or to human health (Tait et al, 2001).

Public attitudes, regulation and the response of highly concentrated European food retailers and manufacturers are now having a major impact on European demand for GM crops and food. Citizens Associations (Greenpeace, Green political parties and other environmental groups) have played a crucial role in widening public debate about the implications of GMOs for crops and food, and their ideas have been widely disseminated through the media. As a result negative public attitudes to GMOs in crops and food are now widespread, although the strength of antagonism varies from country to country. Three main groups can be discerned. The public has a very negative attitude to GM crops and ingredients in foods in Austria, Germany, Greece and the UK although the Greek public was rather late to become aware of potential problems. All these countries have Citizens and Consumers Associations which have taken an active part in stimulating public debate on the topic. Their activity, promoted by wide media coverage, is particularly strong in the UK. A large PINGO campaign in the UK aiming for a moratorium on the commercial introduction of GM foods and crops included more than 90 organisations. Food retailing is highly concentrated in Austria, Germany and the UK and the major companies have responded to consumers' negative attitude by removing GM ingredients from their products. Greek food retailers and manufacturers have adopted the same position. In Austria added opposition to GM agriculture comes from the small-scale, family-run farm sector, which wants to protect its image of being an organic food pioneer.

Public opposition to GM crops and foods is not so strong in France and The Netherlands. Media interest in the GM debate has increased in France since 1997. There has been growing distrust by the public for GMOs and a great deal of uncertainty about GMO regulations resulting partly from a "lack of decision making" by politicians in this domain. Several consumer associations have organised boycotts of products containing GMOs, and the pressure on the concentrated food retailing sector has forced them to avoid GMO food. Public opposition to GMOs however, does not yet seem to have affected field trials in France or the commercial activities of agro-food biotechnology firms. This may be explained by French industrial attitudes in the chemical sector which have been described as firms reacting to government plans to gain the best advantage, rather than as taking their own initiatives (Brickman et al, 1985).

The Dutch public is more knowledgeable about biotechnology than those in other European countries, due to the long-standing work of non-government organisations such as the Rathenau Institute (the Dutch Office of Technology Assessment). Dutch experience shows that there is no correlation between the degree of public knowledge about and acceptance of biotechnology, implying that mere information campaigns are not sufficient to positively influence public acceptance. Rather, what turned out to be more important was involving the public in biotechnology related policy decisions. The Dutch have developed a tradition for seeking public opinion and this is taken into account by policy-makers. Debates do not occur solely in the media but also take place in public fora which provide information and seek the views of the public. Dutch attitudes towards biotechnology have not changed markedly over time, but the public is well informed and understands both the positive and negative aspects of the technology. Thus, despite negative publicity about cloning and genetic modification, the Dutch acknowledge the possible advantages of biotechnology and they judge the risks involved as being acceptable; they remain somewhat negative about applications to food. An important principle with respect to GM food is that the consumer has to have all the information about the product and the process to allow them to make well-informed decisions about purchasing. This is the environment in which the use of GM soy in food products was recently approved by the Dutch government.

There is less public opposition to GM food and crops in Spain than in the other countries. The agricultural tradition, the relevance of this sector and limited public reactions against plant biotechnology in Spain have led to agribusiness and public research centres conducting field trials. The Irish public is relatively optimistic about modern biotechnology in general but GM food seems to attract little public support.

The European regulatory framework adopted in the early 1990 (Directives 90/219 and 90/220 on the contained and deliberate release of genetically modified organisms) and subsequent modifications to directive 90/220 on mandatory labelling for GMOs have played an important, if largely negative role in shaping developments. Gaskell et al (2000) suggest that regulation and public opinion co-evolved in Europe and US. In the EU, increased regulatory oversight coincided with growing negative public opinion about agro-biotechnology and diminishing trust in public authorities and regulatory agencies. Two elements reinforced public distrust of regulation: First, crises like BSE and foot and mouth disease increased public anxiety about the agro-food and agriculture sectors. Secondly, a constantly changing

regulatory environment has been perceived as an institutional vacuum and this has been filled by private initiatives. Food retailers and food producers moved quickly to establish voluntary standards and labels relevant for their markets in an attempt to gain market share by meeting perceived public demands. With almost no exceptions, voluntary standards have been set up with zero (or almost zero) tolerance for products, generating "no-GMO" or GMO-free claims. Zero tolerance standards have led to reformulation of processed foods to remove biotechnology products or their derivatives and to identifiable supply chains which ensure the absence of such products. Thus, voluntary GMO-free standards have quickly become the standard, making other standards and regulation mechanisms irrelevant.

The demand for notification of deliberate field trials under Part B of Directive 90/220/EEC provides information on the extent of field trials which have taken place in EC countries since 2001, as shown in Table 2. This shows that France has conducted one third of all EU field trials. The other countries in our study with a significant number of field trials are The Netherlands, Spain and the UK.

Table 2: No. of Field Trials in EC Countries 1991-2001

Country	No.	%
Austria	3	0.2
<i>Belgium</i>	110	6.9
<i>Denmark</i>	39	2.4
<i>Finland</i>	17	1.1
France	484	30.2
Germany	109	6.8
Greece	19	1.2
Ireland	4	0.3
<i>Italy</i>	262	16.3
The Netherlands	113	7.0
<i>Portugal</i>	12	0.7
Spain	167	10.4
<i>Sweden</i>	61	3.8
UK	203	12.7
Total for the European Union	1603	100

Source: JRC website of deliberate releases at: <http://biotech.jrc.it/gmo.asp>

3.3.5.3 Equipment and Supplies

There is no publicly available statistical information for the biotechnology equipment and supplies sector because it exists only on the basis of our definition. The lack of information about market size, growth rates etc. makes it difficult to make statements in general about the development of this sector.

Our study gives strong indications that the market for biotechnology equipment and supplies within a country is influenced by the amount of relevant research undertaken in the public and private sectors. During the late 1990s, public sector research funding agencies in Germany, The Netherlands and the UK gave biotechnology a high priority thus creating a favourable environment for biotechnology equipment and supplies companies. The rapid growth of dedicated biotechnology companies in these countries, and the R&D activities of multinational companies using biotechnology tools and techniques (in agrochemicals, food and pharmaceuticals) increased the market for biotechnology equipment and supplies. Conversely, the low number of firms in the equipment and supplies sector in Austria, Greece, Ireland, Spain may be explained by the small size of the market, both public and private. Funding for public sector research is limited, and few companies are involved in biotechnology R&D. Most equipment may be imported and domestic firms may primarily be trading organisations which are not involved in manufacturing.

The low number of equipment and supplies firms in France is rather surprising, given the potential demand provided by high investment in public sector biotechnology research. There are several possible explanations: the lack of a French tradition in instrumentation development and limited demand from the private sector. On the one hand dedicated biotechnology firms were slow to develop in France and secondly, much R&D activity is in subsidiaries of Swiss multinational companies in France. Their equipment and supplies may be sourced from Switzerland.

Compared to the other two fields (bio-pharmaceuticals and agro-food) the equipment and supplies industry appears to be only slightly affected by numerous European and national laws and regulations which could influence the development of the industry. However, certain regulations may provide the foundation for the business of some companies. One example is firms that sell equipment to detect GMOs in food or the environment. Their business is actually mainly based on EC Directives 90/219 (contained use) and 220 and on negative public attitudes to GMOs. A principal Directive for the biotechnology equipment and supplies companies is 90/679 (protecting workers from risks associated with biological agents).

Standardisation and certification is a major issue for equipment and supplies products. There are around 500 standards in Germany alone with potential impact on product and technology development for companies in this sector. Some of the existing *de facto* standards could be based on historical and cultural differences. This may limit the potential to introduce common standards across Europe that meet the needs of the single market. The following paragraphs therefore discuss the relevance of standards.

The complexity and systems character of modern biotechnology has led to an increasing number of standards in the industry. These standards affect R&D, production and market penetration and thus influence innovation (diffusion), productivity, and market structure. The main benefit of introducing standards into the biotech equipment and supplies sector would be to ensure complementarity between elements within a system. The optimal interface allows for multiple component designs to coexist (David and Steinmueller 1994). According to industry experts, this is quite difficult in biotechnology. In consequence, it is more likely that users will favour systems provided by one and the same supplier rather than a conglomerate of components optimised in isolation.

Standards can be further delimited by type, according to their influence on competition and their proximity to a public good:

1. *Product element standards* can lead to competitive advantage for those manufacturers who already own or control the desired key element of the product. Many submarkets of the biosupply sector (like DNA sequencing, gene cloning, imaging) currently are at the transition between intense competition between alternative technologies and the dominance of a particular version once it has gained sufficient market share to become the *de facto* standard.
2. *Nonproduct standards* concern test and measurement methods, scientific and engineering databases, and standard reference materials (Tassey 1997). Standards derived from a technical base show many characteristics of a public good. They occur frequently in biotechnology because they often concern standards (based on physical or chemical laws) for scientific applications. Basic and laboratory standards may later become industry standards for methods, procedures, or norms. The International Conference on Harmonisation (ICH) aims to provide consistent guidance for quality testing of biologically developed pharmaceuticals and devices (among others) on a

global level. The specifications are designed to be applied to different parts of the development and production process and therefore influence quite a wide range of equipment and supplies products.

In a situation before a standard has been established or in "open systems", small and medium companies can more easily participate in markets for system technologies by supplying components in which they have a comparative advantage, thus increasing price competition and diversification. However, this variety (and flexibility) may lead to excessive customisation, by both users or suppliers, and prove critical to innovation. User-defined attributes for specific applications make plug-and-play solutions and interchange impossible, or prohibit comparability of measurements and tests. In such an environment, an industry consortium may be able to implement limited or partial standards. There is a trade-off between early standardisation (and thus cost efficient development) and compromising the range of performance attributes desired by different users. Complete standardisation too early in the technology life cycle can constrain innovation. In the equipment and supplies sector of biotechnology, new technologies are continuously being introduced into ever expanding possibilities and needs. Early standardisation could as well exert pressure to adjust the standards after a short time, e.g. to reflect changes in the core underlying technology, to adapt to toleration of faults, (more) rapid response to input data, or (more) user-friendly interfaces.

The use of voluntary standards provides a technical basis for several rules contained in European directives and regulations relevant to the equipment and supplies sector. Standards and codes of practice in Europe are implemented by the European Committee for Standardisation (CEN and CENELEC) in co-operation with the national entities. The standards provide a set of technical recommendations and specifications, which are adopted on a voluntary basis and there are no regulatory requirements (Lunel 1995).

3.4 National Strengths and Weaknesses in the Three Sectors

3.4.1 Biopharmaceuticals

In terms of the knowledge/skills network, France, Germany and the UK far outstrip the other countries in terms of funds allocated to public sector research, the number of university departments and Research Institutes carrying out research, and in the numbers of post-graduate students being trained. The Netherlands and Spain have broadly comparable, but more modest achievements in these areas, but the difference in population size between these two countries suggest that per capita expenditure on biotechnology research is probably higher in The Netherlands than in Spain. The other countries allocate significantly less funds to relevant research and research training.

The industry/supply network appears to be strongest in France, Germany and the UK. These countries are home to multinational pharmaceutical companies and the vast majority of SMEs. These three countries and The Netherlands have attracted foreign pharmaceutical multinationals to establish research-active subsidiaries and also have strong BINGOs to represent the interests of the business community. Subsidiaries of multinational pharmaceutical companies involved in R&D can also

boost national activity. For instance, they account for most industrial biotechnology research in Austria and Spain.

The importance of national PSR partners in SMEs' R&D collaborations suggests that countries with a strong knowledge base (the UK, France and Germany) help their SMEs to thrive. However, the importance of the US for SMEs' private collaborations emphasise the global nature of this sector.

The size of the market and the regimes followed for procuring pharmaceuticals by national healthcare systems clearly influence the activities of companies in the larger countries. Countries with strong control of pharmaceutical prices, particularly The Netherlands, Spain and Greece, seem to have a negative impact on the development of national pharmaceutical companies. Among the smaller countries Austria seems to have attracted inward investment by its previous policy of providing an agreed margin for products manufactured inside Austria. Austria, like Ireland, has a rather strong pharmaceutical sector based around the activities of foreign subsidiaries. Both countries serve as good entry points to larger markets: Ireland to the EU and Austria to Central and Eastern Europe.

In terms of the factors affecting demand and social acceptability, there is no difference between countries in terms of regulation. The common approach to regulation mainly follows EC Directives and, for the approval of new biopharmaceuticals, rests with the European Medicines Evaluation Agency. Nor could any differences be discerned between countries in terms of the acceptance of biopharmaceuticals. PINGOs could, in theory affect the public acceptance of biopharmaceuticals, but they did not appear to have any major effect in the countries studied.

There has been long-standing and strong technology policy to support the development of biotechnology firms in the UK, Germany and Ireland, including mechanisms to encourage technology transfer. Until recently, policy to promote biotechnology innovation or technology transfer was weak in France, The Netherlands, Austria, Greece and Spain. France and The Netherlands are now doing more to support the creation of small firms. With the exception of Greece, technology policy has also improved in the other countries. Availability of finance capital can affect the creation of start-up firms. Conditions are favourable in the UK, Germany, France and The Netherlands but poor in Austria, Ireland, Greece and Spain.

To sum up: the UK and Germany have an environment where most factors are supportive or strongly supportive of innovation in biopharmaceuticals and none impede the development of the sector. Most factors in France provide some support to the sector, but there are also several areas which have so far acted as a brake on innovation, although recent policy is now attempting to address these handicaps. The Netherlands has a mixture of both positive and negative influences on innovation. The negative effect of the small market size is compounded by low expenditure on pharmaceutical products and this seems to outweigh many positive factors which could encourage pharmaceutical innovation. Austria and Ireland, by contrast, have only a few positive factors. Demand-side factors, particularly the opportunity to provide a launch-pad for access to adjacent markets, however, seems

to allow these two countries to play a bigger role in biopharmaceutical innovation than might otherwise be expected. Spain has certain strengths in knowledge and skills and engages in public-private R&D cooperation. However, the potential for biopharmaceuticals innovation is limited by widespread weaknesses, especially strong control of pharmaceutical prices. Greece invests in scientific education, but most of the other factors affecting innovation suffer from weakness and impede national innovation. This analysis appears to suggest that though all the factors may have a role to play in contributing to innovation, their significance in the process varies. More importantly, it indicates that demand is one of the strongest promoters of innovation.

3.4.2 *Agro-food biotech*

The leading countries in public agriculture and agro-food research are Germany, France and the Netherlands. Their investments in basic science in the area mainly focus on plant biotechnology. The UK and Ireland also invest in plant biotechnology and plant science but these investments do not generate private investment in agro-food biotech. Austria, Spain and Greece are building a scientific base, which may or may not be dedicated to agricultural biotechnology, but Spain has a growing position in agro-food.

The industry/supply network is strongest in Germany, France and The Netherlands, partly due to the activities of large, domestic multinational companies and their subsidiaries. Technology transfer and small business creation was, however, neglected until recent years when it has received increased public policy emphasis. In terms of SMEs, the leading countries are France, The Netherlands and Spain, with Germany in fourth place. Agro-food SMEs dominate Greece's very small number of biotech firms, but there are only a tiny number in the UK. Technology policy is little different from that for biopharmaceuticals but there is some indication that venture capital firms are loathe to invest in firms in this sector, because of the strength of public opposition.

There is low demand or public acceptance for GM crops and food, although the strength of public opposition varies from country to country. Concentrated food retailers and manufacturers have played a major role in eliminating these products from the products they stock. Despite the EC providing a common, background regulatory framework, national agencies have sometimes adopted a more stringent approach at the detailed level. Thus there is fragmented regulation and competition between European and national agencies to promote the precautionary principle or other ethical standards. In addition, food retailers and manufacturing have introduced *de facto* regulation by introducing "zero-tolerance" to GM ingredients.

It is very difficult to interpret data on field trials for GM crops, especially since they dates back to 1991, when public opposition to GM crops scarcely existed. The concentration of these trials in France, however, confirms that public opposition is lower here than in the other countries in our study. There may also be less public opposition to GMOs in Spain and The Netherlands since a significant percentage of trials also take place in these two countries. The strong agricultural traditions of France, The Netherlands and Spain, together with public attitudes, may explain why these countries also have the most SMEs in the sector.

The results for the UK are difficult to understand. It has a strong science base in the area and there is a national emphasis on commercialising that science base. Although there have been a significant number of field trials, there are very few SMEs. The campaigns of PINGOs, reinforced by media coverage and the response of concentrated food retailers appear to have created an environment where venture capital is loath to invest in these firms. Alternatively those companies which are involved are not prepared to admit that they are active in the area. Another possible explanation is related to the importance of subsidiaries in this sector. Multinationals may choose to locate subsidiaries in countries where public acceptance is higher than in the UK. This hypothesis is partly borne out by data about the countries which appear to have the highest number of field trials for GMO crops.

To sum up, the development of the agro-food biotech sector faces considerable barriers. The countries best placed to develop their competences in the area are France and The Netherlands, based on their science base, the presence of influential multinational companies and less vociferous public opposition to GMOs than in other countries. Spain's fast-growing science base and relative lack of public opposition to GMOs gives it the potential to develop national strength. The main brake on the development of agro-food biotechnology, however, is the weakness of private investment in R&D, together with non-availability of venture capital to support the formation of small firms. Germany has a large number of domestic agrochemical multinationals; they may choose to use the knowledge developed in the public sector for applications and field trials in other parts of the world where there is less public hostility.

3.4.3 Equipment and Supplies

The market for the equipment and supplies sector is stable and robust because its products are used in a number of industries and by a wide range of PSR organisations and institutions. Unlike other sectors, companies do not appear to have to cope with negative public attitudes to their work. However, the proliferation of standards throughout Europe may hinder the long-term development of the sector.

A comparison of the eight countries reveals similarities between the situation in Germany, The Netherlands and UK. Although there are some differences, these three countries form a cluster where the biotech equipment and supplies sector is well developed. These countries maintain numerous institutions devoted to scientific research and education. The number of scientists per capita and the pool of academics engaged in advanced scientific research in these countries are high. The stronger the tradition for scientific research and education is, the more readily available a highly qualified pool of researchers will be. This is considered a key success factor for a national biotech industry (Kenney 1986). The scope of basic research funding may also serve as an important demand factor for the equipment and supplies industry. There is also considerable investment in research by various multinational chemical and pharmaceutical companies in these countries, as well as a growing population of new biotechnology firms. All these national research actors provide both a market for equipment and supplies and may also stimulate the development of new generations of products (as suggested by Irvine in section 3.2 above). The domestic market in Germany and UK is large enough to induce further growth of the sector. The businesses in The Netherlands have strong links to firms in

other countries which may compensate for the relatively small domestic market. The strong venture capital markets in these countries nurture the foundation and growth of small start-up companies, mostly established independently. The three countries deviate most in their approach towards public-private and interfirm collaborations. Whereas firms in The Netherlands strongly emphasise these partnerships, they are less popular in Germany and UK.

The other cluster comprises Austria, France, Greece, Ireland and Spain. Except for France, public research funding in the countries of this cluster is low compared to other countries, thus hampering the development of a large pool of creative scientists. In addition, Austria, Spain, Greece and Ireland have few biotechnology firms and though Austria, France and Spain host R&D-performing subsidiaries of multinational pharmaceutical and/or chemical companies, these companies may well source their equipment and supplies from their home countries. In France, academic and industrial research communities may be healthy but they are poorly linked, and institutional mechanisms have failed to exploit these strengths. The weak cluster of countries does not have much of a tradition in engineering or in the development of instrumentation; its academic researchers have a low commercial orientation, and availability of venture capital is poor.

3.5 Competitiveness of European and US companies

This section reviews the competitiveness of European companies against their US counterparts by sector, including a comparison of EC and US policy for the science base, patenting and SMEs. The general aspects of these policies are discussed as a preliminary to the sectoral comparisons.¹¹ Specific aspects are included in the sectoral reviews.

There are moves afoot to develop a unified system for the regulation of biotechnology in Europe. This has been achieved for biopharmaceuticals with the setting up of the European Medicines Evaluation Agency (EMA), see section 3.5.3 below. In relation to agro- and food biotechnology, responsibility for the implementation of EC Directives lies with member states, which allows national authorities to interpret and implement them in ways which conform with existing national practice (see section 3.5.4 below).

¹¹ Information on policy is drawn from J. Senker and P. van Zwanenberg (2000)

3.5.1 EC and US Policy for the Science Base

EU support for biotechnology research dates back to 1981, and Framework Programmes gradually increased their investment in the area. In some programmes, such as FLAIR or SCIENCE, biotechnology was a subsidiary interest under broader themes. The Biomedical and Health Research Programmes - BIOMED 1 (1990-94) and BIOMED 2 (1994-98) were similar. They included some themes which contributed to biotechnology research, e.g. one of the themes in BIOMED 2 was human genome research. 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). The EC's Framework Programme (FP) 5, commencing 1999, has unified its funding for biotechnology research in the Quality of Life and Management of Living Resources programme, although the emphasis has shifted away from supporting biotechnology specifically and to providing support for the biosciences in general. It is worth bearing in mind, however, that

the EC's total research budget is rather small compared to the spending of the 15 Member States.^[12] In 1996 it was approximately 10% of the research spending by the Member States; this includes the joint research centres and programmes like Eureka, ESA, EMBL, etc. (Enzing et al, 1999)

Support for biotechnology research is extremely diffuse in the United States. In addition to the twelve Federal agencies which support programmes related to biotechnology, many states support biotechnology centres working on state-wide or regional biotechnology development. Each centre has a different mission, funding source and series of programmes. Some support industrial research and university/industry links, others are more concerned with promoting technology transfer. It was estimated that the Federal Government spent about \$4.3 billion on biotechnology research in 1994 (Biotechnology Research Subcommittee, 1995) an increase of over 25% on 1990 expenditure of \$3.4 billion (Office of Technology Assessment, 1991). It is estimated that annual Federal investment in biotechnology research is now approaching \$6 billion.¹³ (It should be pointed out that it is difficult to compare such figures with European data due to the lack of official and comparable definitions and statistics related to biotechnology.) At the Federal level research support is directed towards university scientists conducting basic research; applied research and development have always been considered the responsibility of industry.

3.5.2 EC and US Policy for Patenting

a) Patenting in EU member states is governed by two different systems, neither of which is based on EU legislation:

- the national patent system; and

¹² Enzing et al (1999) made a conservative estimate of €10 billion for the period 1994-1998.

¹³ Personal communication from Maryanna Henkart, Division Director, Molecular and Cellular Biosciences, National Science Foundation, October 1999

- the European patent system governed by the European Patent Convention EPC (1978).

Inventors wishing to patent a biotechnology invention can file a patent under the national patent system or file a European patent application at the European Patent Office (EPO). The EPO provides a centralised office for the filing, searching and examining of applications. It has also harmonised much of the patent law of the contracting states so that, when granted, the application can be validated in the designated states of the EPC, which include: Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Monaco, Netherlands, Portugal, Spain, Sweden, Switzerland, Liechtenstein and the United Kingdom. Thus, all the countries of the EU may be designated in a European patent application in addition to Cyprus, Monaco, Switzerland and Liechtenstein. Ultimately all EPO applications, if unopposed, go on to be converted into national patents. The corresponding national laws therefore govern the effect of these patents. So although the application stages are dealt with by either the EPO or national office, most legal processes and interpretations after grant (and opposition) are dealt with in the national courts of each country for which patents have been granted.

EPO applications cost in the region of €15,400, rising to €31,000 if the applicant wishes to gain protection in many EPC countries. Much of this goes towards translation costs because although the initial application only needs to be made in one official EPO language (English, French or German), it must still be translated into the national language of each contracting state when granted and converted into national patent. In the nine months after the grant of a European patent, EPO 'opposition' proceedings are commonly brought with the aim of having the patent revoked or its scope reduced. EPO procedures usually focus on technological issues, and have flexible rules of evidence. In competitive industries such as pharmaceuticals, firms monitor the grant of competitors' European patents and, if it is in their interests, file strategic oppositions. The results of these procedures are binding in all EPC countries.

The 1970 Patent Co-operation Treaty (PCT) provides for the filing of an international application to have the same effect as a national application in each of the contracting States designated in the application. It can be superimposed on the national and European systems and applications may apply for protection in one country or a set of countries. International patent applications can be examined by the EPO or an approved national office.

In 1988 the EC proposed a Directive for biotechnology inventions 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, 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. (Crespi 1993; Scott-Ram and Sheard, 1995). The EC's Directive 98/44/EEC on the Legal Protection of

Biotechnological Inventions was formally adopted by member states on 6 July 1998. The member states had until July 2000 to make their national patent laws consistent with the Directive. Only the UK and Germany agreed to amend their laws but the other countries are challenging the legality of the Directive. When the unitary patent becomes available, it will extend the range of possibilities for patenting in Europe by offering a third alternative to the existing European and national patent systems.

The most significant provisions of the Directive are those which prohibit the patenting of the human body and the cloning of humans, but sanction the patenting of elements isolated from the human body which are produced by a technical process. For patenting to be acknowledged, the Directive also demands the patent application to disclose the industrial application, or utility, of a sequence or a partial sequence of a gene (Cornish, 2000).

b) Patenting applications in the United States, made to the Patent and Trademark Office (USPTO) differ in important respects from those in Europe. An important difference is patent document publishing procedures. (Publication occurs when the application is made public.) In Europe patent applications are usually published 18 months after application but protection is provided from the date on which the patent application was first filed. In the US a patent application is only published if the patent is granted. This may take as long as five years (OECD, 1994). However, the American Inventors Protection Act 1999, which will come into force in late 2000, will also make patent applications subject to publication 18 months after filing (Tzevdos et al, 2000). In the United States patents are prohibited if the invention has been described in a printed publication anywhere more than one year prior to filing the patent application. If the inventor describes the invention in a printed publication he/she must apply for a patent before one year has gone by, otherwise any right to a patent will be lost (USPTO, 1997). Foreign patent laws in this regard can be much more restrictive than US laws. In Europe, for instance, discussion of academic work prior to filing a patent can lead to the loss of patent rights.

Guidelines for determining whether a gene-related patent will be granted are expected to be released soon by the US PTO. The guidelines follow similar principles to the stipulation in 98/44/EEC that DNA sequences must show utility to be patented. The USPTO guidelines will tighten former standards and demand that patent applications show "specific, credible and substantial utility for gene sequences" (Grisham, 2000).

3.5.3 EC and US Policy for SMEs

a) The main way in which the EC has supported the development of small and medium sized firms (SMEs) has been through offering them the opportunity to participate in its Framework Programmes (FPs) for research. However, SME participation has been low, with large firms taking the largest proportion of funding in FPs II and III. In 1996, the Commission introduced an Action Plan for SMEs to help speed up applying for grants. It also introduced new initiatives to provide seed-corn capital and loan guarantee schemes for start-up firms and established a number of Innovation Relay Centres which aimed to promote technology transfer (Peterson and Sharp, 1998).

In recognition of the critical importance of SMEs to the development of a European biotechnology industry, Directorate General III published a *Users' Guide for SMEs in the Biotechnology Field* in 1999 (EC, 1999a). It provides information on both EC and national policies to promote SMEs.

The FPs are still the main EC measure to help biotechnology SMEs, but the Fifth FP (1998-2002), attempted to be more "user-friendly" to SMEs. One of its four thematic programmes (Quality of Life and Management of Living Resources) focuses on the biosciences, and provides opportunities for SMEs to participate in shared cost, collaborative research projects. One of its three horizontal programmes is specifically concerned with promoting innovation and encouraging the participation of SMEs. It allows a single point of access for SMEs to all the FP's research activities and results. In addition, it aims to develop technology transfer mechanisms and easier access to finance. Specific measures to encourage SMEs to take part in the framework programmes include:

- Co-operative Research Project (CRAFT) allows SMEs with similar technical problems but insufficient research to engage third parties to carry out research on their behalf.
- SME Exploratory Awards provide part of costs of preparing a proposal for the FPs.

There are also several programmes outside FP5 which are relevant to SMEs. SMEAP (SME Programme) helps SMEs to participate in the Internal Market and promote their internationalisation. SMEAP is supporting the development of mutual guarantee schemes, encouraging the growth of EASDAQ and improving access to private venture capital. SMEAP also supports 232 Euro Info Centres (EIC) and 20 Correspondence Centres which provide information and advice to businesses on Community legislation and programmes. 37 centres with a particular interest in R&D are members of an EIC R&D Group. Co-operation networks help companies develop transnational partnerships with other SMEs.

Some actions focus specifically on biotechnology SMEs. These include Industrial Platforms which aim to maximise technology transfer from academia to the industrial sector. Industrial Platforms were established on the initiative of industry around specific areas of EC Biotechnology programmes. Any European company can be involved, irrespective of their participation in a specific EC project.

SMEs in disadvantaged member countries - Portugal, Greece, Ireland and Spain - are also supported by the European Regional Development Fund and the European Social Fund through development programmes drawn up in partnership between member states and the EC. SMEs apply for these funds through national or regional authorities, but the EC plays no part in the selection of projects.

The EC has also launched various schemes and information programmes to improve the availability of seed capital and venture capital for high technology companies.

b) The Federal Technology Transfer Act of 1986 (FTTA) was designed to promote the transfer of government developed technology to the private sector. FTTA

authorises Cooperative Research and Development Agreements (CRADA) for joint research between a company and a Federal laboratory. The company acquires patent rights arising from the research but is expected to share royalties with the government inventors (The President's Council on Competitiveness, 1991).

There are no special programmes to support biotechnology SMEs, but they are eligible to apply for financial support under the Small Business Innovation Research Program (SBIR), to which the National Institute of Health (NIH) contributes significant funds. The Small Business Development Act was passed by Congress in 1982, requiring all major Federal agencies to conduct a Small Business Innovation Research Program. This calls for the Federal agencies which conduct 99% of total U.S. Government R&D to publish and distribute annually a comprehensive description of their R&D programs. Each agency must also solicit research proposals from small business and fund a minimum of 1.25% of their external research from this source.

The program is also designed to provide a means for converting government R&D into technology, so increasing the commercial returns from Government research. Government funds 100% of small firms' R&D to produce commercial products if the R&D also meets a government requirement. There is no requirement for payback or recoupment, and the program offers world-wide commercial patent rights to the small firm for any patents resulting from the research.

Financial support is provided in three phases: the first phase provides limited funds for short-term feasibility studies - both technical feasibility and firm capability. Firms demonstrating adequate progress receive more substantial funds over 1-2 years under Phase II for taking research ideas through to the prototype stage. Phase III involves securing private funding for taking the prototype through to the market. Few small firms receive Phase II grants without obtaining in advance a signed contingent follow-on funding commitment from a third party firm. Large companies and venture capital firms have become enthusiastic about the SBIR program as a test bed for high-risk ideas (Tibbetts, 1990).

The Advanced Technologies Programme (ATP), part of the National Institute of Standards and Technology, supports the high development risks of innovative technologies by providing support for research projects undertaken by companies of all sizes, working alone or in partnership with other companies, universities, federal laboratories or non-profit independent research organisations. ATP awards are competitive and made on the basis of rigorous peer-review, but proposals can only be submitted in response to specific, published calls. The proportion of costs provided by awards depends on the size of the company. For example, joint ventures involving two or more companies must pay at least half of the project costs. SMEs in single firm projects must pay a minimum of all indirect costs associated with the project. Since 1990 ATP has funded 468 projects. Over half these awards have been made to individual SMEs or to joint ventures led by an SME. Other SMEs are involved in awards to joint ventures led by larger firms.

Between 1994-98 most ATP funding was allocated to specific focused program areas. In the biotechnology area, these included Tools for DNA Diagnostics (\$145M funding 1994-98) and a Tissue Engineering program which commenced in 1997.

3.5.4 Bio-pharmaceuticals

In terms of the knowledge/skills network, it has been estimated that annual US Federal investment in biotechnology research for the period 1994-98 was at least \$20 billion. In the same period, European member states spent approximately half this amount - €10 billion, with almost 50% dedicated to research relevant to biopharmaceuticals. It has been assumed that the US dedicates a similar proportion of total funds to this area (Senker, 2000). There are very different mechanisms for promoting the commercialisation of public research in the two regions. In the US firms have considerable opportunities to exploit NIH research results through the funding provisions of the SBIR programme, and the results of the programme may serve to convince large firms and venture capitalists about the feasibility of some high-risk ideas. In addition the requirement for US agencies to fund at least 1.25% of their external research from SMEs may be a very useful method for these firms to develop their capabilities. In Europe the main way to promote knowledge flow is through public-private research collaboration and use of public sector research results. The companies in the eight countries in our study mainly collaborate with national PSR, confirming Jaffe et al's finding (1993) that knowledge flows from universities to firms are highly localised at the regional or state level. Linguistic and cultural differences within Europe, as well as lack of knowledge about PSR in other European countries, may have a greater effect on firms' choice of collaborative partner than occurs within the US as a whole.

In terms of the industry/supply network, Ernst & Young (2001) estimates a total population of 1,273 US and 1,570 European companies, but gives no breakdown by sector.¹⁴ However European companies are less mature than their US counterparts. Europe has half the number of public companies, with less than 40% of employees in US companies. Moreover the market capitalisation of Europe's public biotech companies is €75,000M, just 20% of the market capitalisation of their US counterparts which stands at €376,000M. Ernst & Young (2001) believes that one of the major problems for European biotech companies, not faced by US companies, is their inability to raise significant sums of follow-on finance.

Until recently each member state of the European Union had its own set of pharmaceutical regulations, enforced by its own national regulatory authority. This created an enormous duplication of effort for pharmaceutical companies, because gaining approval for the sale of a drug throughout Europe required authorisation by each national authority, many of which had different standards and procedures (Crowther et al, 1999). This situation changed in 1995, with the inauguration of the EMEA which co-ordinates and manages the drug approval system within Europe. Since the beginning of 1998 all new medicines have had to be approved by EMEA, unless they are to be marketed in a single member state only (EMEA, 1998). EMEA has different procedures 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

¹⁴ Previous Ernst & Young reports suggest that the majority of these are in the biopharms sector, e.g. Ernst & Young (1998).

are made directly to EMEA. Product approvals by EMEA are valid in all member states (Griffin 1995).

EMEA has a scientific committee to prepare opinions about the authorisation of medicinal products. The committee has two members from each member state and is assisted by experts on its working parties and expert groups. The opinions of the scientific committee are based on scientific consensus or the position of the majority of the committee. One of the committee's members acts as rapporteur for the coordination of the evaluation, and the applicant's preference for rapporteur is taken into account in the selection of rapporteur.

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. It is involved at two key stages in the drug development process: (i) approving an investigational new drug application (IND) and, (ii) after clinical trials, approving a new drug application (NDA). Filing an IND occurs after preclinical testing and before the drug is tested in humans. It becomes effective if not disapproved by the FDA within 30 days, but clinical trials must be reviewed and monitored by an Institutional Review Board (IRB) where the trials are conducted, and progress reports must be sent annually to the FDA (Crowther et al, 1999).

The NDA takes longer to review. The company must present data from all three phases of clinical study and demonstrate both effectiveness and safety. By law the FDA must review an NDA within six months. In practise the average NDA review time was 16.2 months in 1997. It had decreased from three to four years in the late 1980s, despite the number of drug approvals nearly doubling, due to a deliberate decision to expedite review. Potential new drugs must, from the outset, be produced in facilities approved by the FDA (Ibid).

US companies perceive major differences between the role which the EMEA and FDA have adopted towards regulatory approval for biopharmaceuticals. The FDA is perceived to be concerned with both a drug's safety and its efficacy. By comparison, EMEA is thought to concentrate on product safety and allow the market to decide whether the product is efficacious. In consequence clinical trials and their evaluation are considered to be quicker and cheaper in Europe than in the US (Ward 1995), Quick procedures are encouraging US firms to use Europe a launch market (Crowther et al, 2000).

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) and the EU, US and Japan are now working together through the International Conference on Harmonisation (ICH) to recommend practical ways to achieve greater harmonisation of quality, safety and testing requirements (EMEA 1996).

Henderson et al (1999) consider that the greatest difference between the US and other countries is the structure of health care system and systems of reimbursement. In the US

"companies' rents from product innovation were ... protected by the fragmented structure of health care markets and by the consequent low bargaining power of buyers. ... Moreover, unlike in most European

countries ... drug prices in the United States are unregulated by government intervention.

In contrast each European country has a different method to control the price paid for pharmaceutical products, restricting the potential rewards for companies and requiring companies to deal separately with each government. The transparency created by the Euro could be detrimental for pharmaceutical companies if it leads for demands by all countries to have the same lowest price.

3.5.5 Agro-food

The findings of our study show that a high proportion of innovative small firms in this sector are diversifying into biotechnology.

Tait et al (2001) found that US agro-biotechnology MNCs are stronger in the US than in Europe, but their European counterparts are strong in both Europe and the US. European and US MNCs hold a similar share of Latin American markets. Seeds companies' R&D is widely distributed. Agro-chemical MNCs, however, tend to centralise their R&D and European firms often locate their R&D facilities connected with biotechnology in the US to benefit from its science base, although pesticide R&D is still located in Europe. However, should the link strengthen between chemical and biotechnology strategies, European research may become sidelined. Trends in this direction may have a negative impact on public sector research and the opportunities for small firms in the sector, already adversely affected by public opinion, may decline even further.

The US arrangements for plant IPR differ from those in the EC, which may provide greater incentives to small firms to enter this area. US patenting law allows a novel plant variety to be protected by a utility patent. Asexually reproduced plant varieties can also be protected by a patent under the Plant Patent Act 1930, and sexually produced or tuber-propagated plant varieties can be protected by a certificate under the Plant Variety Protection Act 1970 (Agris, 1999). The European Patent Convention, however, does not allow patents for a plant variety or biological process for producing the said plant variety. It is possible to obtain "breeder's rights" protection for plant varieties under the International Union for the Protection of New Varieties of Plants convention. The EC's Directive 98/44/EEC on the Legal Protection of Biotechnological Inventions takes a similar stance and does not allow plant varieties or biological processes for the production of plants to be patented. However, inventions concerning plants or animals can be patented if the invention is not confined to a particular plant or animal variety.

The principal European regulations for bioagrofoods consist of what are variously described as 'horizontal' or 'process-based' pieces of legislation. This means that the process or technology itself is the focus of regulation rather than a specific product. Under process-based legislation, all innovative activity is subject to regulation from the R&D stage through to commercialisation and permission must be given to grow, sell and/or market the crop and the final product. The two principal 'horizontal' Directives which set out the framework for bioagrofood regulation are the Directive 90/219 on the contained use of GMOs which stipulates community-wide controls on laboratory research with genetically modified micro-organisms (GMMs) and Directive 90/220 on the Deliberate Release of GMOs which stipulates EU-wide

controls on the deliberate release of all genetically modified organisms into the environment, both for research purposes and for commercial purposes

Directive 90/220 on the Deliberate Release of GMOs requires anyone intending to release GMOs for experimental purposes or to market products containing or consisting of GMOs to obtain prior consent from national competent authorities. The Directive's objective is to prevent any adverse effects on human health and the environment. The Directive is based on a precautionary approach in so far as it outlines a step-by-step process of approval whereby the containment of GMOs is reduced and the scale of release increased gradually, step-by-step, but only if evaluation of the earlier steps indicates that the next steps can be taken. The idea is that progressively decreasing physical containment allows safety and performance data to be collected. Competent authorities are responsible for evaluating submissions within 90 days. Applications to market a product must also be cleared with other member states via the Commission. If another member state formulates objections, a vote on whether to grant a marketing consent is necessary. Final approval applies to all member states.

Directive 90/220 formed part of the EC's programme for overcoming internal trade barriers under the Single European Act, but rather than seeking uniform standards, it sought mutual recognition of national standards. The precise determinants of how member states should evaluate risk are not stipulated and the issues to be considered in a risk assessment have proved to be a source of disagreement between countries. Disputes between national regulatory authorities about the safety of certain products, has extended the time to commercialisation and led to uncertainty about the future shape of regulatory controls.

There have been several amendments to the Deliberate Release Directive. They include Regulation 258/97 – the Novel Foods and Novel Food Ingredients Regulation – on seeking consent for final food products containing or derived from GMOs. It also stipulates rules for labelling foods produced using genetic modification. Applications for the deliberate release of GMOs for cultivation (seed) or use as a feeding stuff must still be made under Directive 90/220. There have been on-going plans to amend Directive 90/220 since late 1996. In 1998, amid escalating consumer concerns about GMOs, the European Parliament proposed over 100 amendments to make the approval of GMO releases even more difficult than under the current Directive. In 1999 the proposals were voted on by the European Parliament and the Council of Ministers reached a political agreement on the proposed revisions. The amendments went to the European Parliament for a second reading in April 2000, leading to 29 amendments being adopted. The Commission does not accept all these amendments, and a conciliation process will take place to resolve differences. This will take at least six months, and even when a revised Directive is agreed by the Council of Ministers and the European Parliament, individual member states will have 18 months to implement it (Hodgson, 2000).

The Council of Ministers' negotiations over the Directive were overshadowed, however, by heated debate over whether new authorisations for marketing GMOs should be suspended until the revised Directive entered into force. Member states divided into three camps. One group of member states (Denmark, France, Greece, Italy and Luxembourg) issued a joint statement calling both for stricter regulatory

controls and the suspension of new marketing authorisations pending the entry of the amended Directive. A second joint statement (by Austria, Belgium, Finland, Germany, the Netherlands and Sweden) called for the same regulatory controls, but no suspension of marketing authorisations. A third and final group of member states (the UK, Spain, Portugal and Ireland) declined to sign either statement on the grounds that anything that appeared as if it were a moratorium would have no legal basis and would open the EU to potential challenge under World Trade Organisation rules. The net result of the differences of opinion however is a *de facto* moratorium on GMO approvals in the EU (ENDS, 1999). The proposed revision will exempt trial releases and marketing releases from the Directive if the releases are covered by other Community legislation for specific products.

In mid 1997, the EU introduced new rules for the labelling of some, but not all, GM foodstuffs (Novel Foods Regulations 258/97). The rules have subsequently been amended to cover GM soya and maize (EC Regulation 1139/98) and additives derived from GM materials (EC Regulation 50/2000). EC Regulation 49/2000 provides a 1% labelling threshold for the accidental presence of GM material (Directorate General for Health and Consumer Protection, 2000). These rules were introduced into a revised Directive 90/220 (Deliberate Releases into the Environment) in summer 2000 and the revised Directive will come into force in member states in Spring 2002 (Hodgson, 2000a).

The US has a more relaxed and stable regulatory environment than Europe. Product approval comes under existing regulations which focus on the risks of the product *per se*. US bioagrofood regulation is often characterised as a 'product-based' form of regulation, in contrast to Europe's 'process-based' form of control. This refers to a regulatory focus on the risks of the product *per se* and not the process used to produce the product. Thus release and product approval in the US is achieved under existing legislation, rather than specific laws covering genetic manipulation. Nevertheless, the US regulates laboratory work (under general factory safety legislation) as well as field trials of bioagrofoods and commercial bioagrofood products. The distinction in principle between product-based and process-based forms of regulation refers mainly to the preferred administrative arrangements for regulation.

There are differences in the regulatory function between the US and European regimes. For example, until 1992, the EPA required all field releases to be subject to an environmental assessment, as is still the case in Europe. Since April 1993, however, most US field trials have been allowed to proceed based on what are termed 'notifications'. These require the applicant only to provide 30 days notice of a field trial with no requirement on the part of the regulator to evaluate and grant applications. Notifications apply only to six crops: maize, cotton, potatoes, soybeans, tobacco and tomatoes but these accounted for 85% of field tests in 1993.

For releases that are subject to assessment, rather than just notification, the information required by the USDA is almost identical to the information required in the EU under Directive 90/220/EEC (House of Lords, 1999). However, the criteria used to define risk differ. For example, in the United States, the transfer of genes to plants which are not significant in agriculture is only important if there is a likelihood that the genes will cross back into the agricultural (managed) environment (Ibid). In

the EU, the protection of the natural (unmanaged) environment, as well as the agricultural environment, is considered important.

Finally, the FDA, who is responsible for regulating food and feed derived from biotechnology, does not require pre-market approval of GM foods, so long as they do not contain substances that are 'significantly different' from those already in the diet. Furthermore, the FDA requires labelling only if the composition of a food developed through genetic engineering 'differs significantly' from its conventional counterpart (US Food and Drug Administration, 1995). The FDA suggests that an example of a significant difference might be where a food contained a new sweetener derived from genetic modification, or if a new food contained an allergen that consumers would not expect in that food. The Agency notes that "[t]o date, FDA is not aware of information that would distinguish genetically engineered foods as a class from foods developed through other methods of plant breeding and, thus, require such foods to be specially labelled to disclose the method of development" (Ibid).

The OECD's online Biotech Database (OECD, 2001) contains 75 genetically engineered crops which have been approved for commercialisation, have obtained approvals which allow commercialisation or are in the process of being approved. The majority (63) have gained approval for commercialisation in North America (23 in Canada) and 72% of the 98.6 million acres planted with transgenic crops in 1999 were in the US (Thayer, 1999). There are a variety of reasons for the predominant activity in the US including the size of the market and the suitability to US climatic conditions of some of the crops first modified. Differences in regulation and in public acceptance between the US and Europe appear to be far more significant. It is not clear whether the European public is generally more concerned about the risks of GMOs than those in US due to the effects of BSE and other crises connected with food production (listeria, salmonella etc). Alternatively, fears about GMOs may have spread rapidly throughout Europe because the process of developing common regulations, and disagreements between countries on those regulations, provided a platform for PINGOs to draw attention to potential risks.

3.5.6 *Equipment and Supplies*

Small firms trying to exploit experimental niches have shown impressive growth both in the US and Europe. Larger companies in the life science supply chain are focusing on building their market share, which may lead to consolidation in the industry and increased competition between the larger supply companies. The leading companies will focus on offering systems solutions for specific experimental techniques that integrate instrumentation and reagents. Emphasis is anticipated on proteomics and genomics applications, to serve the needs of sophisticated customers. While some firms dominate the DNA sequencing segment, others in (functional) genomics, high-throughput screening and biochips are likely to face more competition, especially the niche players

The US system of innovation in the equipment and supplies sector appears self-sufficient, both in academic excellence and in the critical mass of its science base. Bartholomew (1997) describes the institutional arrangements in the United States as self-contained and market-driven. In particular, the stock of basic knowledge in research institutions, the flow of knowledge between research institutions and industry, and the stock of industry knowledge is well supported (Gelijns and Rosenberg 1999).

Heavy federal investment in basic research has a long tradition in the USA. In the last 50 years, accumulation of knowledge in the life sciences has been substantial. The universities have emerged as major centres of research, particularly in biomedicine (Mowery and Rosenberg 1993). Given the underlying commercial orientation of the American university system, university scientists were quick to recognise the commercial opportunities of their findings. The close coupling of the university system with industry, linking basic research directly to commercial opportunities was clearly advantageous to the growth of the bioinstruments sector. The large number of start-up companies emerging out of university or public/private research centres reinforced this trend and the venture capital industry poured vast amounts of seed capital into biotechnology.

The strong tradition in (bio-)pharmaceutical R&D of the US has served as an important demand factor nurturing and collaborating with the supplies and bioinstrument firms. In exchange, gains in efficiency through modern tools in R&D further underpinned the dominance of US pharmaceutical corporations. Shan et al (1994) describe this situation as a symbiotic interfirm co-operation in biotechnology research and development. Moreover, the US has a single market for research equipment and supplies because it does not suffer from a proliferation of standards caused by national and cultural differences across Europe.

European equipment and supplies firms that have developed expertise in other fields of biotechnology (apart from bio-pharmaceuticals) should thus have the possibility to compete with their US counterparts. In addition, most US firms have not established a considerable (R&D) presence in other countries and may be dependent on local firms if they intend to expand their geographical orientation.

The lead of US-American equipment and supplies firms clearly represents a competitive advantage. Commercialisation of the strong science base in bio-pharmaceuticals started earlier in the US than in Europe. Along the bio-

pharmaceutical trajectory, genomics enterprises have first been established in the USA, inducing research in equipment and supplies for their needs. European companies often supply niche markets at the moment. In future, there should be abundant business opportunities to step into the large markets of equipment and supplies for functional genomics and protein analysis, where Europe maintains a strong science base.

4. Conclusions and policy implications

4.1 Methodological Assessment

The methodology employed had both strengths and weaknesses. The decision to select research equipment and supplies as one of the sectors to be studied has been completely vindicated. To date this sector has received very little attention but the results of the study show that it covers a large number of profitable firms in Europe, second in number only to bio-pharmaceuticals. The approach also led to the production of eight national case studies based on a multi-factorial approach which adds to knowledge about the strengths and weaknesses of biotechnology commercialisation in each country, especially when there is a comparison with the situation in other European countries. The cross-sectoral studies have also proved useful in understanding the dynamics of biotechnology exploitation in each sector. Finally, the study has led to the development of a database of biotechnology companies in eight European countries. Data on some factors is patchy, but learning from what worked in various questionnaires could improve data collection in any future exercise. In addition, the database could be updated and/or expanded to include other European countries and/or sectors e.g. environmental and/or "other" applications of biotechnology.

However, there were several problems with the methodology, and the national case studies took longer to prepare than envisaged in the research proposal. The first difficulty concerned the lack of comparable data for the public biotechnology science base, either for research funding or for the training/production of PhDs. Some countries do not differentiate between various elements of "life sciences" in their statistics. Moreover, it is unclear what definition of biotechnology is being used by countries which do provide data for the field. The problem of definition is complicated both because of the dynamic nature of the field and because of the emergence of new non-biotechnology areas which are closely linked to biotechnology (e.g. combinatorial chemistry and bio-informatics). Should such areas be regarded as part of the broad biotechnology area? Improved comparable data on the public biotechnology science base will require countries to reach agreement on the use of similar definitions and approaches for producing statistics.

Secondly, it was often difficult to identify firms, or to get useful data about them. Small companies often did not have the time to complete questionnaires, or were unready to provide information which they regarded as confidential. Those which had diversified into biotechnology were sometimes unable to differentiate between their biotechnology and non-biotechnology activities. Our approach to defining sectors by a list of technologies was largely successful. However, the technology is rather dynamic and over time a company's products may become generic in the sense that they turn out to be applicable to more than one sector. There is a risk that the "list of technologies" approach to identifying sectors could fail to identify firms with generic products which might be used in several sectors.

Finally, although NSI focuses on the systematic character of the whole system, our study has not captured sufficiently the links within or between the four networks used as the basis for data collection – the knowledge/skills, industry/supply,

demand/consumer acceptability and finance/industrial development networks. This was partly related to the design of the project. Links are possibly better captured by in-depth, case studies with a small number of companies rather than with extensive industrial surveys. However, a larger part of the problem was related to the vagueness of NSI concepts – it was very difficult to work out how to operationalise identification of the detailed working of network links in a consistent manner. However, this project was not designed to improve methodology, It was an applied project. Future research projects could focus on how to apply the NSI conceptual framework in a consistent manner. They could also map where firms and the public science base are located to see if there are "clusters", or innovative regions which cross borders between countries.

4.2 Conclusions for Theory

The central aim of this study was to identify the extent to which the development of biotechnology in Europe takes place at the sectoral level or, in contrast, is mainly determined by the institutional features of particular 'national systems of innovation' (NSI). Our findings reveal great differences in innovation patterns between the eight countries and three sectors studied. Partial explanations for these differences are provided by the NSI conceptual framework. National case studies confirm that the R&D system, the role of the public sector including public policy, interfirm relationships, the financial system, and the national education and training system are important elements of a NSI.¹⁵ In particular, they show the relevance of taking a systems approach to understanding innovation performance which considers the relationships between these elements. In this respect our results confirm the conclusions of the ISE¹⁶ project which pointed out the importance of complex interactions, particularly during the development of science-based and interdisciplinary technologies such as biotechnology. Moreover, although some of the difference in national innovation performance in biotechnology is related to public policy for developing the science base (including the date when policy was introduced), such policy also had to be associated with mechanisms to link the science base with industry and to overcome cultural traditions in universities which acted as a barrier to small firm creation. NSI is also correct in suggesting that the existing national structure of production will influence innovation patterns. ("Path-dependence" could be another way to describe this phenomenon.) The strength of France, Germany and the UK in biopharmaceuticals is partly related to existing national strength in the pharmaceuticals sector. Moreover, the strength of Germany, The Netherlands and the UK in the equipment and supplies sector appears to be related to R&D activities in domestic and foreign-owned chemical/pharmaceuticals MNCs, as well as substantial investment in public sector research. The findings may also be related to the fact that emerging technologies often demand the development of new markets. It could be that only countries with large markets (or those that are internationally-oriented) are able to exploit these opportunities at the early stages of development. Despite the usefulness of NSI in explaining the findings, however, it does not fully capture all the significant factors explaining variation in innovation between countries and sectors.

¹⁵ The internal organisation of firms is another key element, but consideration of this factor was beyond the scope of this specific study.

¹⁶ Innovation Systems and European Integration TSER No. SOE1-CT95-1004

Strong differences in the framework conditions for innovation in the three sectors are summarised in Table 3. (This excludes the finance/industrial development network, since it is largely the same for all three sectors). Table 3 highlights the emphasis on and presence of a knowledge/skills network for bio-pharmaceuticals in every country. Agricultural and agro-food biotechnology knowledge and skills are also present in every country, but are only given priority in a few of them and receive a small fraction of the funds dedicated to biopharmaceuticals. There is no specific science base for equipment and supplies (if we ignore the fact that the materials and techniques developed during the course of any biotechnology research may be relevant for the sector). Industrial activity concentrates on the biopharmaceutical sector and occurs in every country, is least evident (or hidden) in the agro-food sector and only occurs in some countries in equipment and supplies. Moreover, firms in the biopharmaceuticals sector are mainly new start-ups, but there is a high proportion of diversified firms in the agro-food sector and a mixture of both types of firm in the equipment and supplies sector. The nature of risk and the opportunities for new firms also varies by sector. Demand, and public acceptance also shows great variation between the sectors.

Table 3: Characteristics of Framework Conditions for Innovation by Sector

	Biopharmaceuticals	Agro-Food	Equipment and supplies
Knowledge/ Skills	<ul style="list-style-type: none"> • Expertise in every country • Major focus of public research funding 	<ul style="list-style-type: none"> • Higher priority for public sector research in Spain and Ireland • Draws on wide science base 	<ul style="list-style-type: none"> • Neglected by public research funding • No specific science base
Industry /Supply	<ul style="list-style-type: none"> • Commercial activity in all countries • High share of new start-ups • Medium risks and high opportunities for new business creation 	<ul style="list-style-type: none"> • Poor (or hidden) commercial activity in many countries • Diversification rather than new start-ups • Very high risks and limited opportunities for new business creation 	<ul style="list-style-type: none"> • Commercial activity concentrated in countries with large science base and strong pharmaceutical or chemical MNCs • Diversification + new start-ups • Low risks and high opportunities for new business creation
Demand/ Social Acceptance	<ul style="list-style-type: none"> • High potential demand • High social acceptance 	<ul style="list-style-type: none"> • Unknown customers • Weak demand and exploitation • Strong social opposition 	<ul style="list-style-type: none"> • High actual demand • High potential demand • Demand related to science policy • Not an issue in public debate

The industry surveys indicate that while all the framework conditions are necessary to encourage innovation by companies, they do not have an equal effect, and that demand and social acceptance appear to be the principal factors which prevail over all the others. There is high social acceptance for biopharmaceuticals and strong public opposition to agricultural and agro-food biotechnology. The equipment and supplies sector does not appear to be affected by public opinion in any way. The nature of demand and the market also varies very strongly by sector, and may be influenced by public attitudes. In agro-food biotechnology the market is

characterised by close links between producers, distributors and final consumers (the food chain). Demand has been affected by a combination of public opposition to GMOs, media coverage and the response of concentrated food manufacturers and retailers and led to relatively low [overt] innovation activity by firms. Some entrepreneurs have turned public opposition to their advantage by developing diagnostic kits able to identify (for example) GMOS. The market for GM seeds is more global than the food sector, and European MNCs in the agrochemical/seeds sector are pursuing their activities overseas. Demand and innovation activity in the equipment and supplies sector concentrates in those countries where a healthy market is guaranteed by high investment in public and private sector research. National demand for biopharmaceuticals is affected by the size of the country, per capita expenditure on pharmaceutical products and the public procurement regime. Innovation clusters in countries with large markets and procurement policies¹⁷ which guarantee certain profits or in smaller countries which give access to adjacent markets. However, this sector operates at the global level and though innovation may be supported by national demand characteristics, it is also driven by the potential of the global market.

The comparison of the differences in demand for the three sectors highlights the distinction between sectors which are shaped by national or global demand. Some new biotechnology firms are able to take advantage of global markets, but they are mainly exploited by MNCs. As suggested by NSI, the existing national production structure, including the existence of domestic MNCs influences national patterns of innovation. Chesnais (1992) suggests that MNCs in global competition may challenge the autonomy of national systems of innovation, and create a more important role for public policy. Our study shows some of the benefits of national MNC activity, especially by domestic MNCs. Benefits can also flow from the innovation activities of foreign subsidiaries. For example, foreign subsidiaries are the main actors involved in innovation in Austria and Spain, and they are significant players in The Netherlands. Although pharmaceutical subsidiaries in Ireland are mainly involved in production, there is now a trend for them to undertake biopharmaceutical research. Our findings underline the views of Chesnais about the important role of public policy in relation to MNCs. National technology policy has influenced countries' potential to stimulate innovation. Countries which originally focused on large companies and neglected the creation of new firms (e.g. France, The Netherlands and Ireland) were slow to develop firms in the biotechnology sector.

The significance of public acceptance and demand in shaping innovation in biotechnology, the difference of these characteristics between sectors, and the differential effect on innovation of sectors with domestic and global markets suggests that the development of biotechnology in Europe takes place mainly at the sectoral level. We therefore conclude, in answer to one of the underlying questions of the project, that each sector has its own system of innovation. The institutional features of particular NSIs do affect biotechnology innovation because sectoral innovation occurs in specific national locations and is dependent on history and the trajectory of innovation. Therefore we tend to agree with Archibugi and Michie (1997)

¹⁷ Gregersen (1992) notes the important role of public procurement in stimulating innovation in certain sectors, including health care.

that "both technology-specific and nation-specific factors shape the innovative process". In biotechnology, however, the NSI appears to be of secondary importance when compared with sectoral characteristics. These findings confirm the views of Malerba (1999) that the development of appropriate public policy requires the description of:

the working, structure and dynamics of a sector in ... developing, producing and selling products and services to a demand composed by users and consumers and the way a sector changes over time. And second, we need to disentangle the relationships between firms' learning processes, competences, organization and behavior, non-firms organizations and institutions in a sector.

A second objective of the study was to add to theoretical understanding and empirical knowledge of 'national systems of innovation'. Our findings reinforce some aspects of NSI, but it is considered to be more useful as a heuristic than as a theory, because it does not provide any clear indicators which would allow analysis to concentrate on similarities and differences between countries. The findings do not challenge the relevance of the NSI approach, but suggest that it does not go far enough. It ignores both demand and social acceptance in explaining national innovation performance. Thus our findings give empirical support to the conclusions of the ISE project which argued, from a systems perspective, that various innovation policies should pay more attention to the demand side. Policymakers may be concerned with understanding how firms react to public policy, but any analysis must be considered in the context of sectoral demand. Porter (1990) highlights the importance of demand conditions. Public acceptance can affect demand significantly and may be crucial in new technologies which are potentially risky or raise ethical issues. Indeed Gaskell et al (1998) suggest that "risk is less significant than moral acceptability in shaping public perceptions of biotechnology ... and across six specific applications.

A third objective of the project was to examine the implications of taking a systemic approach to the formation of national and EU policy aimed at promoting the social management of biotechnology, industrial innovation, and the harmonisation and integration of European markets. The study falls short of meeting this very ambitious objective, but it does throw some light on the issues raised. Regarding the social management of biotechnology, there has been some experience of the effects of organised public debates in The Netherlands. The Dutch government has carried out a number of initiatives since the 1980s to assess the social and ethical effects of biotechnology, to disseminate information to the public and to organise public debates. The Dutch attitude to biotechnology is above the European average, and it is one of the few countries with significant numbers of agro-food biotech firms. A few other countries also have firms in the sector and muted public opposition to GMOs, but they have not organised such initiatives. Therefore it is difficult to know what drives social acceptance and whether it can be influenced by government intervention.

In relation to innovation, the study confirmed the influence of the existing industrial structure. Path dependence is important in the European context because of its existing strength in the pharmaceuticals and agro-chemicals sectors, The current

wave of consolidation among European firms in these sectors may be part of the process of European integration.

With respect to the implications of consolidation for European biotech firms, two opposite trends can be differentiated. Consolidation implies that there will be less, however more powerful, partners for co-operative agreements or as customers. Thus the business environment for biotech firms might become more difficult. On the other hand the need of large consolidated firms for new innovative blockbuster products will increase, so that opportunities for biotech companies to provide input to the product pipelines of these customers would remain or even become more promising. Consolidation is still ongoing; moreover, some of the new giants are also developing completely new strategies for organising their R&D activities (e.g. Pfizer or GlaxoSmithKline). They are establishing a number of more or less independent entrepreneurial research entities, which seem intended to provide the services that are usually offered by biotech firms. Therefore, at the moment, it is not possible to assess which of these trends will prevail.

The concept 'life science company' is another facet of consolidation. It emerged in the mid 1990s in Europe and the US and is based on the rationale that biotechnology provides synergies that could be utilised by both pharmaceutical and agrochemical companies. In particular, the core and enabling technologies of sequencing, gene identification, target identification high throughput screening and combinatorial chemistry to synthesise lead compounds are considered as common across plants, animals and humans. Therefore, establishing a common R&D platform for pharmaceutical and agricultural applications within one organisation was supposed to provide competitive advantage. In the US Monsanto was the main driver for this life science strategy. In Europe the creation of Aventis from the merger of Hoechst and DuPont, and Novartis from the merger of Ciba-Geigy and Sandoz were justified, among other reasons, by the life science argument. In principal, it could be expected that life science consolidation would further strengthen European firms in both sectors due to the benefits of synergy.

However in the late 90s this strategy came into question mainly because of the following developments: a set back over GMOs led to low commodity prices in the agro sector. In particular it was no longer possible to achieve premium prices for genetically modified seeds, and conventional seeds received the premium. More importantly, the assumed synergies between agriculture and pharmaceuticals turned out to be limited. There is no doubt about these effects at the beginning of the product pipeline, where basic discoveries are made using very similar technologies. However, further downstream the commonality between the sectors disappears. This is mainly due to the very different paths for regulatory and market approval which imply contrasting R&D approaches. In addition the cost of R&D, the size of the markets, the type of customers, and the expected margins differ greatly between the sectors. Finally, stock markets also lost their patience with the agro sector and became hesitant to make large investments. There are presently indications that several MNCs are disengaging from the life science concept. For example Novartis and AstraZeneca spun out their agro business and established the new agrochemical firm Syngenta. Aventis is also disposing of its agrochemical activities, and in the US Monsanto has failed with this strategy. On the other hand, there are still some companies such as Bayer or DuPont/Pioneer that seem to adhere to this

strategy. Against these developments we expect that potential benefits of the life science concepts for Europe to be rather limited.

We could find little evidence of harmonisation or integration of European markets for these sectors. The equipment and supplies sector, in particular, is fragmented by a plethora of standards, even at the national level, and there is a relative lack of attention to the European market. The market for biopharmaceuticals is fragmented by different pricing regimes in each country and public antipathy to GMOs, though not equally vehement in every country, is limiting opportunities for innovation in agro-food biotechnology.

Finally, we reflect on whether each country has its own system of innovation in biotechnology and the nature of any relationship between biotechnology sectors at a national and European level. The great differences between countries suggest that each country does have its own pattern of innovation in biotechnology. The results appear to indicate that countries with large home markets appear to have greater ability than smaller ones to exploit the development of new market niches for emerging technologies. They also suggest that the creation of new firms is related to public policy, public perceptions about the potential market and the cultural attitudes of academics towards entrepreneurship. We found some evidence of synergies between sectors at a national level. This was mainly shown in the equipment and supplies sector, where major activity took place in countries with significant R&D activity in the pharmaceutical and chemicals sectors, as well as in PSR. There was also some limited evidence of firms active in more than one sector or attempting to diversify by selling products or services developed for one sector into another. The members of the team engaged in protracted debates about whether this indicated that biotechnology innovation was becoming generic rather than sectoral. Towards the end of the project, the majority of the team agreed that sectoral innovation was most dominant.

Several characteristics of biotechnology firms in the eight countries differentiate them from their US counterparts. First is the high proportion of independently established firms and dearth of university spin-offs. Secondly, we found a significant number of European firms which had diversified into biotechnology, especially in the agro-food and equipment and supplies sector. We do not know whether this shows better diffusion or the benefits of late entry. Patchy data on firms' collaborations, mainly from the pharmaceuticals sector, shows that European PSR collaborators come second to national collaborators. (When it comes to collaborations with other firms, however, those in the US are more numerous than either other national or European firms.) Apart from these findings there was little to indicate the existence of a European biotechnology innovation system.

The US appears to be closer to having a national biotechnology innovation system because, in general, there have been similar regulations for each sector, with the USDA and FDA working closely together. In Europe the great fragmentation between social actors prevents the operation of a single market in any of the sectors. This is particularly marked in the agro-food sector, where there are both national and cultural differences in food preferences and the implementation of EC policy. For instance, Greece has forbidden field trials for GM crops and The Netherlands is boycotting the EC's Directive 98/44/EEC on the Legal Protection of

Biotechnological Inventions, suggesting that common European regulation and patents may be a necessary, but not sufficient condition for creating a single market.

4.3 Conclusions for Policy

The results of the study suggest several implications for policy. The first concerns the lack of comparative biotechnology data, particularly about the science base. There is need for EC Member States to agree to use an agreed definition for biotechnology and a common approach to providing statistical data.

A number of policy implications are connected to current widespread public hostility to biotechnology applied to the food chain. The project team considers that there should be continued national and EC funding of public sector research in plant biotechnology. Continued world-wide activity, especially in North America, demands that Europe continues to have the expertise to operate in international networks, for instance to assess the risks associated with these developments, and to participate in international negotiations – as well as capturing spillovers from external knowledge.

Public resistance to agro-food biotechnology has mainly been provoked by the initial commercial activities of the MNCs. The main focus of the private sector has been on six or seven important crops (maize, cotton, rapeseed, etc.), and on applications connected with herbicide resistance. Although these applications of plant biotechnology have been unacceptable to the public, there is enormous unexplored potential for developing knowledge about acceptable applications. For instance, plant biotechnology can be used to develop raw materials for industry or for the production of biopharmaceuticals. Biotechnology can also be used as a tool in plant breeding. Moreover, GM crops designed to reduce levels of pesticide use could benefit rather than harm the environment. To ensure public confidence, however, it is not sufficient to build up research capabilities, it is also necessary to invest in systematic EC bio-safety research and testing capabilities, i.e. field trials, to provide a framework which makes this option possible. This will provide a framework for communicating to the public about safe and beneficial application of biotechnology to agriculture. The example of The Netherlands suggests communication should be associated with public debate and efforts to seek public views. Even if consultations are organised and public is allowed to express its fears and its desires, however, consumers will still want to be able to identify a supply chain free of GMOs. Setting up parallel food chains – one with and one without GMOs – would be very costly (Desquilbet and Bullock, 2001) and it is unclear who will pay for this second supply chain. Indeed, if the GMO free food is more expensive than the food containing GMOs, there will be a loss of welfare for consumers.

Bearing in mind the many small seeds producers in the southern Mediterranean, it also seems relevant for collective research to be funded into horticultural crops relevant to southern countries. This would allow southern Mediterranean countries to capture niche markets and strengthen their competitive advantage. An example might be to decode the melon genome as the basis for improving disease resistance, flavour, or keeping qualities etc.

One of the positive outcomes of the study was identifying the active and profitable European equipment and supplies sector, even though this mainly concentrates in

three countries. The flexibility of European firms to respond to user needs and the variety of products offered could be a strength. However, we believe that these firms should be encouraged to do more to exploit the European market as a whole, and that the European Committee for Standardisation needs to look at the plethora of standards affecting this market and consider whether it is opportune to introduce common standards in any area.

Widely varying pricing regimes for pharmaceuticals across EC Member States are another area of concern. The introduction of the Euro will do much to make these differences transparent and it may be appropriate for consideration to be given to the adoption of similar pricing regimes for innovative new products across the EC, although we recognise that this is a very sensitive issue for national governments.

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6.3 Glossary

ATP	Advanced Technologies Programme
BINGOs	Business Interest Non Government Organisations
BSE	Bovine Spongiform Encephalopathy
CRADA	Cooperative Research and Development Agreements
DNA	Deoxyribonucleic Acid
DNA/RNA	Deoxyribonucleic Acid/Ribonucleic Acid
EMEA	European Medicines Evaluation Agency
EPC	European Patent Convention
EPO	European Patent Office
FDA	Food and Drug Administration
FTTA	Federal Technology Transfer Act
FP	Framework Programme
GM	Genetically Modified
GMM	Genetically Modified Micro-Organisms
GMO	Genetically Modified Organism
ICH	International Conference on Harmonisation
IND	investigational New Drug Application
IP	Intellectual Property
IRB	Institutional Review Board
MNC	Multinational Companies
NDA	New Drug Application
NIH	National Institute of Health
NMR	Nuclear Magnetic Resonance
NSI	National Systems of Innovation
PCT	Patent Co-operation Treaty
PINGO	Public Interest Non-Government Organisations
PSR	Public Sector Research
SBIR	Small Business Innovation Research Program
SME	Small and Medium Enterprises
USDA	United States Department of Agriculture
USPTO	United States Patent and Trademark Office

Project Reports

This final report is based on numerous project reports. Some of the earlier reports are already available in downloadable form from:

<http://www.sussex.ac.uk/spru/biotechnology/Themes.html-European.Biotechnology>

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