AN INTERNATIONAL BENCHMARK OF BIOTECH RESEARCH CENTRES

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A Executive Summary

1 Background to the Study

The study, 'An international benchmark of biotech research centres', was commissioned by the EC with several aims in mind. As well as contributing to the production of new science and technology indicators and improving existing indicators, the focus on biotechnology was prompted by a wish to know more about the performance of European biotechnology research and the main impact of these activities compared with similar centres in the US.

During the 1980s public biotechnology research became recognised as an important strategic area for government investment both at the national level and by the EU. Increasing investment over time has been accompanied by rapid increases in knowledge and the constant emergence of new areas and applications. European biotech centres were created by providing incentives for existing research centres to move into the area, by establishing new centres or by re-labelling existing ones. There is no specific information on US biotech research centres, but a study on US research centres in general found that they have no common characteristics. They vary in scale from a single individual, to segments of a department, entire departments, individuals from several departments, and from various universities and companies. Centres can also provide expensive research equipment that would be beyond the means of a single research group. The formation of a centre is a typical US academic development strategy. Many research centres have been established at universities not ranked among the leading research universities, to act as a focus for capturing new funds and to aid local economic development.

2 Methodology

The project involved the collection of research indicators and data for both EU and US biotech centres. It was necessary to ensure comparability by developing common definitions for "biotechnology" and for "research centre". The study defined biotechnology using a "list-based approach" including the following areas: Plant biotechnology (crops, trees, shrubs, etc); Animal biotechnology; Environmental biotechnology; Industrial biotechnology (a): food/feed, paper, textile, and pharmaceutical and chemical production; Industrial biotechnology (b): Cell factory, including all biotechnology research focused on the cell as producer of all sorts of (food and non-food) products; Developments of human/veterinary diagnostics, therapeutic systems; Development of basic biotechnology.[1] The criteria adopted for defining biotech research centres are broadly related to "intent and content". Thus, biotech research centres were defined as those with at least 50% of their research activities focusing on biotechnology, receiving at least 50% of funding from public sources and having a specific mission related to biotechnology, which could be one or more of the following: providing education and training, building up the knowledge base, creating a national centre of research excellence or fostering commercialisation.

A questionnaire was designed to collect input and output indicators and to discover whether the institutions initially selected for the study met the criteria defined for biotech research centres. It was mailed to 714 biotech institutions and 324 of them responded. There was a good response rate to the questionnaire by EU centres (57%), indicating that the sample is representative of EU biotech centres. The US response rate was low (25%) and may not be a representative sample of US biotech centres as a whole. The analyses are based on 226

[1] For full taxonomy showing all sub-areas see Enzing *et al* (1999), *Inventory of public biotechnology R&D programmes in Europe,* Luxembourg: Office for Official Publications of the European Communities.

centres (194 in the EU and 32 in the US) because 98 responding centres did not meet the criteria developed to define "biotech research centre" and thus were "deselected". The small number of US centres results both from a lower initial population of centres and a low response rate in comparison to EU centres.

Bibliometric and patent databases were searched to identify the publications and patents produced by centres which returned the questionnaire and fulfil the criteria to be considered a biotech centre. Searches of patent databases failed to yield significant numbers of centre patents because patenting is often undertaken by higher level organisations or individuals, rather than by centres themselves. The responses from the questionnaires and the bibliometric searches were entered on a database and the results analysed.

Bibliometric analysis was undertaken to assess how far the research centres included in the study are representative of each country's biotechnology research. Bibliometric data cover a large population of centres' publications. However it is not possible to capture the totality of publications for centres because in some cases the publishing authors do not indicate their affiliation with a centre but rather with the primary organisational unit they belong to, eg, university departments. This is particularly the case when centres are formed of various units or parts of units that belong to other organisations. In general it was found that the centres in this study accounted for a low proportion of total national or EU biotechnology publications, suggesting that biotechnology research centres are not the main producers of published biotech knowledge in the countries analysed.

The very low proportion of publications accounted for by the US centres in this study (0.3%) led to a detailed examination of the centres that had responded to the questionnaire and met our criteria for inclusion. It was found that the US centres did not represent "first movers and major players", or top quality universities. Instead, they represent only "second movers and emerging actors": major research universities late to enter biotechnology research and universities without an established research tradition. There is ambiguity about the interpretation of this finding. On the one hand, the group of US centres included in the study may not be representative of US biotech centres as a whole. On the other hand, they may be representative. In this scenario, non-responding "major players" would not have satisfied the criteria for biotechnology centre, and there were several examples of these among the US institutions that completed the questionnaire. This hypothesis arises from the fact that biotechnology emerged first in the US, and diffused rapidly throughout the existing departments of major research universities and medical schools. Biotech research centres may mainly have been established in US states or universities lacking competence in biotechnology once the economic significance of biotechnology was realised. Ambiguity about the representativeness of the US biotech research centres that responded means it is uncertain whether the results that follow may be considered a valid benchmark. The summary of the main results that follows shows the type of benchmarking that the methodology can produce.

3 Benchmarking Results

The majority of centres in both the EU and US have multiple missions; there is very little difference in the number of centres having the mission to provide education and training, build up the knowledge base or create a national centre of research excellence. Only approximately half of the European centres have a mission to foster commercialisation, compared with almost three-quarters of US centres. Centres not only have multiple missions, the majority are involved in several areas of biotechnology research. US centres allocate a

very high percentage of their expenditure to basic research (50%). Taken together with the strong orientation of US centres to fostering commercialisation, this emphasises the fact that it is important to do basic research to be relevant to industry. EU centres spend over 30% of their budgets on human biotechnology, but basic research (17%), cell factory (15%), plant (12%) and animal (10%) biotechnology also receive a significant share. Although most centres are involved in several areas of research, 57% can be regarded as "single-focus" because a significant proportion of their budget is dedicated to one area. The remaining centres allocate their budgets more or less equally to several areas and can be regarded as "multi-focus".

More than three-quarters of EU centres and all the US centres were established during the last two decades. The remaining EU centres are even older, and seem to have shifted their research focus to biotechnology over time. Continuous growth characterises the development of 70% of all centres. The majority of centres are affiliated to universities. EU centres are also affiliated to a range of other types of organisation, and sometimes to several different organisations. The majority of centres are unitary centres based on a single institution (65%). However there are also a significant number of co-operative or "virtual" centres. Some are based on different institutions in the same town and others on several institutions in different geographic areas. The latter occurs only in the EU.

On average, EU centres are significantly larger than US centres in terms of the total number of research staff. The average budgets of US centres are much lower than those for EU centres and this probably reflects the smaller size of the US centres. There is no significant difference in the average number of staff in single- and multi-focus centres. Among the single-focus centres (both EU and US), however, those specialising in human biotechnology have the highest number of staff and highest budget per member of staff, and are followed closely by centres specialising in animal biotechnology. Basic research and plant biotechnology have the lowest budget per member of research staff. The most significant source of funds is core government funding.

Centres increased employment of all categories of staff between 1998 and 1999. There was a most dramatic increase in the employment of technicians. The highest proportion of technicians to total staff is in centres specialising in animal and human biotechnology. US centres employ a much higher proportion of long-term and fewer short-term researchers than EU centres.

In terms of academic activities (training doctoral students and publications output), we found that 48% of the centres are not permitted to award PhDs, but these centres have similar numbers of doctoral students to those permitted to award PhDs. Doctoral students per centre and per member of research staff are similar in the EU and US, but EU centres have double the productivity of US centres in PhDs awarded for both these measures. EU centres account for 7.1% of all EU biotech publications in the period 1994-1997, and US centres for 0.3% of all US publications. The publications of EU centres received an average of 10.7 citations per publication and US centres 18.2 citations per publication. This is an indication that the impact of the scientific activities of US centres is higher than that of EU centres. Key personnel (those who had published more than 20 publications in the period 1994-99) were identified in 45% of EU centres, but only 22% of US centres. The average number of key personnel per centre is also considerably lower in the US than in the EU. In terms of "prestige" activities (highly active researchers in terms of publications, scientific awards and memberships of external committees), we also found that EU centres have more members of editorial and

scientific committees. EU centres also send far more researchers to transatlantic conferences than those in the US. In terms of industrial activities, a higher percentage of EU than US centres has industrial research collaborations, and a higher average number of collaborations per centre. However, US centres have a higher launch rate for spin-off firms than EU centres.

An analysis of how various characteristics of centres affected their academic, prestige, industry and networking performance was undertaken for all the centres in the study.[2] It found that 72% of centres achieved a high performance in at least one of these areas, but only 2% scored highly in all four areas. Age has a relationship with high performance industrial centres, which are likely to be 12-20 years old and with high performance networking centres, which were formed between 1991 and 2000. High performance academic, prestige and industrial centres are likely to have 25 or less staff, and this characteristic is most pronounced for the industrial centres. In contrast, high performance networking centres are less likely to be in this small size category. High performance academic centres are more likely to specialise in human biotechnology and industrial centres in cell factory; high performance networking centres are also more likely to have a single focus, but not in any specific area. Only 45% of high performance industrial centres have a technology transfer office, so performance does not appear to be affected significantly by such activities.

The final analysis assessed the relative efficiency of centres in terms of inputs (budgets and research staff) and the outputs relating to four missions which they might undertake: research excellence, research training, fostering commercialisation and knowledge production.[3] One fifth of all centres are efficient and over two-thirds inefficient in one of the missions they undertake. Only ten centres (4%) are highly efficient in all the missions they undertake. Half of the 38 centres with four missions are inefficient at all of them, and no centre is efficient at all four missions. An analysis to identify any relationship between efficiency in the four missions found a strong relationship between efficiency in research excellence and research training and a weak relationship between research excellence and fostering commercialisation. It is also significant to mention that the "second movers and emerging actors" group of US centres represent a high proportion of centres efficient at knowledge production and at fostering commercialisation.

The characteristic most closely related to efficiency is having a single research focus. This is strongly related to efficiency in research excellence. The relationship also exists for efficiency in research training and knowledge production, but is weaker. The share of long-term research staff in total staff also has a significant but weak influence on centres efficient at achieving research excellence. None of the characteristics considered (proportion of core funds in budget, proportion of long-term staff in total staff, research focus, age or the existence of a technology transfer office) was found to have a relationship with industrial excellence. This may be due to the fact that efficiency is mainly influenced by intangible characteristics such as management.

4 Methodological Implications

The methodology used to prepare an international benchmark of European research centres proved largely effective. The low response rate by US centres and the use of the term "centre" for a wide variety of different organisational forms that are not strictly comparable

[2] The small number of completed US questionnaires did not allow an EU/US comparison of performance. The US centres were included in the analysis but the results are dominated by the EU centres.
[3] The analysis of efficiency was dominated by EU centres, but the US centres were also included in the analysis.

raise doubts about its general usefulness. If the focus for a benchmarking study is on a specific research area, other research entities may be more appropriate.

Although we believe that the methodology employed for this international benchmarking exercise was valid, there are grave doubts about its extension. The first of these doubts relates to the low response by centres in the US, which have no vested interest in participating in an exercise sponsored by the EC. The response by US centres could be improved in any future transatlantic benchmarking exercises by working in co-operation with US funding agencies, such as the National Science Foundation or National Institutes of Health. It may also be appropriate to gather data by conducting in depth interviews with a stratified sample of centres, rather than relying on questionnaire responses.

Secondly, we do not believe that centres form an appropriate unit of analysis for benchmarking exercises. Our preliminary investigations to select centres and the response to the questionnaires showed that the term "centre" is used for a wide variety of different organisational forms that vary both within and between countries. Some centres are authentic and employ a high proportion of permanent staff. Others have few permanent staff, and can be regarded more as "virtual centres": they act as umbrellas, sheltering loose coalitions of researchers whose main affiliation is elsewhere. Some virtual centres bring together researchers who belong to various departments within a university and others consist of researchers from a wide range of different organisations. Yet other centres serve mainly to provide resources such as research equipment. Thus the benchmarking exercise attempted to compare disparate entities, which are not statistically comparable. The research group could be a more appropriate unit of analysis, although it is difficult to identify active groups in specific research fields.

5 Policy Implications for science and technology indicators

The international benchmark emphasised the need to identify appropriate science and technology indicators for specific units of analysis. It was assumed that there would be no problem in gathering the most commonly used science and technology indicators – bibliometric and patent data – for the biotech research centres which formed the focus of this study. This was not the case, pointing to the need to prepare an overview of indicators relevant to various levels of analysis that draws on existing studies of benchmarking or other comparative analyses. Such an overview would indicate, for instance those indicators best gathered at the national level, those appropriate to entire institutions (university or research institute) and those for lower levels, such as university departments or research groups. In this connection, the questionnaire used in this study was shown to be appropriate for collecting a range of input and output indicators at such lower levels and its use could be extended in this way, subject to minor modifications.

It may also be necessary to develop new approaches to collecting patent data for certain units of analysis, and initial attempts are being developed within the EC's pilot activities on the identification of Centres of Excellence. So far very preliminary results exist for selected research areas. A contribution to knowledge in this area could also be made by a detailed, interview-based study of the barriers and stimuli to patenting for centres or other entities within public sector research organisations.

It does not appear appropriate, however, to extend the work on biotech research centres, because they were found to be an inappropriate unit of analysis. The great variations between the organisation and activities of centres both within and between countries means that such

an exercise fails to compare like with like. Another question that should be resolved before future benchmarking activities are undertaken is to define the level that is intended to be benchmarked: is it the activities within a certain scientific field like biotechnology or is it a specific type of organisation, eg, research centre? In the first case the identification of the major players within the system of innovation should be the starting point. This study showed that research centres do not appear to be the major players in biotechnology. Other organisations seem to contribute more intensively to knowledge generation in the area.

6 Policy implication for European biotechnology

The main result to emerge from the benchmark of biotech research centres is that centres that concentrate most of their activities in a single research area are more efficient than centres that spread their research activities over many areas. Secondly, small research centres produce the highest performance. Small centres that mainly focus on a single area of research can achieve success in a short period of time. In addition, the fact that US latecomer centres at non-prestigious institutions are achieving high performance and efficiency gives hope to peripheral regions. Policy-makers may wish to rethink their policies for concentration of research resources, as this may not necessarily lead to either high performance or efficiency.

The findings also suggest that there is no “best practice” to achieve either high performance or efficiency, and research centres should not all be forced into one mould. As shown by this study, there has been an evolution over the last two decades of a great variety of centres in the EU in terms of their size, organisation, thematic focus, mission or human resources, etc. Since most of these centres developed positively (as indicated by their continuous growth), it is possible to speculate that this variety may be a more appropriate response to the needs of EU biotech than a standardised form of “centre”, and variety could be an important asset of biotech in the EU.

The results also emphasise the urgent need to undertake more research on technicians and their training. The study gave evidence of a strong demand for technicians in both the EU and US, but we have little knowledge of the specific skills these technicians need to deploy. US organisations recruit graduates, some with Masters degrees, as technicians. We do not know what qualifications employers require for technician recruits in Europe, or the extent of any differences between countries in this respect. Secondly, we do not know how the jobs of technicians are changing as the consequence of the rapid expansion of knowledge and the mechanisation of some research tasks. Do they require more theoretical or practical knowledge, and of what types? It is important that this issue is addressed because failing to train technicians with appropriate skills to meet demand will have a negative impact on all organisations involved in biotechnology research – public sector research and companies alike – and not just biotech centres.

The data also shows that in order to perform well in industry related activities, high performance is required in the other activities performed by a research centre. Thus, supporting academic activities leading to research excellence and prestige will increase centres’ attractiveness to industrial enterprises and increase the probability of improving their level of industrial performance. It was also found that focussing on basic research topics is highly relevant for setting up relationships with industry. Thus policy support for basic research can be regarded as an indirect measure to foster commercialisation.

The finding that the proportion of long-term staff relates to the efficiency of centres in achieving research excellence provides a framework for increasing efficiency by focussing more on long term staff rather than on short term, project based contract researchers.

Finally, the bibliometric results, even though they fail to capture total publications output from some centres, in particular “virtual centres”, suggest that biotech centres account for only a small proportion of the universe of public sector biotechnology research. It may not, therefore, be appropriate to concentrate research funding on biotech centres.

B Foreword

The Fifth Framework Programme of the European Community for Research, Technological Development and Demonstration Activities (1998-2002) included an action "Common Basis of Science, Technology and Innovation Indicators (CBSTII)" in its programme *Improving the Human Research Potential and the Socio-Economic Knowledge Base*. The aim of this action is the development of a common information and knowledge base of quantitative information and the analysis thereof and its improvement and extension for use by European policy makers and experts. This report contains the results of a project designed to contribute to this aim.

The study, 'An international benchmark of biotech research centres', was commissioned by the EC with several aims in mind. As well as contributing to the production of new science and technology indicators and improving existing indicators, the focus on biotechnology was prompted by a wish to know more about the performance of European biotechnology research and the main impact of these activities compared with similar centres in the US. It was also hoped that the methodology developed for the study would enable the EC to take a consistent but evolutionary view through applying the methodology to the same or other areas in the future. The EC's invitation to tender for the study stated that every research centre in the US which receives a public grant publishes its key figures and these figures were compiled in a series of reports which are available on the WWW. The EC wished matching input and output indicators to be gathered for European biotech research centres so they could be compared with similar US centres.

The EC was involved in discussions about the design of the process for undertaking the study. At various stages of the project, however, unexpected interim results required adjustments to procedures and methods. The EC was kept informed of the various difficulties encountered and the new procedures being adopted in two interim reports.

To set the context for this study, Part C of this report provides a general introduction to the various domains of biotechnology. It reviews the range of sub-disciplinary fields relevant to biotechnology and the potential applications of the new knowledge that has emerged. Part D contains the main results of the study, a discussion of the problems encountered in applying the methodology, the unresolved questions raised by the results and their policy implications. Two appendices contain:

(a) a stand-alone report giving the key figures for biotechnology research centres;
(b) a detailed description of the methodological approaches employed for the exercise.

C General Introduction to Various Biotechnology Domains

1 Introduction

At the beginning of the 21st century, the promises envisaged for biotechnology are becoming reality, pervading more and more industrial sectors and influencing the daily life of many people. For example, nowadays there is almost no new medical treatment that does not draw on at least some aspect of biotechnology. Other industrial sectors where biotechnology is gaining influence are the chemical industry, the food and agricultural sectors, research equipment and supplies and even the electronics industry. Health care is the area where the general public is most likely to have contact with biotechnology, even though many might be unaware of it. Many diagnostic tests are biotechnology products, there is a growing number of vaccines arising from biotechnology, and finally some of the most important therapeutics such as insulin for diabetes treatment are biotechnology products.

The increasing impact of biotechnology on society and the economy has been accompanied by an expansion of knowledge, tools, methods and strategies that are employed during biotechnology research and development (R&D). The merger of the biological sciences and information technology to create bioinformatics can illustrate this best. In consequence it is becoming more and more difficult to define biotechnology and, not surprisingly, there is yet no agreed-upon, international definition of biotechnology. For this study we use a list-based taxonomy of biotechnology that classifies biotechnology into seven areas: plant biotechnology, animal biotechnology, environmental biotechnology, industrial biotechnology, cell factory, human and veterinary diagnostics and therapeutic systems, and basic biotechnology (see Table 1). Each of these areas is subdivided into between three and nine subcategories, describing specific biotechnology activities in more detail. All R&D activities falling into the range of one of these areas and sub-areas contribute to biotechnology. Our taxonomy covers “modern biotechnology”; traditional biotechnologies that have been used for centuries (for instance in food and drink production) are not considered.

A similar approach is followed by the OECD which is currently developing a framework for biotechnology statistics in OECD member countries. Compared to our list, which was used to prepare an inventory of biotechnology research programmes in the European Union (Enzing *et al*, 1999), the list-based biotechnology definition of the OECD focuses mainly on different methods and does not cover the main application areas of biotechnology as our list does. In addition to these list-based approaches, there have been several efforts to develop a general definition of biotechnology over the past three decades. The current understanding of biotechnology is summarised in the following broad definition suggested by the OECD:

> [Biotechnology is] “the application of science and technology to living organisms as well as parts, products thereof, to alter living or non-living materials for the production of knowledge, goods and services” (OECD, 2001).

The public as well as politicians in European countries are becoming more and more aware of the growing significance of biotechnology. At the same time general knowledge of the field tends to be somewhat poor due to rapid scientific progress. The objective of this part of the

Table 1: Taxonomy of biotechnology

B.1	**Plant biotechnology (crops, trees, shrubs, etc), including**
1.1	reproduction and propagation
1.2	genetic modification introducing new/excluding existing genes (mono- and polygenic traits)
1.3	growing conditions
1.4	plant protection
1.5	plant pathogen diagnosis
1.6	genome mapping
1.7	biodiversity of plants in agriculture/horticulture
B.2	**Animal biotechnology, including**
2.1	reproduction
2.2	production
2.3	breeding, incl. genetic engineering in animals (creation of transgenics)
2.4	animal health care,
2.5	genome mapping
2.6	biodiversity of farm animals
B.3	**Environmental biotechnology, including**
3.1	microbial ecology
3.2	biosafety
3.3	microbial functions for degradation/transformation of pollutants
3.4	isolation, breeding and genetic engineering of pollutants; degradation micro-organisms
3.5	biotechnological processes for soil and land treatment
3.6	biotechnological processes for water treatment
3.7	biotechnological processes for air and off-gas treatment
B.4	**Industrial biotechnology: food/feed, paper, textile, and pharmaceutical and chemical production**
4.1	enzymatic processes
4.2	development of bioprocessing techniques (fermentation, immobilisation of biocatalysts, quality control, etc)
4.3	downstream processing
B.5	**Industrial biotechnology: Cell factory, including all biotechnology research focused on the cell as producer of all sorts of (food and non-food) products**
5.1	plant cell biotechnology: plant cell biology
5.2	animal cell biotechnology: animal cell biology
5.3	bacteria as cell factories: microbiology
5.4	genetic engineering and production of enzymes
5.5	genetic engineering of micro-organisms and yeast
5.6	cell culture techniques
5.7	genome mapping of specific bacterial and yeast genomes
5.8	biodiversity of micro-organisms in production processes
B.6	**Developments of human/veterinary diagnostic, therapeutic systems**
6.1	immunology, therapeutic and diagnostic antibodies
6.2	vaccinology
6.3	human genome mapping
6.4	human gene transfer techniques
6.5	therapeutic proteins and oligonucleotides (substitutes for pharmaceuticals)
6.6	tissue engineering
6.7	genomics in drug discovery (substitutes for pharmaceuticals)
6.8	DNA diagnostics
6.9	forensics (genetic fingerprinting)
B.7	**Development of basic biotechnology**
7.1	techniques to determine the structure of biomolecules and study the structure-function relationship
7.2	techniques to build biomolecules (nanotechnologies)
7.3	interaction of biomolecules with micro-electronic devices, incl. biosensors, biomonitoring
7.4	genome analysing techniques
7.5	bio-data-informatics (set of tools, which is applied to solve data handling and processing problems in biological research, eg, genome sequencing)
7.6	bio-informatics (application of biological principles to information processing for technical applications)

report is to provide a general introduction for non-scientists about the various biotechnology domains. The current level of scientific knowledge is presented in a structured and easy-to-understand manner and the potential and actual applications of biotechnology are described.

This general introduction to biotechnology has the following structure. Section 2 discusses the basic techniques and instruments used in biotechnology. This chapter refers to area B7 "Development of basic biotechnology" of the taxonomy shown in Table 1. It comes at the beginning because these tools are used by all the other areas of the taxonomy. Section 3 covers biotechnology in agriculture, representing areas B1 "Plant biotechnology" and B2 "Animal biotechnology" of the taxonomy. Section 4, environmental biotechnology,

represents area B3 “Environmental biotechnology”. Section 5 will elaborate on food biotechnology which is related to areas B4 “Industrial biotechnology” and B5 “Cell biotechnology”. In Section 6 the role of biotechnology in health care will be described. This chapter relates to area B6 “Development of human/veterinary diagnostic, therapeutic systems”. Sections 7 and 8 conclude with a discussion of the legal aspects and public acceptance issues connected with biotechnology.

2 Biotechnology techniques and instruments

This section describes the important techniques and instruments employed in biotechnology. It is not intended to provide a complete overview of all biotechnological methodologies. New techniques or variations of existing ones are developed almost daily, and therefore such an overview could never be comprehensive. In addition, it would go far beyond the scope of the project. Therefore, a selection of important and recent methods is presented.

2.1 Genetic engineering

Biotechnology is based on the identification, analysis, understanding, and modification of the genetic information of living organisms that is stored in DNA molecules. All the techniques employed to this end are known as “genetic engineering”. The starting point of genetic engineering is the isolation of DNA molecules from an organism. After disruption of cells and tissues, chemistry is used to extract and purify DNA. Since DNA molecules are too large for further manipulation, it is necessary to prepare smaller DNA fragments. This can be achieved with specific enzymes called restriction endonucleases. These enzymes are able to identify specific sites on a DNA molecule and cut the DNA strand only at those sites. The resulting fragments of DNA are not a random mixture. It is possible to reconstruct them in the correct order along the DNA strand. In this way the genetic information of an organism can be divided into small pieces that are suitable for further analysis. A first step in the characterisation of these DNA pieces is their classification by size. Electrophoresis methods can easily separate differently sized molecules in an electric field. For further characterisation of genetic information it is necessary to identify the sequence of the four building blocks which make up these molecules. Further details are provided in the next section about genomics.

The availability of defined pieces of DNA and specific tools for cutting and joining DNA pieces allows fragments of DNA to be recombined into new DNA molecules. These can be made from the DNA from one organism and also of DNA from different organisms. In order to make use of these new DNA molecules, they must be amplified and made to express proteins. For that purpose DNA is introduced into microorganisms or cells of higher organisms where it replicates and is stimulated to produce proteins. These genetic engineering techniques are known as cloning and gene expression.

2.2 Genomics

Genomics is the elucidation of the complete genetic information of an organism. It is achieved by DNA sequencing which breaks down DNA fragments into its four building blocks: adenosine, thymidine, guanosine, cytidine. A key challenge during sequencing is to recombine information from thousands of small DNA pieces into one consistent sequence for a single DNA strand. This requires comparison of complex information which is supported by special computer programmes. Once the complete sequence of a DNA molecule has been obtained, the function of the sequence needs to be identified. During this step those parts of the DNA sequence that contain the information for a specific protein need to be identified. An example of how this can be accomplished is by comparison with DNA sequences whose

protein-coding is already known. All these steps of DNA sequencing have been automated and are performed by computerised robotic workstations in sequencing factories.

2.3 Proteomics

The complete set of proteins that is coded by the genome of an organism is called the proteom. In higher organisms it is estimated that each gene corresponds to ten different proteins, illustrating that the proteom is at least one order of magnitude more complex than the genome. Additional complexity arises from variations of the proteom over time and in specific interactions between different proteins. The methods to identify and characterise all proteins of a proteom and their interactions are summarised as proteomics. The key method of proteomics is the separation and identification of a large number of proteins. This is accomplished by separating different proteins in electric fields and identifying the separation products either by sequence, by amino acid or by mass analysis. The methods for identifying different proteins or protein fragments are still at an early stage and need further refinement. The goal is to achieve a similar degree of automation and high-throughput as with genomics.

2.4 Bioinformatics

Both genomics and proteomics rely on the ability to handle huge amounts of data and information technology has therefore become crucial for modern biotechnology. The new discipline of bioinformatics has emerged at the interface between biology and informatics. Bioinformatics uses biological data and knowledge stored in computer databases, complemented by computational methods to derive new biological knowledge. In particular the identification of genes from DNA sequences, the assignment of genes to biological pathways, the comparison of genomes from different organisms and the identification of proteins and protein interactions rely heavily on bioinformatic tools.

Biological data are stored in international databases which in many cases are accessible via the Internet. These include databases on DNA and protein sequences, databases for gene identification, databases of protein families and protein sequences, databases with information on the three-dimensional structure of biomolecules, databases on metabolic pathways and databases on human genetic diseases. Specific algorithms for data mining in these databases are being developed worldwide. Considering the vast amount of data on genomes, proteins, metabolic pathways and information flows accumulating at an accelerating rate, the challenges for bioinformatics to extract knowledge from this information will continue to increase for the foreseeable future.

2.5 Biosensors and biochips

Biosensors are analytical tools for detecting substances. They characterise biological and chemical molecules by combining a biologically active component (for detecting any substances) with a physico-chemical transducer to transform signals from the biological component into a measurable physical unit. Biosensors can detect a broad variety of biological components such as antibodies, enzymes, nucleic acids or even whole cells or organisms. In principle, therefore, a very broad variety of different substances can be detected with biosensors.

DNA chips (DNA microarrays) consist of DNA fragments which are immobilised on solid surfaces such as membranes or glass. Up to 250,000 DNA molecules per cm^2 can be packed in such constructs. DNA chips allow the parallel detection of very large numbers of different DNA species which bind to the immobilised DNA fragments. Examples of the detection of DNA by biochips include DNA expression in specific cell or tissue types or under specific

disease conditions. Further applications include the detection of DNA in food or environmental samples.

The next biochip generation also includes protein arrays which could be used in proteomics. However, due to the higher complexity and lower stability of proteins compared to DNA, the development and fabrication of protein chips is much more difficult. Not surprisingly, no protein chips are yet commercially available.

2.6 Combinatorial chemistry

Combinatorial chemistry is a new synthetic chemistry tool that emerged during 1989 and 1990 from independent discoveries in US laboratories. Combinatorial chemistry starts with a set of different chemical building blocks. These building blocks are connected in a systematic way during several repetitive rounds of chemical synthesis. In principle, the synthesis circles continue until all possible combinations of the different building blocks have been produced. The different synthetic reactions are performed in a highly parallel mode. As a result a combinatorial library of the maximum number of different molecules formed by a given set of building blocks is prepared. Combinatorial chemistry is basically a chemical method, but it has been combined with certain biotechnology tools, especially during the development of new drugs or new enzymes.

2.7 Transgenics

Transgenic organisms are organisms that include foreign DNA, integrated by gene transfer. Transgenic microorganisms are rather easy to generate because these organisms are adapted to exchange genetic information even under natural conditions.

Transgenic animals are created mainly for biomedical research, for the production of therapeutic proteins (gene farming) and for agriculture. DNA molecules containing the desired gene sequences are introduced into animal cells so as to integrate this DNA into the animal genome and to express the stored information. In order to achieve this goal, it is necessary to use early embryonic stages of the animals. Several methods for transferring genes into animal cells have been developed. These include microinjection, animal viruses, specific packaging systems for DNA and electrical fields for changing the permeability of cells to DNA. The main problems of applying these approaches to farm livestock are their low efficiency and the largely random integration of the new DNA into the animal genome.

Transgenic plants are created both by indirect transfer of DNA – for example using bacteria as vehicles – or by direct transfer using physical methods. The latter includes particle bombardment where particles are coated with DNA and shot into plant cells, electroporation where cell membranes are perforated by electrical pulses to make them accessible for DNA, liposome fusion where DNA is transported via liposome particles, microinjection or the uptake of free DNA under certain chemical conditions. During recent years these techniques have undergone refinement and improvement, so that transgenic versions of more than 150 different plant species have now been produced, including the main agricultural crops.

3 Biotechnology in Agriculture

3.1 Animal biotechnology

The main applications of biotechnology to livestock breeding and husbandry are diagnostics the production of transgenic animals, animal nutrition and animal health.

Diagnostic and analytical approaches are used during animal breeding, in order to identify phenotypological, physiological or biochemical traits which could be used as targets for breeding programmes. These analytical methods can also be used for proving the origin and parenthood of animals. Compared to traditional methods analytics and diagnostics based on biotechnology are more efficient, rely on smaller samples and provide faster results. A key problem with these techniques is that many traits relevant for breeding programmes have a polygenetic origin (meaning that these traits are coded by several genes), and breeding cannot therefore be focused on a single gene. In addition, there is a possibility that one single gene may affect several traits, leading to further problems for gene-based breeding strategies.

Transgenic animals (see Section 2.7) have an important role as "models" for biomedical research; in agriculture such genetically modified animals are developed not only as livestock but also for gene farming. Gene farming summarises efforts to use livestock as bioreactors for the production of products such as biopharmaceuticals in the animals' milk. Recovering these bio-products from milk is relatively simple. So far, the yields of transgenic animals are rather low, the stability of the new traits in these animals is rather weak and the overall effects on the physiological conditions of the animals are difficult to predict. Hence, the application of transgenic animals to livestock husbandry is still very limited. With respect to gene farming promising results have been obtained with some pharmaceuticals which could be ready for market introduction in about five years. One of the most advanced fields of transgenic animals is in fish. Transgenic fish with improved growth characteristics and cold tolerance are already used in aquaculture.

In animal nutrition a number of biotechnology products such as aminoacids and enzymes are used as feed additives. Biotechnology in animal health is providing similar contributions to those in human health (see Section 6). Several vaccines, diagnostics and therapeutics are already on the market. Further potential applications of biotechnology include hormone treatment of animals and other approaches directed towards improving growth or meat and milk quality. Technical feasibility in this field is high, contrasting sharply with low consumer acceptance of such applications.

In summary, the most important contributions of biotechnology to animal breeding and animal health are analytical and diagnostic methods as well as new approaches to improve feed and animal health. Transgenic animals on the other hand are still rather distant from market introduction.

3.2 Plant production

Biotechnology has introduced new tools and techniques to plant breeding. Using genetic markers during plant breeding allows the selection of desirable traits at an early stage, thereby reducing the costs and time of bringing new plant varieties to market. The transfer of specific genes into plants opens a way to modify plant properties to meet growing conditions and to improve product quality and quantity. The methods to produce such transgenic plants have reached an advanced stage which is indicated by the fact that it is now possible to produce transgenic plants for almost all the main crops. During recent years genome sequencing projects have also been initiated and partly completed for various plants. This will allow better insight into the mechanisms (metabolic pathways) of plants that govern specific agronomically relevant properties. By 2000 the complete sequence of the model plant arabidopsis was elucidated. Draft sequences of two subspecies of rice, which is the most important cereal crop for half of the world's population, were published in 2002, and it is expected that the complete rice sequence will be available in 2003.

The first generation of transgenic plants comprises species where modifications in single genes resulted in improved herbicide- and disease resistance. In particular, resistance against herbicides such as glyphosate and gluphosinate has been transferred to many crops. Another important example of first generation transgenic plants, which has been on the market for several years, is pest-resistant maize; it has been transformed with the gene for a bacterial toxin against certain insects. Another strategy for producing disease-resistant plants is inducing virus resistance by transferring certain viral genes.

A more complex task is the development of plants that are tolerant to adverse environmental conditions such as drought, heat, low temperatures or high salt concentrations. The responses of plants to these factors are influenced by several genes which makes it rather difficult to identify those plant traits that are crucial for the response and that can be modified by genetic engineering.

Current research in plant biotechnology is focussing on the quantitative and/or qualitative modification of the composition of plant ingredients. Thereby, plant traits which are important for plant utilisation as food, feed or raw material could be optimised. A rather advanced example of such strategies are plants with modified fatty acid patterns which are already available commercially. Other intensive research activities focus on transferring to plants the ability of bacteria to synthesise certain aminoacids.

A very recent example of a new generation of transgenic plant which attracted a lot of public attention was the creation of rice containing beta-carotene (pro-vitamin A). Rice has very little vitamin A and therefore people in many third-world countries where the diet is mainly based on rice suffer from diseases connected with vitamin A deficiency. The creation of vitamin A enriched rice promises some improvement to diets in these countries.

The production of raw materials for industry from plants could be a cost-efficient alternative to microbial production systems, especially when large volume are required. Recent examples, which have already entered field trials, include the expression of different enzymes in plants for the food and feed industry, the optimisation of fatty acids in rape seeds for various industrial applications, the optimisation of starch quality and composition in potatoes and the production of bioplastics (eg, polyhydroybutyrate). The production of biopharmaceuticals in plants could be advantageous compared to microbial or cell culture production systems because plant-made products are produced in the correct form (eg, three-dimensional structure and glycosylation patterns), plants can be easily stored without losing the active substances, production costs are relatively low and processing could build upon established technologies. Current research is trying to optimise the intra-plant allocation of the pharmaceuticals, so that they are concentrated in those parts of the plant that are used as food or that allow easy extraction, the improvement of the expression of such proteins in plants, and the analysis of their utilisation in humans, in particular the impact of the plant environment on take-up and metabolism of those drugs.

4 Environmental biotechnology

Environmental biotechnology has been considered as one of the most promising applications since the early days of modern biotechnology. However, compared to biotechnology in health care, food processing or agriculture, diffusion of biotechnology into the environmental sector has been rather slow. In principle, biotechnology can be used for the following purposes: environmental analysis and monitoring, end-of-pipe treatment of pollutants in soil, waste, waste water and exhaust air. In addition, the use of biotechnology for clean products and

processes could help to prevent or minimise environmental impacts in many different industrial sectors.

Classical biological analytics has been used for many years for water and waste water monitoring. This includes the monitoring of oxygen demand in waste water or toxicity testing with living organisms. Advances in biotechnological analytical tools such as immuno assays, DNA tests or biosensors also create new opportunities for environmental analysis. For example, biosensors are now available for measuring oxygen demand and pollutants in waste water. In addition, immuno assays for detecting pesticides in water samples have been developed. DNA analytics allows the detection of microorganisms or viruses in environmental samples. These cannot be used only for detecting any contamination, but also for monitoring the reaction of natural populations of microorganisms to certain environmental conditions. An increasingly important application area for DNA analytics is the monitoring of genetically modified organisms in the environment, for instance during controlled release.

End-of-pipe technologies are still the most important application area for biotechnology in the environment. In waste-water treatment biotechnological processes are state-of-the-art. These are applied not only for metabolising carbon compounds, but also for the elimination of nitrogen, phosphorous and sulphur compounds as well as for organic pollutants such as solvents and pesticides. Biofilters and biowashers have been developed that use enzymes or microorganisms to degrade and eliminate pollutants and odours. The remediation of polluted soil is applied widely on an industrial scale. Research in this area aims to identify microorganisms that are able to degrade several pollutants in parallel and under adverse conditions. Bioremediation is an area where biotechnology competes with other processes such as incineration and the latter could be more cost effective in certain circumstances. Cost effectiveness in these cases is largely influenced by the setting of standards and regulations.

Biotechnological processes for the production and conversion of substances work under mild conditions, in aqueous media and with high selectivity and specificity. They can increase conversion efficiency, increase the yield of industrial production processes, reduce the consumption of raw materials and energy and minimise the production of undesired side products and emissions. They therefore seem to offer substantial potential for production-integrated environmental protection. The main industrial sectors where biotechnology could be applied for this purpose are chemicals and pharmaceuticals, food and drink, pulp and paper, textiles, and leather.

In the *chemical and pharmaceuticals industry* biotechnology is used in fermentation processes, biotransformation of precursors and biosynthesis of drugs by recombinant organisms. Examples of fermentation and biotransformation which are performed on an industrial scale are the production of aminoacids, drugs and their precursors, food and cosmetics, agrochemicals and various other chemicals with acrylamide as one of the most important examples. Biotechnological processes are used almost exclusively for the synthesis of high-value, special and fine chemicals and for the asymmetric synthesis of chiral substances. It is expected that the importance of biotechnology will increase in this sector in the future because pure chiral substances will become more important. This is due to an international trend in approval procedures for drugs and agrochemicals where pure chiral forms seem to be favoured over non-pure mixtures. It is unlikely that biotechnological processes will be established for the production of petrochemical bulk chemicals for the

foreseeable future, because the properties of biocatalysts do not meet the requirements of such processes.

Biotechnology processes may have potential in energy production, specifically in the substitution of renewable plant biomass for fossil feedstock. This will depend on the development of enzymes able to degrade cellulose in plant biomass and designing methods to recycle or dispose of spent biomass.

In the *food and drink industry* biotechnology is already widely applied. The future potential of biotechnology processes rests in innovations where the reduction of environmental load can be coupled to quality improvement, especially for optimising already established processes.

The application of biotechnology processes is gaining interest world-wide in the whole *pulp and paper industry*. In most cases combinations of biotechnology, chemical and physical procedures are applied. Important examples include the following: in biopulping wood chips are inoculated with specific fungi which enhances the mechanical breaking down of wood. Lignin is removed more easily in pulping and energy can be saved to a significant extent. Biobleaching with delignifying enzymes so far is only applied in a few pulping plants. During bleaching enzymes are used for degrading lignin. Other uses of enzymes include lipases which degrade fatty substances that interfere with the pulping process. Finally, waste paper preparation and modification can also benefit from enzymes which improve dewatering properties and can also be used for de-inking.

In the *textile industry* water, chemicals and energy can be saved and processes made more reliable using biotechnology. Biotechnology processes can be applied to the following procedures: in pre-washing substances can be removed from the fibres by enzymatic processes. The desizing of starch is another example where enzymes (amylase) are widely applied. In denim processing conventional bleaching has been replaced by biobleaching using an enzymatic system. Other enzymes are used for the removal of the bleaching agent H_2O_2. Current research focuses on improving dye fixation to fibres, by enzymatic modification of fibres. Another potential application to reduce environmental pollution from dyeing is the substitution of biosynthetic dyes and pigments for chemically synthesised dyes. For almost 15 years cellulase enzymes have partially or completely replaced pumice stones in stone-washing of jeans. These enzymes can also be used to modify the surface of other washout products.

The potential for the application of biotechnology to *leather processing* lies in enzymatic dehairing, the conversion of waste from leather production into useful substances, the biotechnological production of vegetable tanning agents and in leather recycling where biotechnology could contribute to recycling of toxic agents.

5 Food biotechnology

In food production and food processing biotechnology is mainly used during those steps which require enzymes and microorganisms. These include in particular the dairy industry, the production of raw sausages, baking, alcoholic beverages, food additives such as vitamins, aminoacids or organic acids and enzyme preparation. In addition, biotechnology is increasingly used for food analytics.

Biotechnology can help to optimise the microorganisms that are widely used as starter cultures during food processing. The main targets are the improvement of process stability, increasing nutritional value, manufacturing new products and the reduction of health and safety risks. A more general goal is to increase the profitability of microbiological food processing. In order to achieve the desired outcomes, specific traits of the microorganisms need to be optimised by genetic engineering and many of the important food-processing microorganisms are open to these methods.

The most advanced area of biotechnology in food processing is the use of enzymes. Leading world-wide enzyme manufacturers have recently established genetic engineering as the key method for enzyme production. Genetic engineering allows the utilisation of new enzyme types and of new organisms as well as considerable cost reduction during production. Time to market has been shortened and product safety increased. Currently, more than 60% of all industrial enzymes are produced by genetically modified organisms. However, so far only a few of these enzymes are commercially available for food processing. Well-known examples include chymosin for cheese production and amylase for starch processing.

Traditionally, bacteria, yeast and fungi have been used to produce enzymes. Increasingly genetically modified plants are also used for this purpose. Another trend is the optimisation of specific enzyme properties such as substrate specificity, pH- and temperature dependency or long-term stability. A very new development in enzyme optimisation is the application of genomics and combinatorial chemistry. Combinatorial strategies for enzyme optimisation comprise the generation of thousands of variants of certain enzyme functions which are tested against specific substrates. Only those enzyme variants that exhibit desired properties are used in a second round of tests. During this second round variants of the selected enzyme modification are again introduced and tested for their function. Applying a number of these variation/testing cycles rapidly yields enzymes with improved properties.

Food diagnostics are becoming increasingly important, and have benefited from recent food scandals with BSE-infected meat or the use of antibiotics. Biotechnology contributes to food diagnostics in several ways. A key area is the detection of pathogens. DNA diagnostics are very efficient for this purpose, especially since the genomes of important pathogens such as salmonella or listeria have been sequenced. Other food diagnostic approaches rely on immuno diagnostics, detecting specific bacterial or viral antigens in food samples. In addition, food biochips have been developed for the simultaneous detection of several pathogens. Biochips and DNA diagnostics can also be used for detecting the DNA of genetically modified organisms in food. This is becoming increasingly important due to labelling requirements in force in various countries.

A new trend in food processing and food production is functional foods. These are products which not only provide nutrition but also promise additional benefits. This could be the improvement of physiological or mental well-being. Functional food contains substances that affect one or several body functions in a positive way. It is claimed that certain nutrition-related illnesses such as cardiovascular diseases or certain variants of cancer, diabetes or osteoporosis can be prevented or positively affected by functional food. In order to "functionalise" food, the following strategies are followed: removal of substances which cause unintended effects (allergenic proteins), increase of the concentration of specific naturally occurring food ingredients such as dietary fibres, addition of substances that are not found in the particular food (eg, antioxidants), substitution of food ingredients that have

negative health impacts (eg, in some types of fats), improvement of the bioavailability of those food ingredients that have positive impact on health.

Functional food can be produced by the same biotechnology methods and processes used for traditional food processing, or for plant and animal production. These mainly include enzymatic and microbial processes for the production of functional ingredients, the use of enzymes for the elimination of certain substances or enzymatic or microbial modification of substances, in order to increase bioavailability. In principle, genetic engineering could also be used for modifying the concentration and quality of certain food ingredients.

6 Biotechnology in health care

Biotechnology mainly plays two roles in health care. Firstly, it has emerged as one of the key methods for medical and pharmaceutical research, because biotechnology approaches contribute significantly to the elucidation of the regulatory and physiological mechanisms of disease. An important example of this contribution is human genome research which is discussed in Section 6.1. Secondly, biotechnology is central for research, development and production of new pharmaceutical products, namely diagnostics, biopharmaceuticals and vaccines.

6.1 Human genome research

In 1990 the human genome project was initiated in the USA under the leadership of the US Department of Energy and the National Institutes of Health. Several other countries joined in, resulting in a world-wide public sequencing project. In 1998 a private sequencing project started to compete with public efforts which greatly accelerated progress. In February 2001 the draft human genome sequence was published in two papers by the public and by the private consortium. The draft sequence covers about 90% of the gene-rich (euchromatic) portion of the genome; each base pair of the 90% was sequenced four times on average. The complete sequence is expected by 2003. In total, the human genome contains 3.2×10^9 building blocks. Only between 1.1% and 1.4% of the total sequence encodes proteins. A very surprising result of the draft sequence analysis was that the total number of protein-encoding genes is surprisingly low, and seems to range between 30,000 and 40,000. The forthcoming availability of the complete sequence will allow more precise estimates of these numbers. However, even the current results raise a challenging question: how such a low number of genes can provide the information for the whole set of more than 100,000 human proteins.

After the elucidation of the human genome, the next challenge is to identify genes and their function, which is also an important prerequisite for making use of genome information in health care. The implications of human genome research for health care concentrate on diagnostics and screening; gene therapy; and the identification of new targets for drug development

6.2 Diagnostics

There are two main strategies for diagnostics based on biotechnology: immuno diagnostics and DNA diagnostics. Immuno diagnostics is based on the very specific interaction between antibodies and antigenes. Using radioactive, enzyme, luminescent or fluorescent markers for either component allows very sensitive detection of the immuno reaction. Novel approaches for increasing sensitivity combine immuno reactions with DNA amplification, in a way that DNA tags are used as markers and are amplified by specific DNA polymerising reactions. In human diagnostics immuno assays can be used for identifying specific antibodies or

antigenes which indicate certain disease conditions, such as viral or bacterial infections or cancer.

DNA diagnostics rely on the specific structural features of the DNA molecule which is made up of two stands which bind to each other. This implies that single strands of DNA which code for specific genes can be detected – for example, in preparations of human cells by using the other, complementary strand of DNA. If one of the strands is labelled with a radioactive, chemical or biological marker, the binding reaction produces a measurable signal. This basic principle of DNA diagnostics is also used in DNA chips. However, in this case the binding reaction does not take place in solution but on a solid state surface (see Section 2.5 above). Biochips allow the simultaneous detection of thousands of genes.

Genome research a has strong impact on DNA diagnostics because an increasing number of disease-related genes and their modification is becoming available and can be used for designing specific DNA diagnostic kits. Examples include genes for certain cancers. DNA chips for diagnostic purposes have already been developed for HIV diagnosis, for the detection of cancer-related genes and for the analysis of variations in liver enzymes that are relevant for certain disease conditions.

6.3 Therapeutics

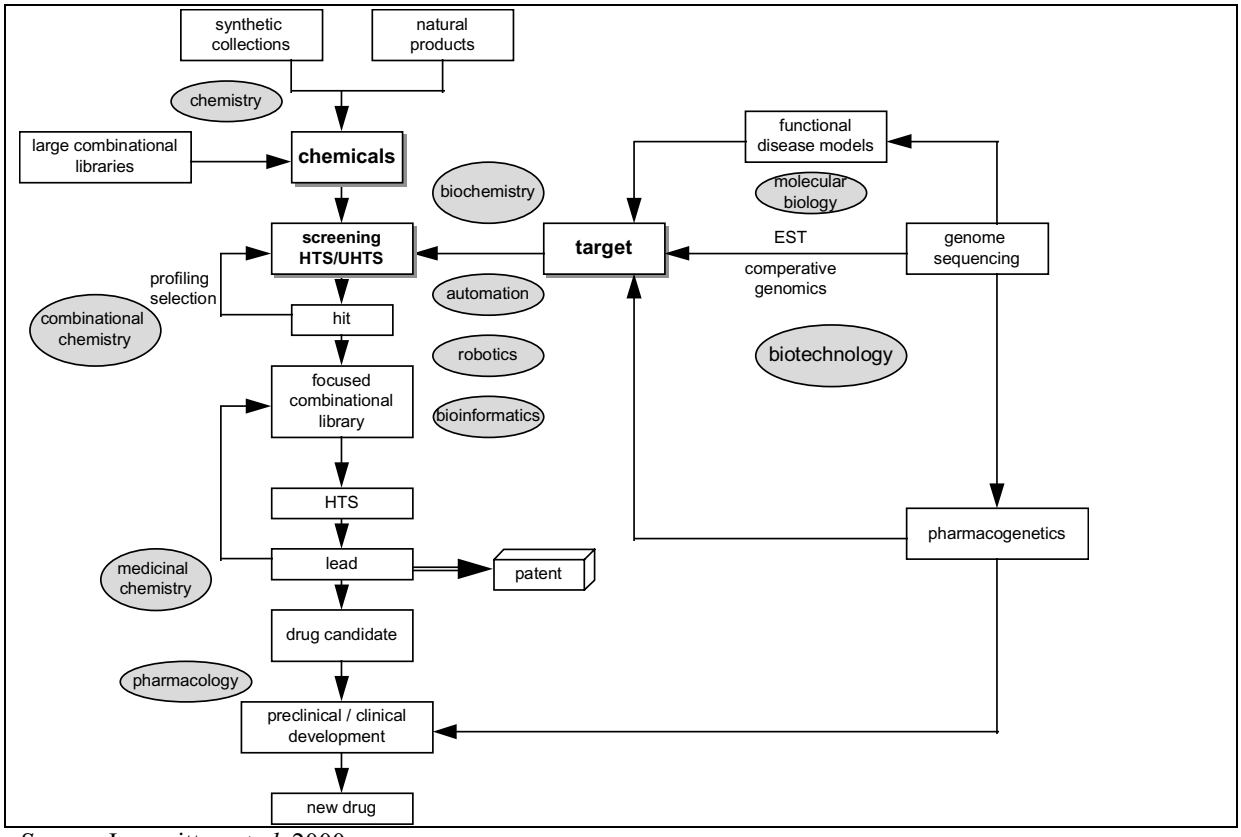
Using genetic engineering it is possible to produce foreign proteins in microorganisms or cell cultures from higher organisms. This basic principle is used for the production of protein therapeutics. An important example of this approach is the production of human insulin. The genes for this protein have been extracted from the human genome and transferred into either bacteria or yeast cells. Both systems allow the expression of the human insulin product which after purification and modification can be used as a pharmaceutical. Other important biopharmaceuticals on the market include erythropoietin, growth factors, interferons and tissue plasminogene activators (TPA). In the year 2000 about 370 biopharmaceuticals were in the pipeline of pharmaceutical and biotechnological companies. Even though the use of biotechnology for producing biopharmaceuticals has been quite successful, the potential of this approach is probably limited. According to expert estimates it is unlikely that biopharmaceuticals will gain more than 10% of the total market for pharmaceuticals.

More important than the use of biotechnology as a production method is its application as an R&D tool in drug discovery. Biotechnology as an R&D tool is considered to be one of the main driving forces of innovation in the pharmaceutical industry, leading to a shift in the paradigm of drug discovery and development. An overview of the new, biotechnology-driven mode of drug discovery is given in Figure 1. An increasing number of new drug targets will be detected from the human genome sequence information. Of the 30,000 to 40,000 presumed human genes only a minority might turn out to be interesting drug targets. However, this may still account for 3,000 to 10,000 new targets. Compared with the existing number of drug targets this would still correspond to an increase of about one order of magnitude.

The increasing number of potential new drug targets eliminates an important bottleneck in the drug discovery process. At the same time, the assessment of the usefulness of new targets introduces a new barrier. The key words are target validation. A validated target is achieved when treatment with the therapeutic compound leads to desirable clinical outcomes. The validation of new targets requires biological information on the physiological role of the putative targets. A number of new approaches like analysing the expression of genes,

comparing genome information between different organisms and between healthy and disease conditions or even the use of three-dimensional information of the structure of potential drug targets are used in this context.

Figure 1: Biotechnology-driven drug discovery



Source: Jungmittag *et al*, 2000.

Screening for the usefulness of putative new drug targets is nowadays performed in a high-throughput manner, an approach that made impressive progress during the last decade. In the early 1990s it was possible to scan about 4,000 substances for the effect on a drug target. Today 100,000s of substances can be screened per day fully automatically. The increased screening capacity requires the availability of a sufficient number of chemicals to be tested for potential pharmaceutical use. For that purpose, combinatorial chemistry approaches as described in Section 2.6 are used in the drug discovery process.

A common feature of this new process to drug discovery is that highly automated high-throughput approaches are used which require the integration of different disciplines and new types of knowledge which are not familiar to the traditional pharmaceutical industry. In particular, sequencing genomes, deriving information from genome sequences, parallel handling of large numbers of samples and large pieces of information, computation of an increasing abundance of information, high-speed screening and new synthetic chemical approaches like combinatorial chemistry are becoming crucial tools. These new skills are emerging not only in an evolutionary manner within a broader disciplinary framework. Rather new disciplines at the borderlines of traditional disciplines are becoming important. The implication for the pharmaceutical industry is that strategies need to be developed for drug development which allow the integration of the new knowledge and technology.

6.4 Pharmacogenetics

Pharmacogenetics means the study of polymorphisms in genes that affect the response of an individual to drugs. More efficient clinical trials could be achieved by using this information to select patient groups for clinical trials where a good response and low side effects from the new treatment can be expected. The long-term goal of pharmacogenetic approaches is the development of customised and personalised medicines. By identifying the genetic uniqueness of an individual, the therapeutic strategies for treating a particular disease state can be refined. It should be pointed out that such pharmacogenetic approaches rely on the availability and utilisation of individual genetic information. This implies that procedures and structures need to be established which assure confidentiality and responsible handling of such individual information.

6.5 Vaccines and antibiotics

Vaccines are considered to be among the most powerful health care tools of the 20th century. They contribute both to preventing disease, disability and death and to controlling health care costs. Even though impressive success has been achieved by vaccination, including the global eradication of smallpox, tremendous problems remain to be solved with respect to infectious diseases, the leading cause of death world-wide. No effective vaccination is yet available for some traditional diseases such as tuberculosis and malaria, but new and re-emerging diseases pose a continuing threat to health. Moreover, antimicrobial resistance is developing widely. These examples indicate the increasing need for new and improved vaccines.

Biotechnology provides new approaches to solve the scientific problems previously associated with vaccine development. This includes a new generation of vaccines based on specific parts of the protein of the infectious agents, which are produced by genetic engineering. Other new strategies include the development of DNA vaccination or the genetic engineering of plants to produce edible vaccines which may facilitate simple and effective vaccination administration.

The increased resistance of pathogenic microorganisms against commonly used antibiotics, the growing frequency of infections, and the emergence of new pathogens poses major challenges to health. The availability of genome sequences for an increasing number of microorganism (approximately 60) provides opportunities for the development of new antibiotics. Sequence information enables the identification of the bacterial gene products that are most appropriate for targeting by antibiotics.

7 Legal issues

Research, development, industrial applications, approvals and the marketing of biotechnology are regulated at the international, European and national levels. The general goals of the various regulations are to provide a framework that ensures safety for humans and safety and preservation of the environment. Most of the international regulations are recommendations which depend on ratification by national authorities and require implementation of national rules. The following discussion focuses on regulations that are relevant mainly for applications of biotechnology in agriculture and food production. A complete coverage of all regulations related to biotechnology is not possible within the scope of this study.

At an international level the *Convention on Biological Diversity*[4], which was passed during the Rio Conference in 1992, aims to preserve biological diversity, assure sustainable use of

[4] www.biodiv.org/

biological diversity and achieve a just distribution of the benefits of the utilisation of genetic resources. The *Convention on Biological Diversity* can be considered as an important innovation in a sense that it was the first time that the idea of sustainable development was linked with the preservation of biological diversity. In addition, the convention acknowledges that genetic resources fall under the sovereign rights of States and that the authority to determine access to genetic resources rests with the national governments and is subject to national legislation. The convention also covers some specific issues which are directly relevant for biotechnology. For example, ratifying nations are obliged to agree upon measures which allow safe handling, utilisation and transfer of genetically modified organisms. This should help to avoid negative impacts on the preservation and sustainable use of genetic resources.

This intention of the *Convention on Biological Diversity* was specified in the *Cartagena Protocol on Biosafety*[5] from 2000. The main issues of this protocol are the following: If genetically modified organisms are exported to another country and intended to be released there, a so-called advanced informed agreement procedure has to be followed. This includes an obligation on the exporting nation to provide all information that is necessary to assess the safety of the organism to the importing nation. In the case of qualified doubts on the safety of these organisms, the importing nation has the right to forbid the import without any additional scientific proof. Other regulations concern the labelling of imported genetically modified organisms. It requires the clear labelling of organisms which are imported with the purpose of being released into the environment or for generating seeds. Finally, all nations ratifying the protocol on biosafety pledge to make accessible to an international clearing house all information relevant to the safety of genetically modified organisms, so that importing nations can use such information.

The WTO's agreement on *Trade-related Aspects of Intellectual Property Rights*[6] (TRIPS) has an important impact on international intellectual property rights and is also relevant to biotechnology. In particular, the agreement aims to narrow the gap in the way these rights are protected around the world and to bring them under common international rules. A basic principle of TRIPS says that intellectual property protection should contribute to technical innovation and the transfer of technology. Both producers and users should benefit and economic and social welfare should be enhanced. Concerning patents, which are only one type of intellectual property (others include copyright, trademarks, geographical indications, industrial designs, the design of integrated circuits and trade secrets), the agreement says that patent protection must be available for inventors for at least 20 years. TRIPS covers almost all fields of technology, but certain areas can be excluded by governments, eg, diagnostics, therapeutic and surgical methods, plants and animals and biological processes for the production of plants and animals. It is significant to plant biotechnology that according to TRIPS, plant varieties must be protectable by patents or by a special system such as the Breeders Rights provided in the conventions of the International Union for the Protection of New Varieties of Plants. This ruling of TRIPS could imply that the availability of seed could be restricted in the future.

A number of directives and regulations have been developed for biotechnology since 1990 at a European level (a summary of European legislation can be found at: http://biosafety.ihe/be/Menu/BiosEur.html). The *Directive on the Contained Use of*

[5] www.biodiv.org/biosafety/
[6] www.wto.org/english/tratop-e/trips-e

Genetically Modified Microorganisms (90/219/EEC) regulates the handling of genetically modified organisms in contained systems and considers measures to protect human health and the environment. This guideline has subsequently been modified and expanded by several other European decisions. The last modification took place in 1998 (98/81/EC). It obliges the member states to regulate the application of genetically modified organisms in contained systems and to restrict possible negative impacts on human health and the environment. Depending on the risk genetically modified organisms are classified into two groups which require different levels of safety measures.

Another general directive at the European level is the council directive 90/220 of April 1990 which regulates the deliberate release of genetically modified organisms into the environment. It specifically regulates the authorisation process for genetically modified seeds, genetically modified organisms intended for use as animal feed as well as their deliberate release into the environment. According to the directive, the authorisation process serves to protect human health and the environment when carrying out the deliberate release of genetically modified organisms. The applicant has to submit a notification to the competent national authority of the country where the initial release will take place. The notification must include an extensive technical dossier including detailed information about the organism itself and its possible interactions with the environment, information about monitoring programmes, waste treatment and emergency response plans. According to the directive, no member states can refuse the approval of a genetically modified organism or of a product containing genetically modified organisms if the organism or the product comply with the guidelines.

During the 1990s two properties of transgenic plants gave aroused concern during the application process: the first was the use of antibiotics in some of these plants as a marker for the success of the genetic modification. The second concerned insect resistance of some of these plants. In the first case the further spread of antibiotic resistance in the environment was considered to be a risk; in the second case the main argument was that such plants could also harm useful insects.

Since March 1998 no new applications for marketing transgenic plants have been approved, so that at the end of the year 2000 at least 14 processes were waiting for a decision. In June 1999 an unofficial moratorium was concluded by the ministers of environment, saying that no applications for the marketing of genetically modified organisms should be approved until sufficient scientific proof was available of the safety of such products for health and environment.

In early 2000 the new directive on deliberate release was passed (2001/18/EC). Compared to the previous guidelines the new version envisages more intensive participation of the public during the approval procedure, and in general a higher degree of transparency in the whole process. This requires that information must be shared with the public on the deliberate release of genetically modified organisms in a country, exchange of information between the national authorities and the European Commission, as well as scientific assessments of the genetically modified organisms and products. A publicly accessible inventory is to be established which lists all approved releases for experimental purposes with the respective sites. In general, approvals for marketing of genetically modified organisms are given only for a limited period of ten years. Renewal of approvals is possible after this period. The use of antibiotic resistance as markers of genetically modified organisms are to be reduced step-

wise and from the year 2005 organisms containing such antibiotic resistant markers will no longer be approved.

Since May 1997 the *Novel Food Regulation* (258/97/EC) includes the regulation of genetically modified food. This regulation is not specific to biotechnology. Rather six different categories of novel food are defined, only two of these refer to biotechnology: food which by itself is genetically modified (eg, a genetically modified fruit) or which contains genetically modified organisms (eg, milk products containing genetically modified microorganisms), and products which are extracted from genetically modified organisms but by themselves do not contain the organism (eg, oil extracted from genetically modified herbicide-resistant soybeans).

Free marketability of food is generally guaranteed within the European Union. The underlying assumption is that food products do not bear any risk for the consumer and their labels do not misguide consumers. In this context, approval for new food products according to the *Novel Food Regulation* requires applicants to explicitly demonstrate, before introducing the products into the market, that these products bear no risk for the consumer, do not misguide consumers and, in addition, are not different to other foodstuffs for which they substitute, in that nutritional deficiencies could be expected from eating this food.

These regulations established a withdrawal by the European Commission from the otherwise free marketability of food in Europe. Applicants for approval according to the *Novel Food Regulation* must demonstrate that these products bear no risk for the consumer, do not misguide consumers and are not different from other foodstuffs, for which they substitute, in that nutritional deficiencies could be expected from eating this food. The new feature of the regulation is that the applicant who plans to market a novel food must prove that the product complies with these criteria.

A key issue during the debate on novel food regulation was the labelling of such food. The ruling now is that food or food ingredients which contain genetically modified organisms or which are produced from such organisms need to be labelled if the respective organism can be detected in the foodstuff with acknowledged scientific procedures. In other words, the requirement for labelling is linked directly to the state-of-the-art of analytical tools. As a consequence of this principle there were problems in many member states with implementing labelling. In this context, several additional regulations were developed by the European Commission, partly for specific products. An important example is directive 49/2000/EC, January 2000 dealing with the labelling of traditional food contaminated by genetically modified organisms. According to this directive, labelling is necessary if an unintended addition of genetically modified material to food products exceeds a threshold of 1%.

During 2000 several new proposals of the European Commission to regulate novel food have been made. These include the suggestion that the link between labelling requirements and detectability of genetically modified substances in food should be abolished. Instead it is proposed to label any food product that was produced using genetically modified organisms during any step of its production. Such a new ruling would require complete documentation of the whole production chain.

In summary, during the last few years the creation of an efficient, transparent, harmonised, stable and reliable legal framework for biotechnology has become a priority of EU policy. Accordingly, genetically modified organisms and food or feed produced from genetically

modified organisms should be only approved if their risk has been evaluated comprehensively using scientific criteria, and in consequence can be considered as safe for the health of humans, animals and the environment. Social, economic, traditional, ethical and ecological issues as well as the feasibility of controls are to be considered during decisions about approvals. Consumers and users should be informed comprehensively about the existence of genetically modified organisms or genetically modified material.

8 Issues of public acceptance

Since 1999 the public attitude towards biotechnology has been analysed on a regular basis during four so-called Eurobarometer Surveys. The latest Eurobarometer Survey was carried out in November 1999 and included about 16,000 respondents from 16 European countries.

The overall results of this survey show the continuation of a trend of declining optimism about biotechnology. Compared to 53% of the respondents in 1993 and 50% in 1996, in 1999 only 56% thought that biotechnology would improve their way of life in the next 20 years. In contrast to biotechnology, optimism has been stable over the same period in five other technologies such as telecommunication or solar energy. Looking at individual European countries differences in the overall perception of biotechnology can be observed. Finland, Portugal and Spain are the most supportive. Denmark, France, Ireland, the United Kingdom, Belgium, Germany, Italy and the Netherlands are in the middle of the scale, while Greece, Norway, Austria, Luxembourg and Sweden are relatively more negative. There was a shift in public attitude between 1996 and 1999 in some countries. In particular Greece has become more negative, whereas Germany, Italy and the Netherlands have all become relatively more positive.

An important result of the Eurobarometer Surveys and also of other surveys of public perception of biotechnology is that there are pronounced differences between different application areas of biotechnology. The perception of medical biotechnologies and environmental biotechnologies is very positive among all European countries. Agricultural biotechnology is perceived as neutral, but genetically modified foods and the cloning of animals are opposed.

Discussions about public acceptance of biotechnology among public authorities, scientists, industry, but also non-governmental organisations (NGOs) have been mainly risk-led, in the sense that the perceptions of risk by the public and the "real" scientific risk from the use of genetically modified organisms are the key issues in this debate. The latest results of the Eurobarometer Survey and also other investigations of public acceptance indicate that this has been a misconception. Rather than real or perceived risks, the usefulness of particular biotechnology applications seems to be the crucial factor shaping acceptance. Applications perceived to have substantial benefits are supported despite a certain level of risk. This holds true for many applications in medicine, where not only "theoretical" risks could be imagined, but where real risks for individual patients could occur. This had not had a negative impact on the positive perception of medical biotechnology applications. On the other hand biotechnologies perceived to have only low benefits, such as genetically modified crops, do not find support even though the risks may be relatively low. The significance of the perceived benefits of biotechnology applications is also indicated by qualitative analyses of public perceptions (using a focus group approach), where it became very clear that the public wants to know why genetically modified organisms are needed and who would benefit from their use.

Another set of factors that influence the acceptance of biotechnology seem to be moral and ethical considerations. This is indicated by the fact that even among the supporters of biotechnology, there is a great deal of concern about the implications of biotechnology for the natural order. Finally, the relationship between information and acceptance needs some rethinking. On the one hand about 80% of the respondents of the Eurobarometer Survey say that they are insufficiently informed about biotechnology, and that they would take time to read or watch something about biotechnology in the media. On the other hand the fact that supporters and opponents alike feel poorly informed indicates that the effects of information may be unpredictable. In any case there is no positive correlation between the level of information and acceptance.

The analysis of public perceptions of biotechnology over time also indicates that public acceptance issues need to be taken seriously. For example, the Eurobarometer results of 1996 revealed broad support for medical applications of biotechnology, opposition to the use of transgenic animals in medical research and some signs of concern about agricultural and food biotechnologies. In the following years, acceptance of food biotechnology declined dramatically in Europe and it was too late to prevent this shift by regulatory or communication measures.

D Results of the International Benchmark Study

1 Introduction

The main aim of this study was to collect input and output indicators to benchmark and compare the performance of biotech research centres in Europe (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, Switzerland and the United Kingdom) with those in the United States The terms of reference provided by the EC for the study stated that "In the US each research centre that receives a public grant, however small, is publishing its key figures. These figures are further compiled in a series of reports that are available on the WWW. For European research centres similar figures are not yet available. As a result many of the European research centres use the indicators of the US biotech research centres as benchmarks". The EC required this study "to aim to fill this information gap" by gathering matching input and output indicators for European biotech research centres so they could be compared with similar US centres. The first problem to be solved was to identify publicly available research indicators for US biotech research centres. The EC was unable to provide the website address that contained reports on these figures. Three US agencies involved with US biotech centres – the National Institutes of Health, the National Science Foundation and the US Council of Biotechnology Centers – were therefore contacted. The NIH responded, saying that they were "unaware of quantitative Biotech Research Indicators for individual institutions". The NSF has a programme funding "Engineering Research Centres (ERC)", and one of the four focus areas it supports is Bioengineering. There are six centres currently funded in Bioengineering.[7] According to the NSF, centre specific data was not available and data on the different subject areas was not compiled within their own evaluation of the centres.

Two reports (Committee on Science, Engineering and Public Policy, 1996 and 1999) gave us reason to believe that such indicators did not exist.[8] Even if key indicators of US research centres had been available on the WWW, however, it would have been necessary to use the same methodology to gather indicators in both regions, to ensure comparability.[9] The project therefore involved the collection of research indicators and data for both EU and US biotech centres.

It was also necessary to ensure comparability by developing common definitions for "research centre". This was difficult because there is no unambiguous definition for the term 'research centre'. Eurostat (1996) defines a research centre as a "unit performing R&D located physically/geographically in one place". In contrast, the US National Science Foundation delimits research centres according to the kind of grants they receive, hence there

[7] Georgia Tech/Emory Centre for the Engineering of Living Tissues (founded in 1998), Marine Bioproducts Engineering Centre at the University of Hawaii (founded in 1998), Computer-Integrated Surgical Systems and Technology ERC at the Johns Hopkins University, Baltimore (founded in 1998), Biotechnology Process Engineering Centre at the Massachusetts Institute of Technology, Cambridge (founded in 1985), VaNTH ERC in Bioengineering Educational Technologies at Vanderbilt University, Nashville (founded in 1999), and the Engineered Biomaterials Engineering Research Center at the University of Washington (founded in 1996).

[8] The 1996 report reviews an evaluation of the NSF's Center Program. The analysis of the data was found to have serious deficiencies, and helped the NSF to recognise how future evaluations might be carried out. The 1999 report discusses how research performance might be measured. It notes that "both basic and applied research can be evaluated meaningfully on a regular basis ... But it is important that agencies evaluate their research programs using measurements that match the character of the research". It concludes that "the most effective way of evaluating federally funded research programs ... is expert review...".

[9] One of the key problems in comparative policy studies is using truly comparable measures of the same things in different countries (Heidenheimer, Heclo and Adams, 1990).

are research centres with a clinical orientation or an engineering emphasis. In addition, biotech centres, both in the US and Europe, undertake a diverse range of activities. An EC-funded inventory of biotechnology research in 17 European countries (Enzing *et al*, 1999) notes that centre activities can include building up critical mass, the provision of specific expertise to industry, the development of commercialisable ideas or research collaboration with industry. Similarly, US biotech centres may be concerned with economic development, research, education and training, technology transfer, and societal issues. Although some centres may be established and supported by government funding agencies to fulfil a certain mission, other centres may be set up by a small number of researchers, a university department or a larger institution with the aim of attracting research grants. This study focuses on biotechnology research centres that have been established by government funding agencies or evolved to fulfil an identified mission and/or receive at least 50% of their funds from public sources.[10] Private sector research centres and those funded by charitable foundations have been excluded.

The background to the study, presented in Section 2, informed decisions about the design of the study. The methodologies employed for the study are summarised in Section 3; full details are provided in Appendix II. The main results of the study are given in Section 4. The report considers the benchmarking and methodological results of the study, as well as the implications for future benchmarking exercises in Section 5. It concludes in Section 6 with a discussion of the policy implications of the study, both for science and technology indicators and for European biotechnology.

2 Background to the study

Background information for the design of the study comes from several sources including literature on the performance of public sector research, on the development of biotechnology and on the role of research centres. The conceptual framework for the performance of public sector research groups is based on the "compass card" model (Larédo and Mustar, 1996) which suggests that research groups participate in five contexts to achieve reputation and wealth:

a) Publishing papers in refereed journals (to certify knowledge);
b) Training doctoral students (to reproduce knowledge);
c) Links with application (industry, clinical research, etc);
d) Participation in achieving public goals (serving on government committees);
e) Involvement in public debate about science and technology.

The output indicators collected for biotech centres reflect the first four of these contexts.[11] The study also acknowledges the finding that research groups (or centres) differ in the strategies they adopt, and these strategies may affect their performance (Joly and Mangematin, 1996 and Larédo, 1999).

The second input to our study comes from knowledge of the characteristics of biotechnology. During the 1980s public biotechnology research became recognised as an important strategic area for government investment both at the national level and by the EU. Increasing investment over time has been accompanied by rapid increases in knowledge and the constant

[10] This includes research centres established at universities, but excludes departmental activities at universities.
[11] The fifth context, involvement in public debate, was not included because it is difficult to identify appropriate indicators to measure this activity.

emergence of new areas and applications, as described in Section C.1. Biotechnology research, which is often multidisciplinary, is conducted in many research institutes or centres, university departments and medical schools which do not focus on biotechnology *per se*. Biotechnology research, or its techniques are applied as part of these research institutions' broader research activities. In addition to the biotechnology activities of existing public research organisations, many new biotechnology institutions have been established in recent years.

Public sector biotechnology research tends to have close links with industry including the establishment of academic spin-off firms, especially in the US. European governments' policies have supported biotechnology research to assist economic development, but as indicated above, biotechnology centres have been set up with a variety of missions – to aid economic development through technology transfer, to be scientific centres of excellence, to provide access to large pieces of equipment, or a mix of these objectives.

The analytical report of the *Inventory of Public Biotechnology R&D Programmes in Europe* (Enzing *et al* 1999, 20-21) comments on the origin of biotechnology research centres in Europe. Their creation was stimulated in some countries by providing incentives for existing research centres to work in specific areas and build collaborative networks; in addition some countries created new biotech research centres or relabelled existing ones and others established gene centres linked to the emergence of genomics.

We do not have specific information on US biotech research centres, but a study on US research centres in general notes that they undertake collective, interdisciplinary research and originate from joint research projects undertaken during World War II (Etzkowitz, 1998). One estimate suggests that as many centres were created in the past decade as in the past century (David and Steinmueller, 1993). Centres have no common characteristics:

> Centres vary in scale from a single individual, to segments of a department, entire departments, individuals from several departments, and from various universities and companies. … many arise informally. … Some … grow into large organisations; others remain small or disappear. … Although they vary widely in scale and scope, a centre represents an intention to achieve distinction in a special field, typically supported by external funding (Etzkowitz, 1998).

Centres can also provide expensive research equipment that would be beyond the means of a single research group. Etzkowitz also notes that the early centres established by elite universities helped them to consolidate their research leadership. The concentration of research funds at leading research universities has recently been mitigated by direct appropriations to smaller, newer universities. The designation of a centre, along with congressional appropriations to establish research centres at minor-league universities, allows less research intensive regions to compete with the existing research intensive parts of the country and leading universities. As they build up their capacities, these new players capture an increasing share of their funds through conventional peer review procedures (*ibid*). Public research funding appears to be increasingly competitive and harder to obtain in the US, even as research funding grows, especially in the biomedical areas. One reason is that an increasing number of universities have competitive research capacities, often built utilising the centre mechanism to concentrate resources both from inside and outside the university. Such centres may also draw in researchers from firm and government laboratories in order to create a critical mass of research capabilities.

The formation of a centre, to act as a focus for capturing new funds, is a typical academic development strategy, especially for emerging universities. Utilising the centre mechanism, rather than a department which necessitates recruiting across various specialities to cover an entire discipline, allows for a specific focal area to be created. Several people, whose recruitment could not be justified by teaching needs alone, work on a common research topic. A centre typically brings together available researchers in areas designated as strategic along with new recruits. Designating certain areas as "centres" helps to justify the concentration of resources to create "steeples of excellence", rather than distributing resources throughout the university and failing to create critical mass in any area.

US academic centres in a given field are invariably highly competitive with each other, especially since they typically compete for funds from the same sources. US funding usually focuses at the individual investigator (research group) and centre level, rather than at networks or collaboration among research groups and centres (Etzkowitz, 2001). Few mechanisms exist to bring groups together to cooperate, other than those for traditional scientific collaboration. The US model contrasts strongly to both the Canadian Networks of Centres of Excellence, encouraging long-term collaborations of research groups at different universities, or European approaches that emphasise inter-European networking among research groups and centres.

3 Methodology

The methodology designed to cope with the issues identified in the previous section had eight stages:

i) developing criteria for identifying "biotech research centres";
ii) selecting potential candidate centres for the exercise;
iii) determining the input and output indicators for which to gather data;
iv) preparing a questionnaire and mailing it to identified centres;
v) screening the responses to eliminate centres which did not fully meet the criteria for "biotech research centre";
vi) conducting bibliometric and patent searches for centres which did meet the criteria;
vii) designing and entering data about centres on a biotech research centre database;
viii) analysing the database, including an assessment of how far the biotech research centres in the study represent the total public biotech research effort in Europe and the US.

The methodology is summarised below; full details about the specific approaches adopted for each of the above stages, the problems encountered during the project and the solutions adopted are provided in Appendix II.

The main criteria adopted for identifying biotech research centres are broadly related to "intent and content" and demand that:

- at least 50% of the centre's budget is allocated to research in fields in the taxonomy of biotech areas (see Table 1 above);
- at least 50% of funding comes from public sources;
- the centre has a specific mission related to biotechnology.

A broad range of centres was selected as recipients of the questionnaire. We anticipated that questionnaire responses might lead to the elimination of some of these centres at a later stage.

Use of the *Inventory of Public Biotechnology R&D Programmes in Europe* (Enzing *et al* 1999), supplemented by "expert" advice and the database of all biotechnology groups entering the EC's QoL and BIOTECH programmes produced a total of 504 European biotech research centres. The US sub-contractor identified US biotech research centres by first using information from the US Council of Biotechnology Centres, and then following leads mentioned by people in the initial sample ("snowball" effect) and by tracing web-links from one centre to another. This procedure resulted in a total of 210 US biotech research centres.

The questionnaire[12] was developed in close discussion with the contracting EC unit in order to ensure that the needs of the EC were reflected adequately in the data and indicators collected, included questions related to the identification criteria and about the centre's organisation and development. It also asked for information about personnel and finance for the years 1998 and 1999 to serve as input data, and about its activities for the same two years (research, doctoral training, contacts with industry and other external activities) for output data. It was mailed to 714 biotech centres and 324 of them responded.[13] An analysis of questionnaire responses showed that 98 responding centres did not meet the criteria developed to define "biotech research centre". The analyses in Section 4 below are based on 226 centres in total (194 in the EU and 32 in the US). The small number of US centres results both from the lower initial population of centres and a low response rate in comparison to EU centres. Moreover, those US centres that responded appeared to be a skewed sample of US biotech centres as a whole.[14]

Bibliometric and patent databases were searched to identify the publications produced and patents granted to centres which returned the questionnaire and fulfil the criteria to be considered a biotech centre. For reasons explained in Appendix II, the search of patent databases discovered very few patents. The responses from the questionnaires and the bibliometric searches were entered on a database and the results analysed to yield the results presented in Section 4.

3.1 Representativeness of centres

Before presenting the results, it is relevant to assess how far the research centres included in the study are representative of each country's biotechnology research. The most satisfactory method for such assessment was found to be the use of bibliometrics to assess the proportion of total national biotechnology publications accounted for by the centres in this study. (Other methods tested and their limitations are discussed in Appendix II.)

The results, shown in Table 2, suggest that biotechnology research centres are not the main producers of published biotech knowledge in the countries analysed, although they are more important in Portugal than in other countries. These results, however, should be treated with caution. They may under-represent centres' publications, especially when centres are formed of an agglomeration of parts of units that belong to other organisations (see Section 5.2 and methodological discussion in Appendix II).

[12] The questionnaire used in a study of human genetics research groups (Larédo, 1999) contributed greatly to the questionnaire design for this study.
[13] Copies of the European and US questionnaires are in an Annex to Appendix II.
[14] This issue is discussed in detail in Section 5.1

Table 2: Centres' biotechnology publications as a proportion of all national biotechnology publications 1994-1999[15]

Country	National publications	Sum centres' publications	Share national publications (%)
Austria	7589	513	6.8
Belgium	11647	1003	8.6
Denmark	9007	329	3.7
Finland	8402	957	11.4
France	58490	2421	4.1
Germany	71007	7426	10.5
Greece	3365	264	7.8
Ireland	2429	113	4.7
Italy	34021	1017	3.0
Luxembourg	118		0.0
Netherlands	23697	1775	7.5
Portugal	2241	630	28.1
Spain	20677	2417	11.7
Sweden	19415	154	0.8
Switzerland	18128	321	1.8
UK	76830	5880	7.7
Sum EU (ex.CH)	348935	24899	7.1
Sum EU (inc. CH)	**367063**	25220	6.9
USA	345206	1072	0.3
Sum EU (inc. CH) + USA	**712269**	**26292**	**3.7**

Source: SCI, Online via Host STN

The low proportion of publications accounted for by the US centres led to a detailed examination of the centres that had responded to the questionnaire and met our criteria for inclusion. With one exception, the US centres do not represent "first movers and major players", for instance those defined as "top quality universities" by Zucker, Darby and Brewer (1998). Instead, they are a skewed sample, representing only the "second movers and emerging actors" strata, which can be divided into two sub-categories: major research university latecomers (ie, late to enter biotechnology research)[16] and upcoming university newcomers (ie, those without an established research tradition).[17] This group of centres may not be representative of US biotech centres as a whole, and the overall performance of US biotech centres may not be reflected by US data. The results of comparisons in Section 4 must therefore be treated with great caution, and viewed solely as an indication of the type of results that might be achieved with a truly representative sample of US centres.

[15] There was a total of 824,816 biotechnology publications in the period 1994-1999.

[16] According to the Carnegie Foundation for the Advancement of Teaching classification (2000), only nine of the centres are in the top ranking research universities.

[17] According to the Carnegie Foundation for the Advancement of Teaching classification (2000) 13 centre are in second rank research universities. The remaining centres are not in research universities, or are not associated with universities.

4 Results of analyses

This section presents the results of the analyses conducted on the data collected through questionnaires and by bibliometrics for biotech research centres. The main focus of the analyses is the similarities and differences between the EU and the US centres in terms of:

i. their characteristics (mission, specialisation, age, affiliation, size, evolution and composition of staff);
ii. funding;
iii. activities (publications, training, networking, achieving public goals and links with application); and
iv. the overall performance of centres in terms of outputs and efficiency.

4.1 Similarities and differences between the characteristics of EU and the US centres

4.1.1 Mission

In the questionnaire we asked whether the centres had a mission related to biotechnology. We distinguished between four different missions:

- to provide education and training,
- to build up the knowledge base in biotechnology,
- to be a national centre of research excellence, and
- to foster commercialisation and economic development in industry

As shown by Table 3, most centres have multiple missions (six centres which indicated that they had a specific mission related to biotechnology did not specify the nature of that mission).

Table 3: Biotech research centre missions (allowing for double counting)

Mission	Centres EU	Centres US
Education and Training	161	27
Knowledge Base	156	28
Research Excellence	152	23
Foster Commercialisation	85	23
Total centres	194	32

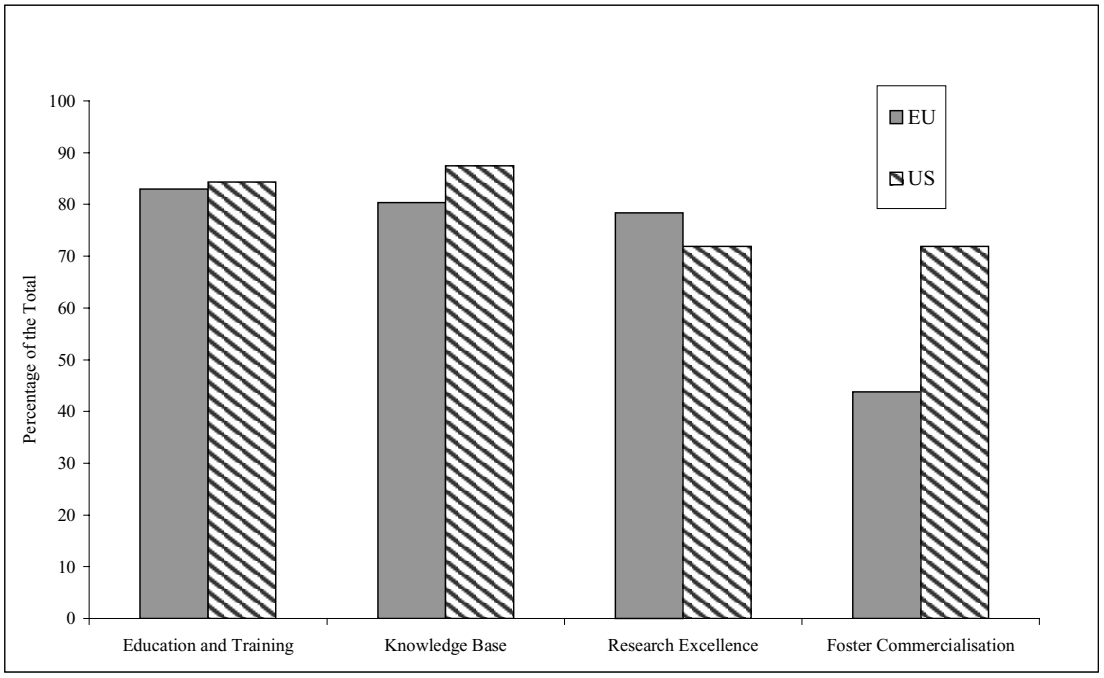
- 73 centres had all 4 missions
- 84 centres had 3 missions
- 48 centres had 2 missions

15 centres had one mission only:

- 2 German and 1 US centre had *only* the mission to foster commercialisation and the economic development of industry.
- 5 centres (all from different countries) had *only* the mission to provide education and training.
- 3 centres (all from different countries) had *only* the mission to build up the knowledge base in biotechnology.
- 4 centres (2 from Germany) had *only* the mission to be a national centre of research excellence.

Figure 2 compares the missions of EU and US centres. It shows that fostering commercialisation is relatively more important to US than EU centres while there are hardly any differences concerning the relative importance of the other mission statements defined.

Figure 2: Biotech research centre missions: EU and US



4.1.2 Specialisation

As Table 4 illustrates, the majority of centres are involved in more than one focus area, as defined by the taxonomy of biotechnology areas.[18]

Table 4: Research focus of biotech research centres (EU and US)

Number of focus areas	Number of centres
8	1
7	11
6	15
5	31
4	45
3	45
2	42
1	24
No information	12
Total	**226**

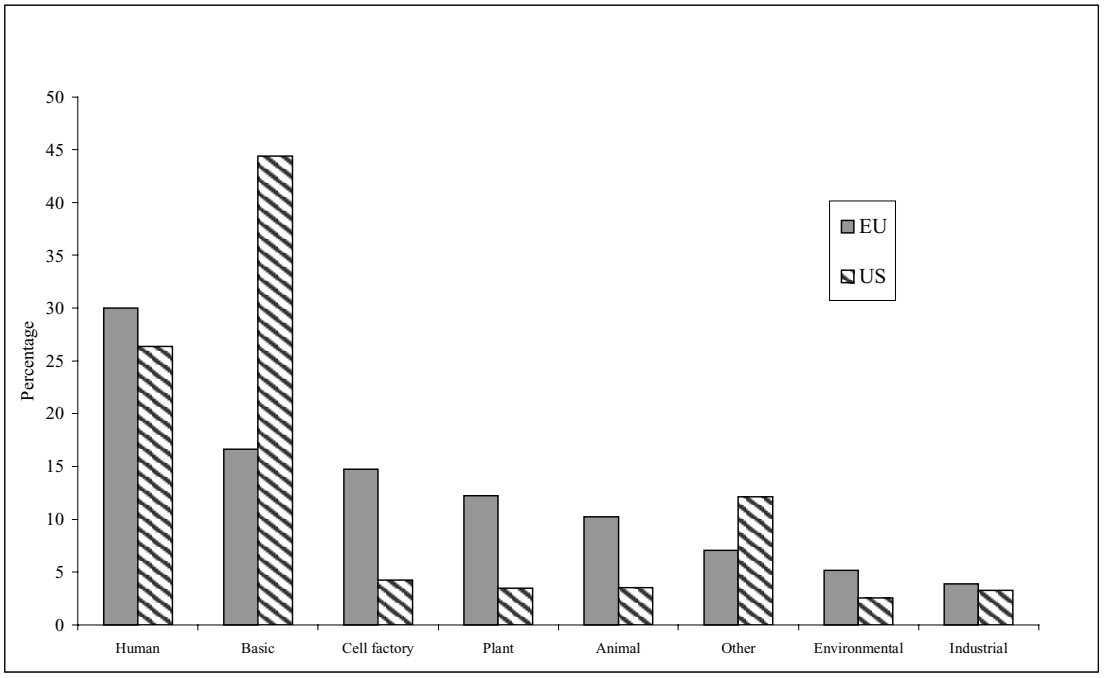
The overall expenditure on each focus area is shown in Figure 3. It is based on aggregating the amount allocated to each focus area by the EU and US centres.[19] It indicates that the US

[18] See taxonomy in Table 1, Section C.1

[19] The amount for each centre was the total budget (question 10) divided by the proportion allocated to each area (question 2).

spends relatively more on basic biotechnology than the EU, and less on cell factory, plant, animal and environmental biotechnology research than EU centres.

Figure 3: Distribution of Expenditure by Research Area (average budget 1998-1999) (n=188; 161 EU, 27 US)



As the majority of centres specialised in more than one area of biotechnology, basing other types of analyses on these figures resulted in simply replicating the same proportions. For these reasons we allocated each centre to *one* focus area only, including an additional 'multi-focus' category, which represents those centres that could not be clearly assigned to one specific focus area. We therefore used the following procedure to identify centre specialisation:

a) Centres with >50% of their activity in one focus area were allocated to this single-focus area (over 80% of all single focus centres).[20]
b) Of the remaining centres, those with 30% of activity in *one* focus area only (and <30% of activity in several other areas) were also allocated to this single-focus area.
c) Centres that had >30% of activity in several focus areas were identified as 'multi-focus'.

The results of this analysis (which we have called 'Focus area 1') found that 43% of centres specialised in more than one area of research. Table 5 shows the breakdown of all centres into single and multi-focus centres

Table 5: Share of centres with single- or multi-focus (EU and US)

Focus area 1	Number of centres
Single-focus	128 (57%)
Multi-focus	98 (43%)

[20] 40% of single-focus centres had over 75% of their activity in one focus area

A comparison of EU and US research centres by 'Focus area 1' shows that there are more single-focus centres in the EU, and more multi-focus areas in the US, as shown in Table 6.

Table 6: Proportion of EU and US research centres by single- and multi-focus

Focus area 1	EU %	US %
Single-focus	59	41
Multi-focus	41	59

We next examined the single-focus centres in more detail, dividing them into eight areas of biotechnology research: human, basic, plant, cell factory, animal, industrial, environmental and other. This allocation is called 'Focus area 2', and the results are shown in Table 7.

Table 7: Single-focus centres by specialisation (EU and US)

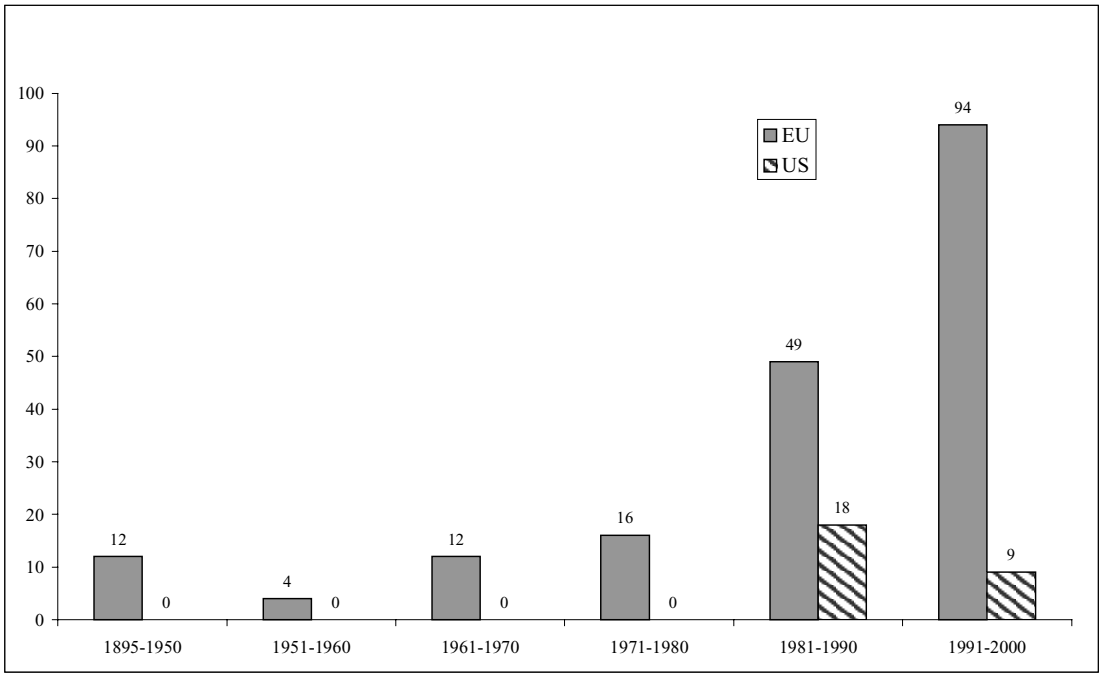
Focus area 2	Number of centres
Human	32
Basic	29
Plant	24
Cell factory	14
Animal	12
Industrial	6
Other	6
Environmental	5

A comparison of EU and US centres' specialisation shows that there are proportionately more US than EU centres specialised in 'Basic' research, with 19% of US centres specialised in basic research in comparison with 12% of EU centres. This does not contradict the finding that US centres have a stronger orientation to fostering commercialisation than EU centres (see Figure 2). It once again highlights the fact that it is important to do basic research in order to be relevant to industry.

4.1.3 Age

We next analysed the date when centres were established. Figure 4 shows the number of biotech research centres by age group. Although EU centres have mainly been established in the last two decades, approximately 23% pre-date this time. It appears that these centres have been based on pre-existing research groups and later evolved to focus their activities on biotechnology. In comparison, all US centres were founded relatively recently. We also compared the size of centres with their age but found that there is *no* correlation between the two variables.

Figure 4: Research centres by age group

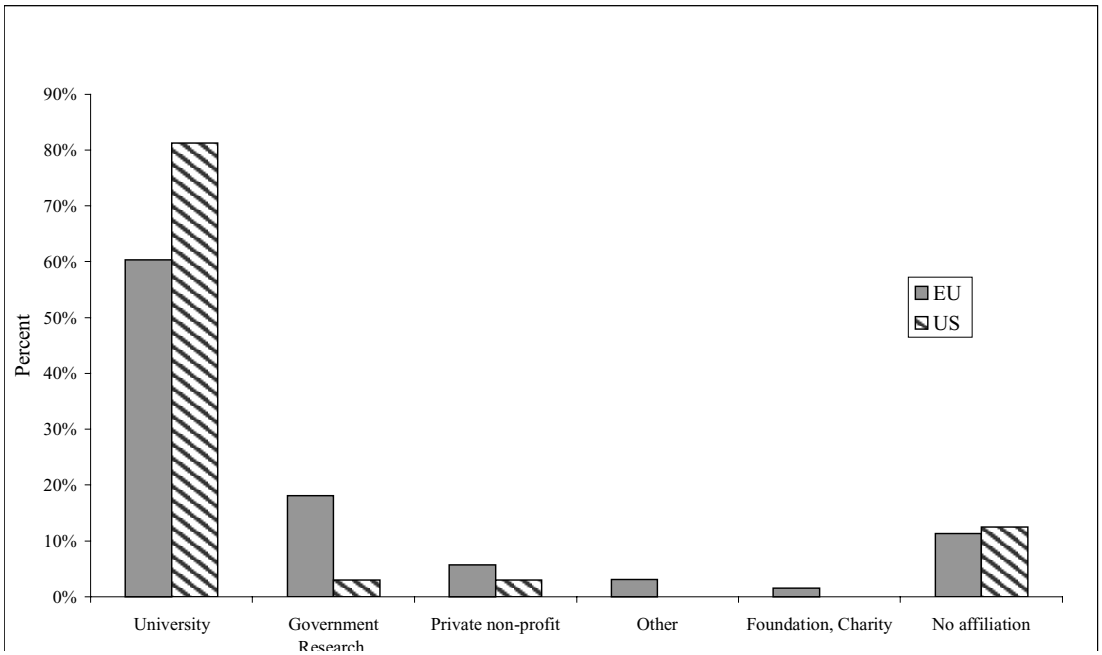


4.1.4 Affiliation

In the questionnaire we asked the biotech research centres about other organisations to which they are affiliated. Figure 5 shows that US centres are more often affiliated with universities than EU centres; the latter are, however, affiliated to a broader range of other types of institution than US centres, and affiliations to government research institutions are relatively more prevalent than in the US.

Several centres are affiliated with a number of different institutions. This made it hard for them to specify only *one* other organisation with which they are associated. One example is a biotech centre which consists of research groups headed by 17 senior researchers at five institutions within a European capital city.

Figure 5: Proportion of centres affiliated with other organisations (n=226; 194 EU, 32 US)



4.1.5 Size

The size of the centre was based on the total number of staff. Several centres did not complete the question about the total number of staff, so in these cases we calculated the total number of long term and short-term employees for 1998 and 1999 and used this number for the analysis. Where centres gave totals which were different from ours, we used our calculations in preference. Centres that did not report on the number of staff were not included in the analysis. The size distribution of centres is based on an average of total staff for 1998 and 1999. The results are shown in Figure 6.

Figure 6: Proportion of centres in each size category (n= 211;186 EU, 25 US)

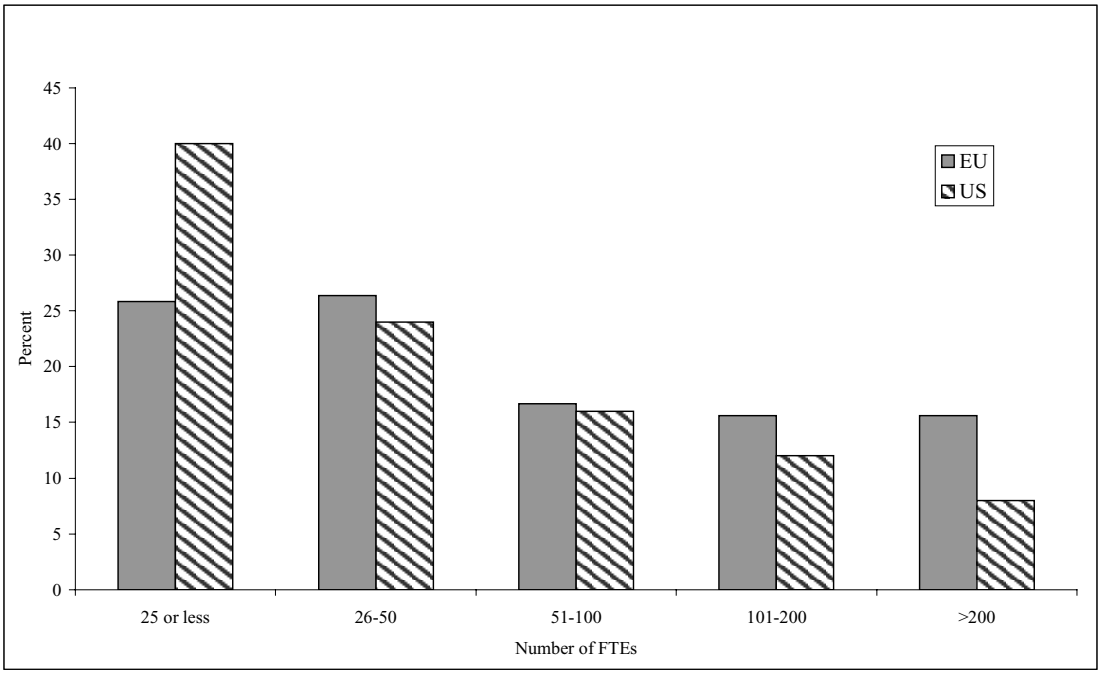


Table 8 shows the average number of staff in EU and US centres. On average EU centres are significantly larger than US centres.

Table 8: Average total number of staff (1998-1999 averaged)

EU	108.6
US	63.2

Table 9 shows that there is little difference in size between the single-focus and multi-focus centres in terms of average number of staff:

Table 9: Average number of staff in single- and multi-focus centres (EU and US)

Focus type	Average size (FTEs)
Single-focus	99.18
Multi-focus	96.63

We next analysed the average budget per member of staff in single focus centres, by specialisation. As shown in Table 10, the highest budget per member of staff was in human

and animal biotechnology while centres that focused on basic and plant biotechnology had the lowest budgets.

Table 10: Average budget per member of staff, by centre specialisation (EU and US)

Single focus specialisation	Average size (FTEs)	Average budget 1998-1999 (€Mio)	Average budget/FTE (€Mio)
Human	129.73	13.33	0.10
Animal	119.67	10.74	0.09
Industrial	114.75	7.08	0.06
Cell factory	105.24	5.09	0.05
Plant	87.81	3.94	0.04
Basic	85.26	2.34	0.03
Environmental	37.3	2.30	0.06
Other	29.92	2.02	0.07

We also looked at whether the number of research staff per project varied between single and multi-focus centres, but found very little differences between them. In terms of the single-focus centres, Table 11 shows that centres specialised in human and animal biotech had the most research staff per project. This may either reflect the need for more research staff or the greater availability of funds for these areas.

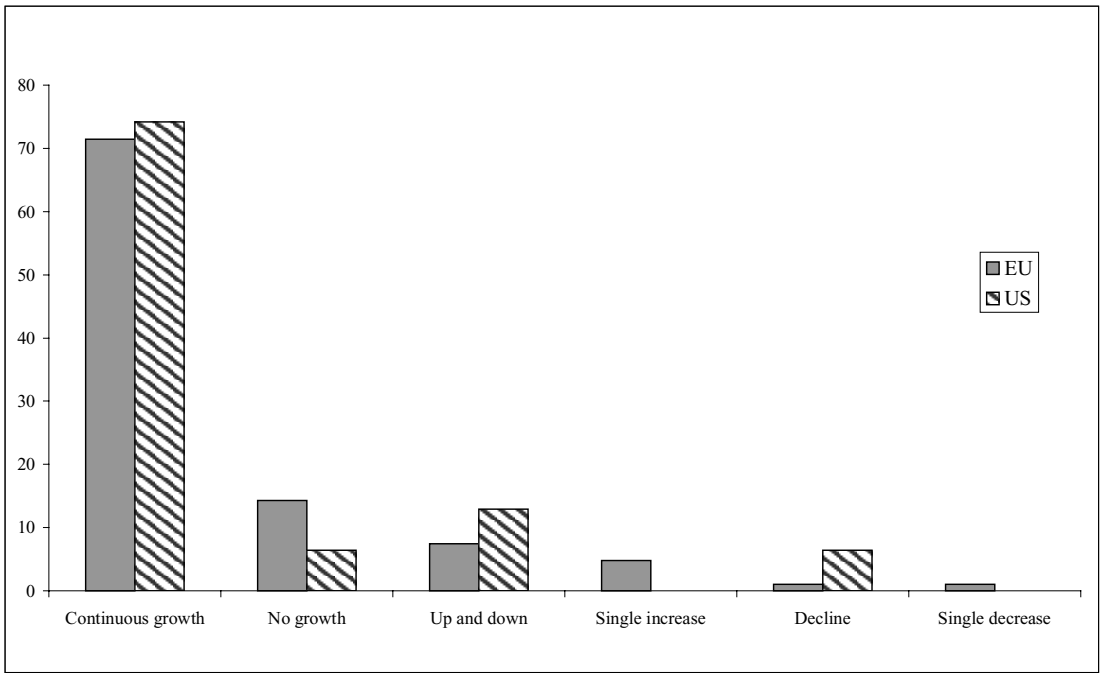
Table 11: Average research staff per project by specialisation (EU and US)

Single focus specialisation	Research staff/project (average)
Human	2.83
Animal	2.01
Plant	1.86
Basic	1.74
Other	1.62
Environmental	1.39
Industrial	1.26
Cell factory	1.10

4.1.6 Evolution

Respondents were asked to indicate the development of their centres described by various graphs. Continuous growth was the most common development form, as shown by Figure 7. The preponderance of centres experiencing continuous growth made it irrelevant to analyse any association of age and research area with the evolution of centres.

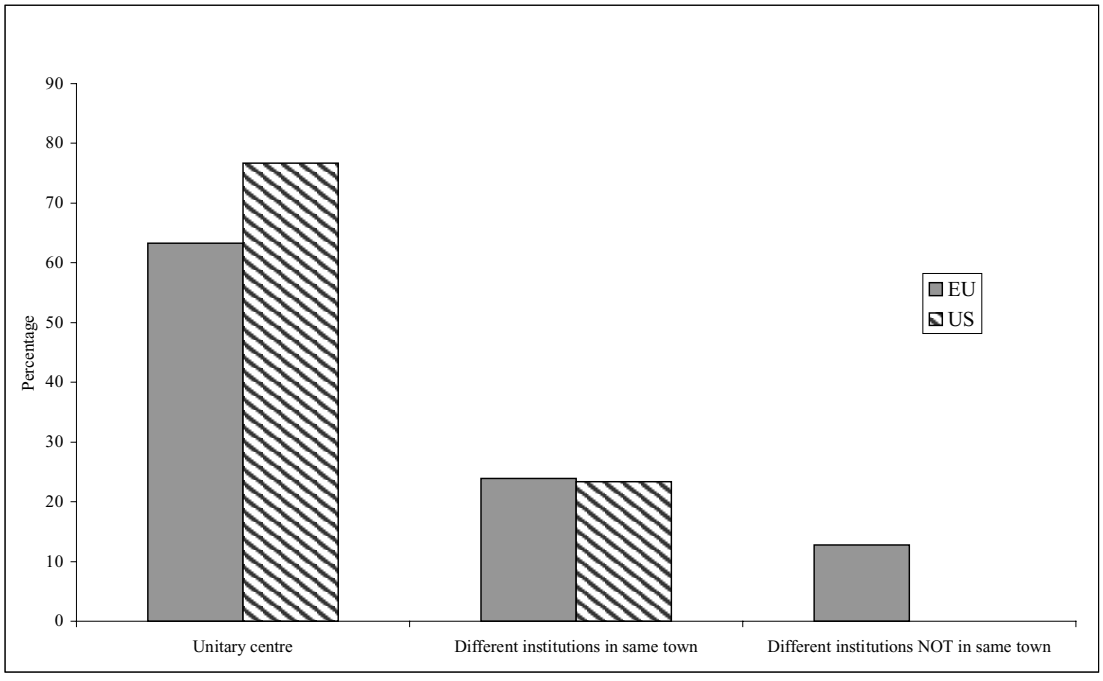
Figure 7: Percentage of centres by each development form (n=220; 189 EU, 31 US)



4.1.7 Organisational form

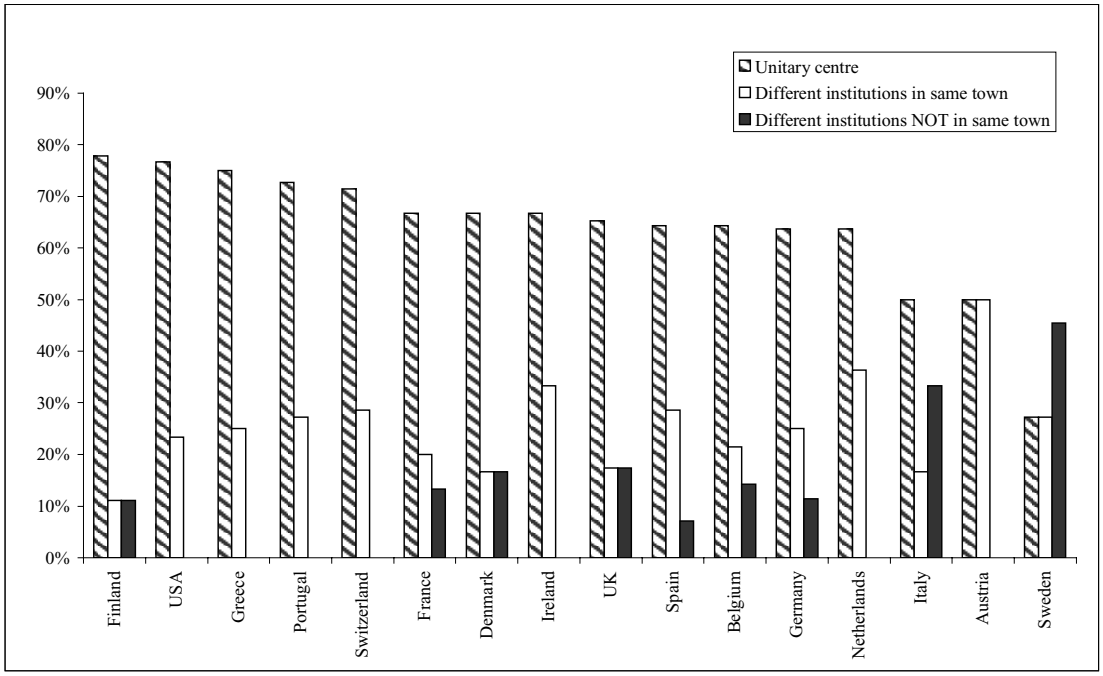
Centres were questioned about the way in which their centre was organised. This question was designed to distinguish between unitary centres based on a single institution and co-operative centres, based on different institutions or parts thereof. We made a further differentiation between co-operative centres in the same town or city and those more widely dispersed. Unitary centres are the most common form of organisation. As Figure 8 shows co-operative centres not in the same city occur only in the EU. We call these centres 'virtual' centres. However, centres that are situated in the same city could also be 'virtual' centres, from an organisational point of view.

Figure 8: Percentage of centres with each organisational form (n=218; 189 EU, 30 US)



We carried out a further analysis by country. As shown in Figure 9, there are proportionately more 'virtual' centres in Sweden and Italy. None of the US centres described themselves as comprised of different institutions from different towns.

Figure 9: Organisational form by country



4.1.8 Composition

An analysis of the composition of staff by type in US and EU centres found increases in all categories of staff between 1998 and 1999, with dramatic increases of both short and long-term technicians. Growth in staff numbers was higher in US than EU centres. Table 12 shows the percentage growth of staff between 1998 and 1999 and Figure 10 compares the proportions of each category of staff in EU and US centres.

Table 12: Growth rates in full-time equivalent posts in EU and US centres, 1998-1999 (n=212; 187 EU, 25 US)

Growth rates 1998-1999	EU	US
Long term professors	115%	159%
Long term researchers	108%	160%
Long term technicians	**121%**	**348%**
Short term professors	104%	200%
Short term researchers	117%	213%
Doctoral students	122%	118%
Short term technicians	**151%**	**227%**
Overall	120%	170%

Figure 10: Composition of staff by category (average for 1998 and 1999)

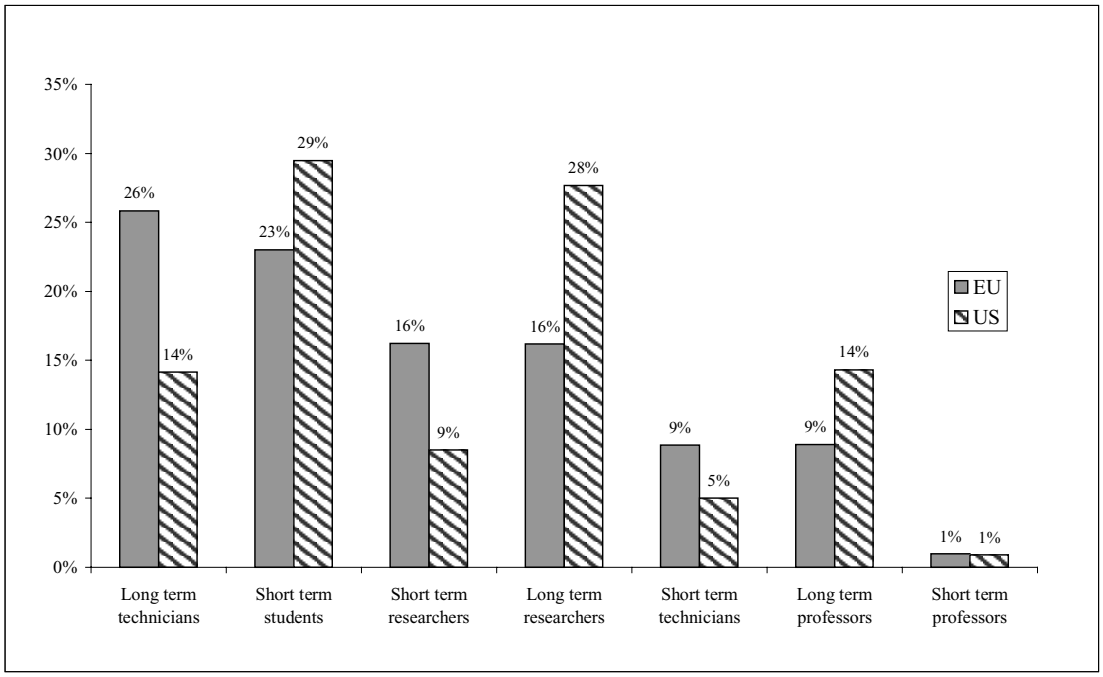


Table 13 shows that, compared to their European counterparts, US centres have a much higher proportion of long-term research staff (professors and researchers).

Table 13: Proportion of long term and short term research staff in EU and US centres (1998 and 1999 averaged)

	Long term research staff	Short term research staff
EU	25%	17%
US	42%	9%

We cannot explain the rapid growth of long-term and short-term technicians shown in Table 12. We examined the number of technicians by single-focus area specialisation (averaging figures for 1998 and 1999 and including both long-term and short-term technicians), and found that centres specialising in human and animal biotechnology have the greatest number of technicians, as shown in Table 14. Growth of technicians may be caused by some biotech research activities becoming routine or performed on specialised equipment rather than demanding original research by bench scientists (eg, sequencing). Increasing funds allocated to the purchase of expensive scientific instruments may also create a demand for technicians to maintain and operate this equipment.

Table 14: Percentage of technicians to total staff, by specialisation (EU and US)

Single-focus specialisation	Proportion of technicians
Animal	47%
Human	37%
Plant	34%
Cell factory	32%
Environmental	26%
Other	23%
Basic	22%
Industrial	2%

4.2 Similarities and differences between the funding of EU and the US centres

4.2.1 Budget

Budget calculations are based on the average of total budgets for 1998 and 1999. Where respondents gave no budgetary information for 1998 we used the 1999 figure only. We excluded from the analysis those centres which had entered zero for their total budget for 1999 or where the 1999 budget was below 10,000 Euros per member of staff. In these cases we assumed that the centre had made a mistake in completing the questionnaire. Table 15 shows that the average budget of US centres is lower than in the EU, probably a reflection of the smaller size of US than EU centres (see also Figure 6).

Table 15: Total, average and median budgets (1998 and 1999 averaged – Mio. €) (n=175; 154 EU, 21 US)

	EU	US
Total	1249.2	101.7
Average budget per centre	8.11	4.84
Median budget	3.03	2.59

We next compared the average budgets of single- and multi-focus centres but, as shown by Table 16, found a very minor difference only.

Table 16: Average budgets of single- and multi-focus centres (EU and US)

Focus type	Average budget 1998-1999 (Mio. €)
Single-focus	7.24
Multi-focus	7.29

A comparison of the average budgets of single-focus centres, however, found that they vary by specialisation. As shown by Table 17, the single-focus centres with the largest budgets are those which focus on human and animal biotechnology, which is again a reflection of the size of those centres as shown in Table 10.

Table 17: Average budgets of single-focus centres, by specialisation

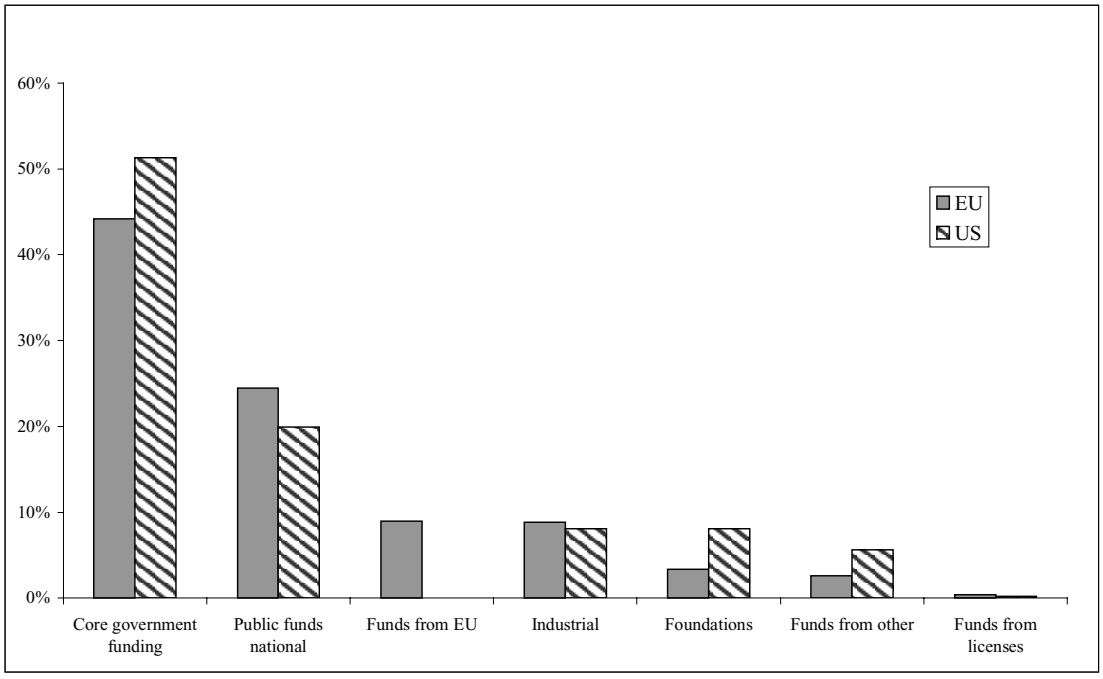
Single focus Specialisation	Average budget 1998-1999 (Mio. €)
Human	13.33
Animal	10.74
Cell factory	7.08
Plant	5.09
Basic	3.94
Environmental	2.34
Industrial	2.30
Other	2.02

4.2.2 Source of funds

We analysed the sources from which centres received their budgets. The results, shown in Figure 11, indicate that core government funding is the most significant source of funds. The categories "Public national funds", "Funds from the EU", and "Funds from industrial" mainly provide project funds. "Funds from foundations" may make a small contribution to core funds, but this category mainly provides project funds.

Higher proportions of core funding for the US than the EU centres suggests that these centres would not exist without core funds. Secondly, higher core funding appears to correlate with a higher proportion of permanent staff.

Figure 11: Sources of funding



(n=206; 178 EU, 28 US)

4.3 Similarities and differences between the activities of EU and US centres

4.3.1 Academic activities

We analysed centres' activities in training PhD students. Only 52% of the centres were permitted to award PhDs; the remaining 48% of centres were not permitted to award PhDs. Table 18 shows that the ability to award PhDs does not have any effect on the number of doctoral students per centre.

Table 18: Average Number of doctoral students/centre, by ability to award PhDs (EU and US)

Average number of students/centre of those that *can* award PhDs	23.55
Average number of students/centre of those that *can't* award PhDs	22.21

The calculation of average number of doctoral students and average number of PhDs awarded, was based on those centres that had at least one doctoral student or PhD (for both EU and US centres). Internally and externally awarded PhDs were summed to calculate PhDs awarded per member of research staff. The results are shown in Table 19. Although students per centre and students per member of research staff are remarkably similar in the EU and US, EU centres have double the productivity of US centres in both the award of PhDs per centre and in PhDs awarded per member of research staff.

Table 19: Doctoral students and PhDs (averages for 1999)

	Students/ Centre	PhDs awarded/ Centre	Students/ Research staff	PhDs awarded/ Research staff
EU	33.97	10.59	0.83	0.36
US	33.33	5.22	0.86	0.17

Number of centres: Students/centre 129 (114 EU, 15 US), PhDs awarded/centre 102 (93 EU, 9 US), Students/research staff 129 (15 US 114 EU), PhDs awarded/research staff 101 (9 US, 92 EU)

To supplement the data gathered from the questionnaire, a bibliometric analysis was carried out using the online version of the Science Citation Index as provided by the host STN. Publication data, representing one form of scientific output created, and citation data, representing the impact or visibility of the scientific activities of the biotech research centres was collected for each centre that answered the questionnaire for the period 1994-1999. In addition total publications for each country were retrieved. Only publications attributed to the area of biotechnology were counted. The data was aggregated at the national level. The results are in Table 20. Note that aggregate data for Europe includes double counting (for those papers with authors in more than one European country) and therefore is not an accurate representation of overall European publications for the centres in our database. A description of the methodology applied to retrieve the data can be found in Appendix II.

As can be seen from Table 20, the US and the EU have a similar share of total scientific publications in biotechnology. Both regions contributed about 42% of all biotech publications. Of the scientific papers in biotechnology, 9.3% come from the United Kingdom which is slightly more than the proportion contributed by Germany 8.6%. These two countries are the most active European players followed by France (7.1%). As already mentioned in Section 3 the share of national biotech papers contributed by the centres

Table 20: Biotech centres' publications and citations, by country 1994-99

	Number of Biotech pubs	% total biotech pubs	Sum centres' pubs	Share national pubs	Sum centre cites	Sum centre cites (no self-cites)	CPP** (self-cites incl)	CPP (self cites excl)
Total Publications	**824816**	100						
Austria	7589	0.9	513	6.8	6295	5978	12.3	11.7
Belgium	11647	1.4	1003	8.6	13746	13226	13.7	13.2
Denmark	9007	1.1	329	3.7	3645	3456	11.1	10.5
Finland	8402	1.0	957	11.4	12649	12173	13.2	12.7
France	58490	7.1	2421	4.1	33772	32442	13.9	13.4
Germany	71007	8.6	7426	10.5	97426	93349	13.1	12.6
Greece	3365	0.4	264	7.8	2884	2766	10.9	10.5
Ireland	2429	0.3	113	4.7	834	787	7.4	7.0
Italy	34021	4.1	1017	3.0	15498	14951	15.2	14.7
Luxembourg	118	0.0		0.0				
Netherlands	23697	2.9	1775	7.5	20344	19411	11.5	10.9
Portugal	2241	0.3	630	28.1	3762	3489	6.0	5.5
Spain	20677	2.5	2417	11.7	22515	21069	9.3	8.7
Sweden	19415	2.4	154	0.8	928	877	6.0	5.7
Switzerland	18128	2.2	321	1.8	3413	3221	10.6	10.0
UK	76830	9.3	5880	7.7	80849	77367	13.7	13.2
Sum EU (excl. CH)	348935	42.3	24899	7.1	315147	301341	11.2*	10.7*
Sum EU (incl. CH)	**367063**	**44.5**	25220	6.9	318560	304562	11.2*	10.7*
USA	345206	41.9	1072	0.3	19999	19487	18.7	18.2
Sum EU (incl. CH) + USA	**712269**	**86.4**	26292	3.7				

* average value **CPP = citations per publication

Source: SCI, Online via Host STN

included in the analysis varies. A possible explanation could be that biotech research centres are not the main players within the national systems of innovation in this area. There are other significant players, for instance university departments, which were not considered in this analysis. However, the proportion of publications accounted for by biotech centres in Portugal is particularly high (28.1% of national publication output). The share of centres' publications in Sweden is very low (0.8%). But as we found that Sweden has a considerable number of so called "virtual" centres, this low proportion might also reflect limitations of the methodology (see Appendix II). On average, the centres included in our analysis contributed about 7% of all European biotechnology publications in the period.

Citation analysis shows that there are national differences in the impact made by biotechnology centres' publications. A European paper in biotechnology received on average 10.7 citations while for the US the value is 18.2 citations. This is an indication that the impact of the scientific activities of US centres is higher than that of their European counterparts. Again, variations can be found within Europe. The highest impact value was identified for the Italian centres, followed by French centres. Only slightly behind these we find the research centres from the United Kingdom, Belgium and Germany. Below average impact values are clearly shown for the Portuguese and Swedish centres.

An examination of the proportion of EU and US centres with key personnel[21] showed that 45% of EU centres have key personnel compared to only 22% of US centres. A comparison of the average number of key personnel per centre in the EU and US revealed that the US average was only 0.34 key personnel per centre, considerably *less* than 2.17 key personnel for the EU centres, confirming that our sample of US centres is not representative of the population as a whole.

In order to assess the "prestige" of centres' staff, the questionnaire asked about the number of research staff involved in editorial committees and scientific committees, and numbers attending EU and US conferences. We analysed these results by dividing them by the total number of research staff in the centre. The results in Table 21 show that EU centres have more members of editorial committees, more members of scientific committees and more attendees at EU conferences per member of research staff than US centres. US centres, unsurprisingly, have more attendees at US conferences per member of research staff, but less attendees at EU conferences than EU centres have attendees at US conferences.

Table 21: "Prestige" activities for EU and US centres

	EU average	US average
Member of editorial committee/research staff	0.13	0.07
Member of scientific committee/research staff	0.25	0.12
EU conferences/research staff	0.68	0.22
US conferences/research staff	0.30	1.30

Table 22 shows the proportion of centres' projects which involve research linkages with researchers elsewhere. It shows that where external links exist, both EU and US centres are

[21] Key personnel were identified as those who had published more than 20 publications in the period 1994-99. This differs from Zucker and Darby's (1998) criteria for star scientists which related to the discovery of genetic sequences. Sequence discovery became routinised during the 1990s and is no longer a measure of research success.

most likely to be involved in projects with other *national* researchers. EU centres are more likely to be involved in projects with EU researchers than are US centres.

Table 22: Proportion of EU and US centres' projects involving external linkage, by region

	EU average	US average
Projects EU researchers/all research projects	0.30	0.10
Projects US researchers/all research projects	0.10	-
Projects national researchers/all research projects	0.40	0.55

4.3.2 Industrial activities

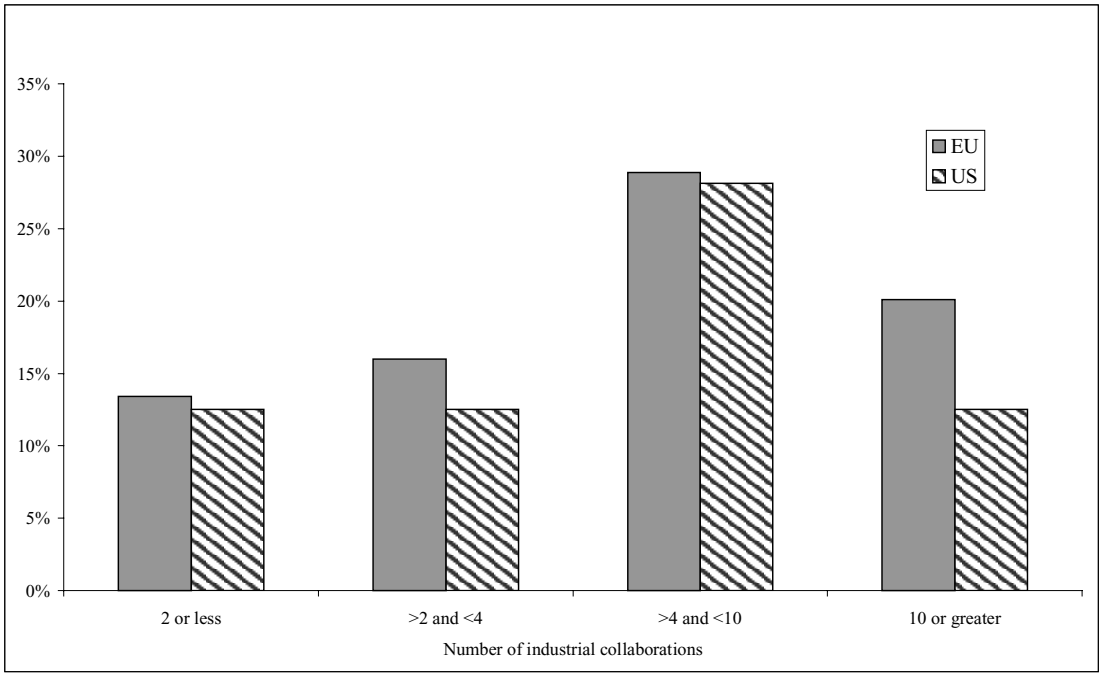
We analysed the number and percentage of centres with industrial collaborations. The results are shown in Table 23. We calculated the average number of industrial collaborations in both 1998 and 1999 for the centres involved. Even though a higher percentage of US than EU centres stress commercialisation as a mission, a higher percentage of EU centres have industrial collaborations, and the average number of collaborations is higher.

Table 23: Centres' industrial collaborations

	EU	US
Percentage of total centres with industrial collaborations	78%	66%
Average number of industrial collaborations per centre	7.91	6.31

Figure 12 shows the extent to which centres are involved in industrial collaborations.

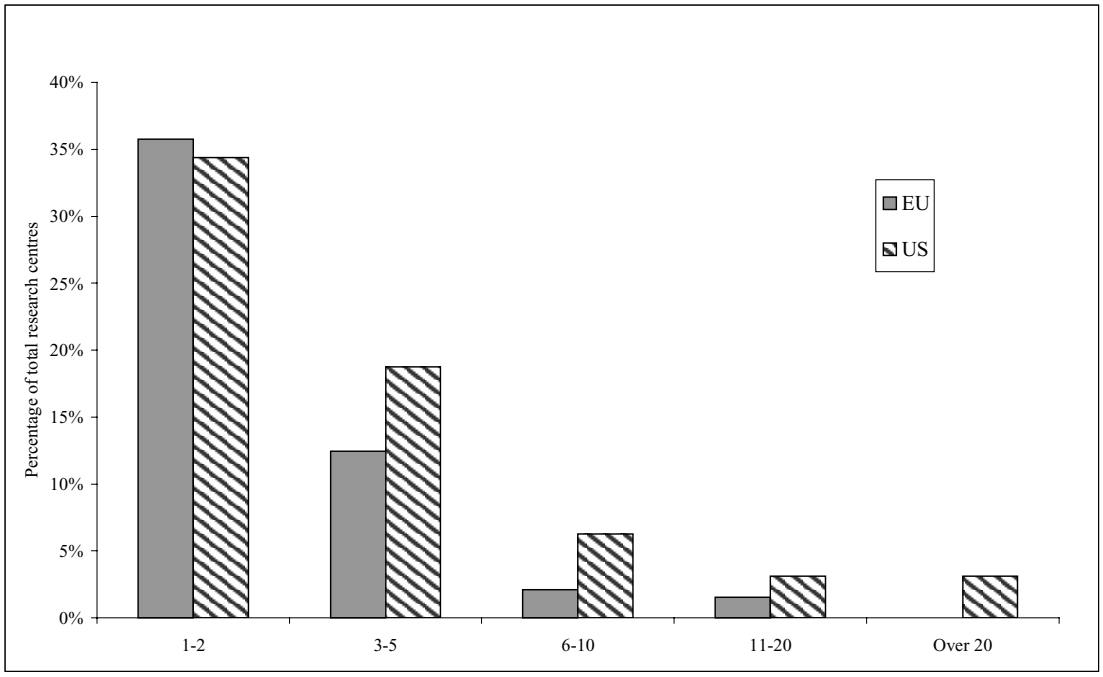
Figure 12: Proportion of centres by number of industrial collaborations



Finally we analysed the number of spin-off firms launched by centres. The results are shown in Figure 13. A slightly higher proportion of US centres (65%) indicated that they had

launched spin-off firms than EU centres (52%). The US centres involved appear to have a higher launch rate than the EU ones. Taken together with the results in Figure 12, this may indicate that commercialisation activities in the EU put more emphasis on industrial collaboration and in the US on launching spin-off firms. In regard to commercialisation, it is also interesting to note that 56% of US centres have a technology transfer office compared to 48% of EU centres.

Figure 13: Proportion of centres launching spin-off firms



4.4 Overall performance of centres

The small number of completed questionnaires from the US (32 only) limits our capability to carry out meaningful comparative EU/US analyses of centres in terms of efficiency and performance. The detailed analyses presented in this section mainly concern European biotech centres, because these dominate our sample, although US centres were included in these analyses. Section 4.4.1 considers the performance of centres in terms of academic, industrial, networking and prestige outputs, but does not take inputs in account. Section 4.4.2 assesses the efficiency of centres, including measures of both inputs and outputs. It assesses efficiency in achieving four missions: research excellence, research training, fostering commercialisation and knowledge production.

4.4.1 Performance of centres

Indices were prepared to assess the relative performance of centres' academic, industrial, prestige and networking activities (Appendix II describes the data used to calculate the indices and the methodology applied). Table 24 shows that only 2% of centres scored highly in all four indices. Overall, however, 72% of centres scored highly in at least 1 index; but 28% failed to achieve a high score in any index. We also conducted analyses to identify whether we could identify any relationship between high performance in various indices. The results are presented in Table 25. The strongest relationship found was between high performance in academic and prestige indices. High performance in the academic and networking indices also seems to be strongly related.

Interestingly, high performance in the industrial index requires high performance in all other indices, which is, however, not the case the other way around. From this data we would conclude that a centre that wants to be attractive to industry must perform well in all their other activities.

We looked at whether the centres that scored highly in the industrial index had a technology transfer office and we found that of the 36 centres that scored highly, 20 (55%) did *not* have a technology transfer office while 16 did.

Table 24: Proportion of centres achieving high scores, by number of indices

	% of total centres
High in all 4 indices	2
High in 3 indices	15
High in 2 indices	17
High in 1 index	38
High in 0 index	28

Table 25: Percentage of centres performing highly in two indices

	High performance academic	High performance prestige	High performance industrial	High performance networking
Also high performance academic	100%	52%	50%	56%
Also high performance prestige	69%	100%	42%	53%
Also high performance industrial	23%	14%	100%	23%
Also high performance networking	45%	32%	42%	100%

We compared the characteristics of high performance centres in each index with the aggregate of all the centres combined in terms of specialisation, age and size. The results are shown in Tables 26-29. They show that:

High performance academic centres are more likely to specialise in human biotechnology than the aggregate, and less likely to specialise in plant biotechnology. They are more likely to have 25 or less staff and less likely to have >200 staff than the aggregate, so they are more likely to be *small* centres.

High performance prestige centres, like high performance academic centres, are more likely to have 25 or less staff than the aggregate, although they are also more likely to have 26-50 staff. They are less likely to have 101-200 staff and >200 staff than the aggregate. Although the picture is a little more complicated in this case, high performance prestige centres, again, are more likely to be small centres.

High performance industrial centres are less likely to be involved in plant biotechnology and in multiple areas of biotechnology than the aggregate. They are more likely to be involved in cell factory biotechnology, which is not surprising since cell factory biotechnology is characterised as industrial biotechnology in our taxonomy. High performance industrial centres are also much more likely to have been formed between 1981-1990 and much less likely to have been formed between 1991-2000, so they are likely to be around 12-20 years old. Like high performance academic and prestige centres they are also

more likely to be *small*, with 25 or less staff (and they showed this tendency more strongly than high performance academic and prestige centres). They are less likely to be in any of the other larger size categories than the aggregate.

High performance networking centres are more likely to be single focus than the aggregate. They are less likely to be involved in multiple areas of biotechnology (like the high performance industrial centres). Centres that concentrate very specifically on certain activities need to be very well interconnected to other players. This seems to be their way to incorporate additional knowledge and contribute to broader developments. Furthermore, these centres are much more likely to have been formed between 1991-2000, so they are *younger* than the aggregate of all the centres. Unlike the high performance academic, prestige and industrial centres, they are *less* likely to have 25 or less staff than the aggregate.

In Tables 26-29 those figures underlined indicate 5% difference from the aggregate of all centres and the figures in **bold** indicate 10% difference from the aggregate of all centres.

Table 26: Percentage of centres in each focus area

	% all centres	% HP* academic	% HP prestige	% HP industrial	% HP networking
Multi-focus	43	45	45	39	38
Single-focus	57	55	55	61	63

* HP = High Performance

Table 27: Percentage of centres in each single focus area

Field	% all centres	% HP academic	% HP prestige	% HP industrial	% HP networking
Animal	7	7	8	8	8
Basic	17	16	17	19	21
Cell factory	8	12	9	19	10
Dispersed	24	24	21	15	17
Environmental	3	3	4	4	2
Human	19	24	23	15	21
Industrial	4	3	1	4	2
Other	4	2	5	8	4
Plant	14	9	13	8	15

Table 28: Percentage of centres in each age group

Year	% all centres	% HP academic	% HP prestige	% HP industrial	% HP networking
1895-1950	6	7	6	3	2
1951-1960	2	1	0	9	0
1961-1970	6	7	5	6	5
1971-1980	7	5	7	6	5
1981-1990	31	35	30	**41**	27
1991-2000	48	45	52	**35**	**62**

Table 29: Percentage of centres in each size category

Size of centre	% all centres	% HP academic	% HP prestige	% HP industrial	% HP networking
25 or less	26	33	33	**48**	18
26-50	28	29	35	21	30
51-100	15	15	15	9	16
101-200	17	14	8	12	19
>200	15	10	9	9	18

An analysis in terms of organisational form (not shown here) demonstrated that high performance centres were *not* likely to differ from the aggregate of all the centres.

4.4.2 Efficiency of centres

Data Envelopment Analysis (DEA) was carried out to identify any relationship between financial and human inputs and various outputs according to the four main missions of biotech centres, as shown in Table 30. (Details of the DEA methodology are contained in Section A11 of Appendix II). It was only possible to include those centres that provided input data in the questionnaire. Since DEA analysis compares the efficiency of all the centres against each other, centres with zero or very low input would distort the results, since they would appear to be the most efficient units. Some centres provided input data that appeared to be incorrect because the number of staff or size of budgets were extremely low. We therefore set a threshold: only those were included where the quotient between budget and staff was at least 10,000 Euros. In addition, only those centres with at least one output were included, as centres with no output would by definition be inefficient. As a result of these exclusions, 58 centres (25.6% of the centres) were excluded from the DEA analysis. The analysis was carried out by mission. The percentage of centres included in the analysis of efficiency in achieving each mission[22] is shown in Table 30.

Table 30: Number (%) of centres included in DEA analyses

Mission	Number of centres with mission	Number of centres included in DEA	% of centres with mission
Research excellence	175	101	58
Research training	188	127	68
Fostering commercialisation	108	82	76
Knowledge production	184	135	73

The majority of the remaining centres were included in more than one of the DEA analyses, as follows:

38 centres were included in all DEA categories
57 centres included in 3 DEA analysis
50 centres included in 2 DEA analysis
23 centres included in 1 DEA analysis

[22] Only those centres were considered which said they had the relevant mission.

The overall results of the analyses showed that no centre was highly efficient in all four missions, but 47 centres were highly efficient in at least one mission (21%) (see Table 31). In addition, ten centres (4%) were highly efficient in all the missions they undertook, including:

1 centre in 3 missions
4 centres in 2 missions
5 centres in 1 mission

The mission in which the highest proportion of centres achieved efficiency was to be a national centre of excellence – 23% of those included in the analysis. Only 10% are efficient at building up the knowledge base and 7% in both research training and fostering commercialisation. Although US centres accounted for only 14% of overall centres in the study, they account for 38% of centres achieving efficiency in knowledge production and 40% of those efficient at fostering commercialisation.

As shown by Table 32, 153 centres were inefficient in at least one mission (68%) and 19 centres were inefficient at all 4 missions.

Table 31: Highly efficient centres

Number of missions	Number efficient centres	Share (%)
1	36	16
2	9	4
3	2	1
4	0	0
Total	47	21

Table 32: Inefficient centres

Number of missions	Number inefficient centres	Share (%)
1	40	18
2	42	19
3	52	23
4	19	8
Total	153	68

We conducted regression analyses to identify any relationships between efficiency and certain centre characteristics for each of the missions. The results of the analyses for **research excellence** is shown in Table 33. Efficiency is significantly influenced by research focus. Single focus centres are more efficient than multi-focus centres (relationship significant at the 5% level). In addition the share of long-term research staff in total staff has a significant but weak influence on the efficiency of centres; the higher the proportion of long term staff, the higher the efficiency (relationship significant at the 10% level). No relationship was found between efficiency and the proportion of core funds in the budget or the age of the centre.

Table 33: Relationship between efficiency in research excellence and centre characteristics

Characteristic (variable)	B	T	Significance
Core funding	0,694	0,718	0,475
Research staff	1,615	1,807	0,074
Research focus	-1,202	-2,225	0,028
Age	2,463E-03	0,184	0,855

The results of the analysis of **research training** efficiency, is shown in Table 34. Again, research focus influences efficiency significantly, but this time weakly. Single focus centres are more efficient than multi-focus centres (relationship significant at the 10% level). We found no relationship between the efficiency of a centre and the other characteristics considered – the proportion of core funds in the budget, the proportion of long term staff in total staff or the age of the centre.

Table 34: Relationship between efficiency in research training and centre characteristics

Characteristic (variable)	B	T	Significance
Core funding	-0,594	-0,458	0,648
Research staff	-1,378	-1,207	0,23
Research focus	-1,28	-1,803	0,074
Age	1,315E-02	0,65	0,517

The results of the analysis of efficiency in **fostering commercialisation** are shown in Table 35. No relationship between the efficiency of a centre and any of the characteristics taken into consideration was found: the proportion of core funds in the budget; the proportion of long term staff in total staff; research focus; the age of the centre or the existence of a technology transfer office.

Table 35: Relationship between efficiency in fostering commercialisation and centre characteristics

Characteristic (variable)	B	T	Significance
Core funding	1,173	0,424	0,673
Research staff	-0,528	-0,207	0,837
Research focus	0,155	0,099	0,921
Age	-2,224E-02	-0,596	0,553
Technology transfer office	2,335	1,483	0,142

The results of the analysis of efficiency in **knowledge production** are shown in Table 36. As was found for research excellence and research training, research focus also influences efficiency significantly. Here again the significance was weak. Single focus centres are more efficient than multi-focus centres (relationship significant at the 10% level). There is again no relationship between the efficiency of a centre and the proportion of core funds in the total budget, the proportion of long term staff in total staff or the age of the centre.

Table 36: Relationship between efficiency in knowledge production and centre characteristics

Characteristic (variable)	B	T	Significance
Core funding	-19,952	-1,149	0,253
Research staff	-25,09	-1,503	0,135
Research focus	-16,841	-1,706	0,091
Age	0,297	1,197	0,233

We finally conducted analyses to identify any relationship between efficiency in the four missions. The results, shown in Table 37, found a significant relationship between research excellence and the three other missions. In particular the relationship between efficiency in research excellence and research training is highly significant at the 1% level. In addition there is a significant but weak relationship between research excellence and fostering commercialisation (relationship significant at the 10% level).

Table 37: Relationship between efficiency in research excellence and efficiency in other missions

Mission (variable)	B	T	Significance
Research training	0,302	3,673	0,001
Fostering commercialisation	9,715E-0,2	1,957	0,056
Knowledge production	9,257E-03	1,658	0,104

4.5 Interesting issues revealed by questionnaire responses

Some of the respondents to the questionnaire took the opportunity to provide fuller information than required. They focused on two topics: virtual centres and dynamism in the field. Although we do not know how far the views expressed can be generalised, they are presented here because they may indicate developments which should be monitored in future benchmarking exercises. In addition, questions raised by some respondents indicate that there are different interpretations about the character of biotechnology as a discipline.

4.5.1 Virtual centres

Some centres had difficulties in completing the questionnaire. In explaining their difficulties, these centres revealed the existence of "virtual centres" and those involving many different types of institution.

For instance one UK centre described itself as a virtual centre. It said that its research projects are subcontracted to other organisations and that "future projects are expected to be pan-European and multidisciplinary". Its 'virtuality' excluded it from filling in the questionnaire. "Because of our structure and flexibility, in terms of ever-changing research groups, we cannot easily be pigeonholed into the questionnaire". Another 'virtual' centre in The Netherlands had problems fitting itself into the questionnaire. It submitted the questionnaire but was excluded because less than 50% of its research focused on biotechnology.

The complexities which arise for centres composed of several different institutions are especially apparent in France. One respondent wrote "It is quite difficult for me to answer those questions related to the research activities: indeed our centre is in fact a dual one. On

the one hand it is a university faculty for training students in various aspects of biotechnology. On the other hand the building also harbours four main laboratories...” (from different research organisations) “...involved in both fundamental and applied research in different fields of molecular and cellular biology”. This centre has the added dimension of being a multinational partnership between four universities in France, Germany and Switzerland.

Directing questionnaires towards those who head the individual laboratories did not necessarily simplify the situation. For instance one respondent wrote “I am rather unsure whether I am supposed to respond in my capacity as Director of a Research Unit, or whether you want this to be filled out by the Dean of the Faculty, or the Director of our Institute …”. There are obviously several levels of governance within this organisation. This particular respondent went on to say “we do not have *per se* a biotech research centre within the faculty...”. The faculty is made up of 8 units from three different research organisations. It is further complicated because “together with 3 other (life sciences) units located in the adjacent institution, the research units within the faculty form a larger research structure”. This centre completed the questionnaire but was excluded because less than 50% of its research focused on biotechnology.

4.5.2 Dynamism in the field

We were informed of some centres that were very recently formed or do not yet exist. We were probably only notified of a small proportion of these, indicating that there is dynamism in the field. For example, a post-genomic programme established in April 2000 could not be included in the survey. The respondent was keen to emphasise that “it is going to be one of two major [national] centres for post-genomic research during the years to come. We expect some 200 research groups in the fields of Medicine, Science, and Technology to work, wholly or partly, with [its] projects”. She also added that many institutions would be involved, since three different universities were involved.

Another soon to be established centre was due to become operational at the end of January 2001. We were informed that this will be one of the largest biomedical and biotechnological research centres in Europe, with some 1000 researchers working in the field of biomedical sciences.

4.5.3 Perceptions about the disciplinary character of biotechnology

Centres have differing perceptions about the character of biotechnology as a discipline. Some questionnaire respondents associated ‘biotechnology’ with industrial and applied projects. As their work was more concerned with basic research they sometimes had to be convinced that biotechnology, as we understand it, does have a basic research component, and they had to be encouraged to fill in the questionnaire. For instance, one respondent argued that

> There is a problem with my filling your electronic form, depending on the precise meaning of biotechnology. We do not have a specific mission related to biotechnology since we are a pure research institute. Yet, we do some of the best biotech work in the world because we are at the cutting edge of research in an area that is central to biotechnology!

This centre was persuaded to complete the questionnaire and is included in the final list of centres. Another centre also did not believe that basic science could be equated with biotechnology and did not know whether to fill in the questionnaire because: ‘Our research

institute performs basic science and biotechnology research (about 50%:50%)'. This centre also completed the questionnaire and is included in the final list of centres. Similarly, another respondent said 'we are more oriented towards basic research than biotechnology *per se* so I may have problems filling out the questionnaire'. This centre completed the questionnaire but was excluded because it indicated that it did not have a specific mission dedicated to biotechnology.

5 Main results

5.1 Benchmarking results

The results of the benchmarking exercise must be treated with caution, since there was a low response rate from US centres and these may represent one strata only of US centres: "second movers and emerging actors". However, there is a possibility that "major players", that were not among the respondents to the questionnaires, do not meet our criteria for biotechnology centre. In other words, they may allocate less than 50% of their budgets to biotechnology, receive less than 50% of their funding from public sources, or not have a mission related to biotechnology. Indeed, there were several "major players" among the US institutions that completed the questionnaire but were excluded from the analysis because they did not meet these "centre" criteria. The fact that biotechnology first emerged in the US may have led to its rapid diffusion throughout the existing departments of major research universities and medical schools. US states lacking competence in biotechnology may have been similar to European countries in establishing discrete biotech research centres to catch up once the economic significance of biotechnology was realised ("second movers"). The high response rate from the EU centres indicates that this is a representative sample of EU biotech centres. This summary of the main results provides comparisons between the EU and US centres to show the type of benchmarking that the methodology can produce. Ambiguity about the representativeness of the US biotech research centres that responded, however, means it is uncertain whether these results may be considered a valid benchmark.

The majority of centres in both the EU and US have multiple missions; there is very little difference in the number of centres having the mission to provide education and training, build up the knowledge base or create a national centre of research excellence. Only approximately half of the European centres have a mission to foster commercialisation, compared with almost three-quarters of US centres. Centres not only have multiple missions, the majority are involved in several areas of biotechnology research. US centres allocate a very high percentage of their expenditure to basic research (50%). Taken together with the strong orientation of US centres to fostering commercialisation, this emphasises the fact that it is important to do basic research to be relevant to industry. EU centres spend over 30% of their budgets on human biotechnology, but basic research (17%), cell factory (15%), plant (12%) and animal (10%) biotechnology also receive a significant share. Although most centres are involved in several areas of research, 57% can be regarded as "single-focus" because a significant proportion of their budget is dedicated to one area. The remaining centres allocate their budgets more or less equally to several areas and can be regarded as "multi-focus".

More than three-quarters of EU centres and all the US centres were established during the last two decades. The remaining EU centres are even older, and seem to have shifted their research focus to biotechnology over time. Continuous growth characterises the development of 70% of all centres. The majority of centres are affiliated to universities. EU centres are also affiliated to a range of other types of organisation, and sometimes to several different

organisations. The majority of centres are unitary centres based on a single institution (65%). However there are also a significant number of cooperative or "virtual" centres. Some are based on different institutions in the same town and others on different institutions not in the same town. The latter occurs only in the EU.

On average, EU centres are significantly larger than US centres. The average budgets of US centres are much lower than those for EU centres and this probably reflects the smaller size of the US centres. There is no significant difference in the average number of staff in single- and multi-focus centres. Among the single-focus centres, however, those specialising in human biotechnology have the highest number of staff and highest budget per member of staff, and are followed closely by centres specialising in animal biotechnology. Basic research and plant biotechnology have the lowest budget per member of research staff. The most significant source of funds is core government funding.

Centres increased employment of all categories of staff between 1998 and 1999. There was a most dramatic increase in the employment of technicians. The highest proportion of technicians to total staff is in centres specialising in animal and human biotechnology. US centres employ a much higher proportion of long-term and fewer short-term researchers than EU centres.

In terms of academic activities, we found that 48% of the centres are not permitted to award PhDs, but these centres have similar numbers of doctoral students to those permitted to award PhDs. Doctoral students per centre and per member of research staff are similar in the EU and US, but EU centres have double the productivity of US centres in PhDs awarded for both these measures. EU centres account for almost 7% of all EU biotech publications in the period 1994-1997, and US centres for 0.3% of all US publications. The publications of EU centres received an average of 10.7 citations per publication and US centres 18.2 citations per publication. This is an indication that the impact of the scientific activities of US centres is higher than that of EU centres. Key personnel were identified in 45% of EU centres, but only 22% of US centres. The average number of key personnel per centre is also considerably lower in the US than in the EU. In terms of "prestige" activities, we also found that EU centres have more members of editorial and scientific committees. EU centres also send far more researchers to transatlantic conferences than those in the US. In terms of industrial activities, a higher percentage of EU than US centres have industrial research collaborations, and a higher average number of collaborations per centre. However, US centres have a higher launch rate for spin-off firms than EU centres.

The next step was to find out whether various characteristics of centres affected their performance. The overall activities of centres were assessed in terms of academic, prestige, industry and networking performance. Seventy-two per cent of centres achieved a high performance in at least one of these areas, but only 2% scored highly in all 4 areas. Age has a relationship with high performance industrial centres, which are likely to be 12-20 years old and with high performance networking centres, which were formed between 1991 and 2000. High performance academic, prestige and industrial centres are likely to have 25 or less staff, and this characteristic is most pronounced for the industrial centres. In contrast, high performance networking centres are less likely to be in this small size category. High performance academic centres are more likely to specialise in human biotechnology and industrial centres in cell factory; high performance networking centres are also more likely to have a single focus, but not in any specific area. Only 45% of high performing industrial

centres have a technology transfer office, so performance does not appear to be affected significantly by such activities.

The last analysis assessed the relative efficiency of centres in terms of inputs (budgets and research staff) and the outputs relating to four missions which they might undertake: research excellence, research training, fostering commercialisation and knowledge production. One fifth of all centres are efficient and over two-thirds inefficient in one of the missions they undertake. Only ten centres (4%) are highly efficient in all the missions they undertake. Half of the 38 centres with four missions are inefficient at all of them, and no centre is efficient at all four missions. However, an analysis to identify any relationship between efficiency in the four missions found a strong relationship between efficiency in research excellence and research training and a weak relationship between research excellence and fostering commercialisation.

It is also significant to mention that the "second movers and emerging actors" group of US centres represent a high proportion of centres efficient at knowledge production and at fostering commercialisation. These results are similar to David and Diamond (1997) which found that there was more mobility in the US research university system than had previously been recognised. Once their relatively small size was taken into account, some smaller, newer universities ranked higher in quality ratings.

The characteristic most closely related to efficiency is having a single research focus. This is strongly related to efficiency in research excellence. The relationship also exists for efficiency in research training and knowledge production, but is weaker. The share of long-term research staff in total staff also has a significant but weak influence on centres efficient at achieving research excellence. None of the characteristics considered (proportion of core funds in budget, proportion of long-term staff in total staff, research focus, age or the existence of a technology transfer office) were found to have a relationship with industrial excellence. This may be due to the fact that efficiency is mainly influenced by intangible characteristics such as management.

The lack of patent data for centres and the difficulty of collecting bibliometric data for "virtual" centres may affect the results concerning the calculation of the academic index and the industrial index as well as the results of the efficiency analysis connected with missions for fostering commercialisation and research excellence, if it is assumed that these are important outputs for centres. Alternatively the lack of this data may reflect the low significance for centres of patenting and publishing, in which case the analyses are valid.

5.2 Methodological results

The methodology used to prepare an international benchmark of European research centres proved largely effective. Dealing with the problems encountered in collecting and analysing data proved very instructive about the phenomenon we have investigated. For instance, we discovered the limitations of using bibliometric or patent databases together with standard search tools to collect data on entities known as "centres". We were unable to gather patent data, because centres are not always the organisations which apply for patents.[23] Future benchmarking exercises of this type should include questions about patents in the

[23] For example, all patents of individual Max-Planck Institutes or Fraunhofer Institutes in Germany are applied for by the headquarters of those institutions or their representatives, and a breakdown to the "centre" level is not possible.

questionnaire, or may need further refinements of search methodologies. These could draw for example on recent methodological developments within EC activities to map European "Centres of Excellence" in the Life Sciences and Nanotechnology. An approach is being developed, for example, that is based on the experiences of the present benchmarking exercise. In order to assign more precise address information to the patent data, this approach attempts to link information gathered from patent applications – applicant and inventor data – to bibliometric information. The initial results of the ongoing, experimental pilot studies point to the fact that scientific institutions can be assigned for about 30% of the patent applications, eg, universities and individual Max-Planck and Fraunhofer Institutes.

Extracting bibliometric data for centres was labour and time-intensive, and fails to capture overall publication performance for centres that are not unitary organisations. In addition, complications were caused when there was no clear separation between researchers' affiliations to several institutional units, and the widespread practice of using the name of the organisation to which centres are affiliated in publication activities. Further problems were encountered for research centres that were either "virtual" or some kind of meta-structure at the university level, ie, a conglomerate of separate units or people from several university departments or institutes. It may be that centres are unlikely to be mentioned on every occasion when people from those units contribute to scientific publications. Thus, the output of the centre might be underestimated to some degree. However, the omission of reference to a centre may also be intentional; when researchers have multiple affiliations to different organisational units, the centre may not always be involved in those activities. Assigning all the publications of every unit connected to such a centre does not seem to be an appropriate solution as this would only introduce the other extreme – overestimation of a centre's performance.

If centres based on loose coalitions of researchers (virtual centres) continue to grow, as seems likely, bibliometric analysis may underestimate a centre's publication activities. When a centre's name is not coupled to that of an author a publication cannot be attributed to a centre even if the researcher is affiliated to it. However this may also be an indication that the centre as such is not yet fully established and acknowledged as an organisational research unit in its own right, and therefore has not reached maturity.[24]

Attempts to assess how far the centres are representative of national biotech research as a whole were very complicated. We had a very good response rate to our questionnaire from European centres (57%), yet the bibliometric results (which may under-represent the output of some the centres) suggest that the centres' contribution is not as important as one might expect. The European centres which responded to the questionnaire and met our criteria account for only approximately 7% of total European biotechnology publications. This suggests that traditional means of supporting biotechnology research (through university departments, research institutes and medical schools, which are not organised as centres) still predominate. We hypothesise that as performance analysis and evaluation become increasingly important for universities, publications will be assigned to those units that are the unit of analysis in evaluation exercises. In addition, low centre publication performance could be an indication that the significance of the centre concept is overvalued. "Normal" university departments are still important contributors to knowledge production in this field.

[24] However, centres should not be asked to supply information on publications as this can lead to over-inflated numbers, double counting, and being given details of all publications rather than refereed journal articles only.

The response to the questionnaire by European centres was excellent, but could be improved by changes to some questions (see Appendix II, Section A4). The poor response to the US questionnaire also reflects lack of vested interest by US centres in a study commissioned by an EU organisation. A better response to a questionnaire by US centres could be encouraged if such a study were to be jointly funded by EU and US funding agencies.

At first, the character of the US biotech centres did not seem to be typical of widespread assumptions about them, and we thought this might be due to the low response rate. However, the validity of questionnaire responses was confirmed by the fact that these characteristics are exactly what might be expected from the category of "second movers and emerging actors" (see Section 3.1 above) that responded to the questionnaire and met our criteria for inclusion in the study. A discussion of these characteristics follows.

The US centres were established more recently than those in Europe. Younger US centres do not receive significant funds from Federal sources (National Science Foundation or National Institutes of Health) but rely on funds from state or local governments, who give funds predominantly to foster commercial development. This could explain why the results show that US centres emphasise the commercialisation mission more than EU centres, particularly the creation of spin-off firms. The relative lack of research alliances may be related to the low academic visibility of these centres (low publications, key personnel or "prestige" activities). Industry usually seeks to collaborate with high performing academics, as shown by the (weak) correlation between efficiency at research excellence and fostering commercialisation. Secondly, centres funded to engage in specific activities require larger permanent staff to organise their activities. This could explain why we had a relatively good response from these centres. The leading centres in the US now receive so many questionnaires that most are ignored. There are other consequences for centres dependent on state or local funds. They are more liable to be affected by political circumstances and this may explain why a higher proportion of US than EU centres have experienced decline or fluctuating growth patterns.

Other results can also be explained by the relative youth of US centres. Their budgets include a higher proportion of core funds than their EU counterpart (see Figure 11), and they have fewer employees with a higher proportion of long-term research staff. We anticipate that core funding will decrease with age. As centres become more successful at winning research contracts from Federal agencies, they will employ a higher proportion of contract research staff and the number of employees will grow. Finally, the youth of US centre may explain why they have half the productivity of EU centres in terms of the average number of PhDs awarded per centre, despite having similar numbers of students and a similar student/staff ratio.

5.3 Implications for future benchmarking exercises

Although we believe that the methodology employed for this international benchmarking exercise was valid, there are grave doubts about its future usefulness. The first of these doubts relates to the low response by centres in the US, which have no vested interest in participating in an exercise sponsored by the EC. The response by US centres could be improved in any future transatlantic benchmarking exercises by working in cooperation with US funding agencies, such as the National Science Foundation or National Institutes of Health. It may also be appropriate to gather data by conducting in depth interviews with a stratified sample of centres, rather than relying on questionnaire responses.

Secondly, we do not believe that centres form an appropriate unit of analysis for benchmarking exercises. Our preliminary investigations to select centres and the response to the questionnaires showed that the term "centre" is used for a wide variety of different organisational forms that vary both within and between countries. Some centres are authentic and employ a high proportion of permanent staff. Others have few permanent staff, and can be regarded more as "virtual centres": they act as umbrellas, sheltering loose coalitions of researchers whose main affiliation is elsewhere. Some virtual centres bring together researchers who belong to various departments within a university and others consist of researchers from a wide range of different organisations. Yet other centres, for instance in France, Sweden and the USA, serve mainly to provide resources such as research equipment. Thus the benchmarking exercise attempted to compare disparate entities, which are not statistically comparable.[25] The research group could be a more appropriate unit of analysis. The difficulty with this approach lies in identifying active groups in the fields. As noted by Laredo (1999) in connection with identifying human genetics research groups:

> Bibliometric approaches proved feasible but were time consuming (taking much longer than had been anticipated). It was not possible to make use of existing scientometric software to harmonise and match addresses. …The second problem faced was to identify the present denominations and heads of labs: this is time consuming, but the generalisation of websites should greatly facilitate this task (p. vii).

This comment highlights the generally difficulty to be faced when identifying the research entities to be benchmarked. It should be remembered that this particular study was greatly facilitated by the existence of a definition for the research field under investigation, and preliminary work about public biotechnology R&D programmes in Europe (Enzing *et al*, 1999). Lack of such definition and/or knowledge about the active entities could pose great problems for benchmarking in other areas of science and technology.

6 Policy implications

To meet the aims of the EC for this study – to contribute to new science and technology indicators, improve existing indicators and understand more about the performance of European biotechnology, this section discusses both the policy implications of the study for improving the future collection of science and technology indicators as well as those relevant to European research performance in biotechnology.

6.1 Policy implications for science and technology indicators

Carrying out the international benchmark was most useful in identifying the need to use appropriate science and technology indicators for specific units of analysis. Before undertaking this pioneering study it was assumed that there would be no problem in gathering the most commonly used science and technology indicators – bibliometric and patent data – for biotech research centres. This was not the case, pointing to the need to prepare an overview of indicators relevant to various levels of analysis that draws on existing studies of benchmarking or other comparative analyses. Such an overview would indicate, for instance those indicators best gathered at the national level, those appropriate to entire institutions (university or research institute) and those for lower levels, such as university departments or research groups. In this connection, the questionnaire used in this study was shown to be

[25] The fact that the DEA analysis did not compare like with like could explain the limited success in identifying relationships between efficiency and various characteristics of centres.

appropriate for collecting a range of input and output indicators at such lower levels and its use could be extended in this way, subject to minor modifications outlined in Appendix II, Section A4.

More thought is required about how to capture a better picture of centres' commercialisation activities, especially their patenting behaviour. A contribution to knowledge in this area could be provided by a detailed, interview-based study of the barriers and stimuli for centres to patent.

It does not appear appropriate, however, to extend the work on biotech research centres, because they were found to be an inappropriate unit of analysis. The great variations between the organisation and activities of centres both within and between countries means that such an exercise fails to compare like with like. One question for future benchmarking activities is to define the level that is intended to be benchmarked: is it the activities within a certain scientific field like biotechnology or is it a specific type of organisation, eg, research centre? In the first case the identification of the major players within the system of innovation should be the starting point. As we pointed out already: research centres do not appear to be the major players in biotechnology. Other organisations seem to contribute more intensively to knowledge generation in this area.

6.2 Policy implication for European biotechnology

The main results to emerge from the benchmark of biotech research centres is that centres which concentrate most of their activities in a single research area are more efficient than centres that spread their research activities over many areas. Secondly, small research centres produce the highest performance. Small centres which mainly focus on a single area of research can achieve success in a short period of time. In addition, the fact that US latecomer centres at non-prestigious institutions are achieving high performance and efficiency gives hope to peripheral regions. Policy-makers may wish to rethink their policies for concentration of research resources, as this may not necessarily lead to either high performance or efficiency.

The findings also suggest that there is no "best practice" to achieve either high performance or efficiency, and research centres should not all be forced into one mould. As shown by this study, there has been an evolution over the last two decades of a great variety of centres in the EU in terms of their size, organisation, thematic focus, mission or human resources, etc. Since most of these centres developed positively (as indicated by their continuous growth), it is possible to speculate that this variety may be a more appropriate response to the needs of EU biotech than a standardised form of "centre", and variety could be an important asset of biotech in the EU.

The results also emphasise the urgent need to undertake more research on technicians and their training. The study gave evidence of a strong demand for technicians in both the EU and US, but we have little knowledge of the specific skills these technicians need to deploy. US organisations recruit graduates, some with Masters degrees, as technicians. We do not know what qualifications employers require for technician recruits in Europe, or the extent of any differences between countries in this respect. Secondly, we do not know how the jobs of technicians are changing as the consequence of the rapid expansion of knowledge and the mechanisation of some research tasks. Do they require more theoretical or practical knowledge, and of what types? It is important that this issue is addressed because failing to train technicians with appropriate skills to meet demand will have a negative impact on all

organisations involved in biotechnology research – public sector research and companies alike – and not just biotech centres.

The data also shows that in order to perform well in industry related activities, high performance is required in the other activities performed by a research centre. Thus, supporting academic activities leading to research excellence and prestige will increase centres' attractiveness to industrial enterprises and increase the probability of improving their level of industrial performance. It was also found that focussing on basic research topics is highly relevant for setting up relationships with industry. Thus policy support for basic research can be regarded as an indirect measure to foster commercialisation. Finally, it is important to recognise that there are many different ways for centres to engage in industry relevant activities, as shown by a comparison of EU and US centres.

The finding that the proportion of long term staff relates to the efficiency of centres in achieving research excellence provides a framework for increasing efficiency by focussing more on long term staff rather than on short term, project based contract researchers.

Finally, the bibliometric results, even though they fail to capture total publications outputs from some centres, in particular "virtual centres", suggest that biotech centres account for only a small proportion of the universe of public sector biotechnology research. It may not, therefore, be appropriate to concentrate research funding on biotech centres.

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Appendix I: Biotechnology Research Centres: Key Figures

A study commissioned by the European Commission collected input and output indicators to benchmark and compare the performance of biotech research centres in Europe (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, Switzerland and the United Kingdom) with the United States. The study focused on biotechnology research centres that met criteria related to "intent and content":

- at least 50% of the centre's budget is allocated to research in fields in the taxonomy of biotech areas (see Table A1-1 below);
- at least 50% of funding comes from public sources;
- the centre has a specific mission related to biotechnology.

This report provides the key figures for the biotech research centres which resulted from the study. Data is based on responses to a questionnaire and on bibliometric searches.

Table A1-1: Taxonomy of biotech research areas

B.1	**Plant biotechnology (crops, trees, shrubs, etc), including**
1.1	reproduction and propagation
1.2	genetic modification introducing new/excluding existing genes (mono- and polygenic traits)
1.3	growing conditions
1.4	plant protection
1.5	plant pathogen diagnosis
1.6	genome mapping
1.7	biodiversity of plants in agriculture/horticulture
B.2	**Animal biotechnology, including**
2.1	reproduction
2.2	production
2.3	breeding, incl. genetic engineering in animals (creation of transgenics)
2.4	animal health care,
2.5	genome mapping
2.6	biodiversity of farm animals
B.3	**Environmental biotechnology, including**
3.1	microbial ecology
3.2	biosafety
3.3	microbial functions for degradation/transformation of pollutants
3.4	isolation, breeding and genetic engineering of pollutants; degradation micro-organisms
3.5	biotechnological processes for soil and land treatment
3.6	biotechnological processes for water treatment
3.7	biotechnological processes for air and off-gas treatment
B.4	**Industrial biotechnology: food/feed, paper, textile, and pharmaceutical and chemical production**
4.1	enzymatic processes
4.2	development of bioprocessing techniques (fermentation, immobilisation of biocatalysts, quality control, etc)
4.3	downstream processing
B.5	**Industrial biotechnology: Cell factory, including all biotechnology research focused on the cell as producer of all sorts of (food and non-food) products**
5.1	plant cell biotechnology: plant cell biology
5.2	animal cell biotechnology: animal cell biology
5.3	bacteria as cell factories: microbiology
5.4	genetic engineering and production of enzymes
5.5	genetic engineering of micro-organisms and yeast
5.6	cell culture techniques
5.7	genome mapping of specific bacterial and yeast genomes
5.8	biodiversity of micro-organisms in production processes

B.6	Developments of human/veterinary diagnostic, therapeutic systems
6.1	immunology, therapeutic and diagnostic antibodies
6.2	vaccinology
6.3	human genome mapping
6.4	human gene transfer techniques
6.5	therapeutic proteins and oligonucleotides (substitutes for pharmaceuticals)
6.6	tissue engineering
6.7	genomics in drug discovery (substitutes for pharmaceuticals)
6.8	DNA diagnostics
6.9	forensics (genetic fingerprinting)
B.7	**Development of basic biotechnology**
7.1	techniques to determine the structure of biomolecules and study the structure-function relationship
7.2	techniques to build biomolecules (nanotechnologies)
7.3	interaction of biomolecules with micro-electronic devices, incl. biosensors, biomonitoring
7.4	genome analysing techniques
7.5	bio-data-informatics (set of tools, which is applied to solve data handling and processing problems in biological research, eg, genome sequencing)
7.6	bio-informatics (application of biological principles to information processing for technical applications)

A broad range of centres was selected as recipients of the questionnaire, but it was anticipated that some would be eliminated because they failed to meet the criteria developed for the study. Table A1-2 shows the number of centres identified for each country, the percentage responding to the questionnaire and the percentage remaining after removing centres which failed to meet the criteria defining biotech research centres.[26]

Table A1-2: Biotech research centres identified and percentage involved in the study, by country

Country	Number of centres identified	Questionnaire response	Number of centres meeting criteria (%)	
Finland	14	71%	9	(64%)
Ireland	5	60%	3	(60%)
Greece	7	57%	4	(57%)
Denmark	23	61%	13	(57%)
Portugal	20	70%	11	(55%)
Belgium	27	67%	15	(52%)
UK	51	67%	24	(47%)
Netherlands	27	63%	12	(44%)
Sweden	30	63%	12	(40%)
Spain	38	47%	14	(37%)
Austria	11	55%	4	(36%)
Switzerland	21	48%	7	(33%)
Germany	139	51%	44	(32%)
France	53	47%	16	(30%)
Italy	38	24%	6	(15%)
Total EU	*504*	*57%*	*194*	*(39%)*
USA	210	25%	32	(15%)
Total	714	45%	226	(32%)

The low response rate from US centres did not represent "first mover and major players". The results must therefore be treated with great caution.

[26] Specific results may be based on less than 226 centres, because some centres failed to fully complete the questionnaire.

The questionnaire asked whether the centres had a mission related to biotechnology. We distinguished four different missions:

- to provide education and training,
- to build up the knowledge base in biotechnology,
- to be a national centre of research excellence, and
- to foster commercialisation and economic development in industry.

Most of the biotech research centres have multiple missions. As shown in Table A1-3, the greatest number of centres have missions to provide education and training or build up the knowledge base. The fostering of commercialisation is much less important in Europe than in the US.

Table A1-3: Biotech research centre missions

Mission	Centres EU	Centres US	% Total EU	% Total US
Education and Training	161	27	83.0	84.4
Knowledge Base	156	28	80.4	87.5
Research Excellence	152	23	78.4	71.9
Foster Commercialisation	85	23	43.8	71.9
Total centres	194	32	100.0	100.0

The aggregate budgets of centres that told us how they distributed funds between research areas amounted to €1148 million in Europe and €93 million in the US in the year 1998/99. It was allocated to research areas in the taxonomy as shown in Table A1-4. US centres allocate a much higher proportion of funds to basic research than those in Europe. This does not contradict the finding that US centres have a stronger orientation to fostering commercialisation than EU centres. It highlights the fact that it is important to do basic research in order to be relevant to industry.

Table A1-4: Centres' funding of research areas 1998/99 (€ millions)

	Amount		%	
Research Area	EU	US	EU	US
Human	344	25	30.0	26.4
Basic	191	41	16.6	44.4
Cell factory	169	4	14.7	4.2
Plant	140	3	12.2	3.5
Animal	118	3	10.2	3.5
Other*	81	11	7.1	12.1
Environmental	59	2	5.2	2.6
Industrial	45	3	3.9	3.3
Total	1148	93	100.0	100.0

***** biotechnology area not included in taxonomy

Most centres specialise in more than one research area; only 24 focus on a single area only. However 57% of the centres dedicate a significant proportion of their effort to a single area. The remaining 43% of centres focus on several areas of research, and can best be described

as multi-focus. More European centres are single focus (59%) and more US centres are multi focus (59%).

As shown in Table A1-5, European biotech research centres were mainly established in the last two decades, but approximately 23% pre-date this time. These centres seem to be based on pre-existing research groups which evolved to focus on biotechnology. In comparison, all US centres were founded relatively recently. Table A1-6 shows the size of centres in terms of number of personnel. No correlation was found between the age and size of centres.

Table A1-5: Year of foundation of biotech research centres

Year of Foundation	Total	US	EU
1895-1950	12	0	12
1951-1960	4	0	4
1961-1970	12	0	12
1971-1980	16	0	16
1981-1990	67	18	49
1991-2000	103	9	94
Total	214	27	187

Table A1-6 shows the average number of staff in EU and US centres. On average EU centres are significantly larger than US centres.

Table A1-6: Size of biotech research centres

Size range	% EU centres	% US centres	All
25 or less	25.8	40.0	27.5
26-50	26.3	24.0	26.1
51-100	16.7	16.0	16.6
101-200	15.6	12.0	15.2
>200	15.6	8.0	14.7
Total	100.0	100.0	100.0

As is shown by Table A1-7, the majority of centres have experienced continuous growth in manpower in the period 1994-1999 (or since the centre's creation). US centres seem a bit more vulnerable to decline or fluctuating resources than those in Europe.

Table A1-7: Development of biotech research centres

	Number of centres			% of centres		
	EU	US	All	EU	US	All
Continuous growth	135	23	158	71.4	74.2	71.8
No growth	27	2	29	14.3	6.5	13.2
Up and down	14	4	18	7.4	12.9	8.2
Single increase	9	0	9	4.8	0.0	4.1
Decline	2	2	4	1.1	6.5	1.8
Single decrease	2	0	2	1.1	0.0	0.9
Total	189	31	220	100.0	100.0	100.0

Table A1-8 shows that US centres are more often affiliated with universities than EU centres; the latter are, however, affiliated to a broader range of other types of institution than US centres, and affiliations to government research institutions are relatively more prevalent than in the US. Almost two-thirds of European and over 75% of US centres are based on a single institution. The remaining US and some European centres (25%) are based on different institutions in the same town. Centres based on different institutions not in the same town are found only in Europe.

Table A1-8: Affiliations of biotech research centres

Affiliated institution	% total EU	% total US
University	60	81
Government Research	18	3
Private non-profit	6	3
Other	3	0
Foundation, Charity	2	0

European centres had an average of 108.6 staff and US centres 63.2 staff. Table A1-9 shows the distribution of staff of different types in European and US centres. This shows that that in European centres, long-term researchers accounted for 25% of staff and short-term contract researchers for 17%. In contrast, 42% of researchers in US centres were long-term and 10% short-term. The most significant change to staff between 1998 and 1999 was a rapid increase in technicians. In Europe long-term technicians increased by 121% and short term technicians by 151%. The increase was even more dramatic in the US, where long-term technicians increased by 348% and short-term technicians by 227%.

Table A1-9: Percentage of staff by type in centres (1998 and 1999 averaged)

Staff type	% EU centres	% US centres
Long term technicians	26	14
Students	23	29
Short term researchers	16	9
Long term researchers	16	28
Short term technicians	9	5
Long term professors	9	14
Short term professors	1	1

Table A1-10 shows the total, average and median budgets of centres. The difference in size of budgets for European and US centres probably reflects the higher number of staff in the former. The amount of total budget differs from that in Table A1-4 because some centres provided information about their budgets, but not about its allocation to different research areas.

Table A1-10: Total, average and median budgets of centres (1998 and 1999 averaged)

	EU centres (Mio. €)	US centres (Mio. €)
Total centres' budgets	1249.2	118.5
Average budget per centre	8.11	4.39
Median budget	3.03	2.23

Table A1-11 on sources of funding for centres shows that core government funding is the most significant source of funds for both EU and US centres. Higher proportions of core funding for the US than the EU centres suggests that these centres would not exist without core funds. Secondly, higher core funding appears to correlate with a higher proportion of permanent staff.

Table A1-11: Sources of funding for centres

Type of funds	% EU centres	% US centres
Core government funding	44.2	51.3
Public funds national	24.4	19.9
Funds from EU	9.0	-
Funds from foundations	3.4	8.1
Funds from industrial	8.8	8.1
Funds from licensing	0.4	0.2
Other	2.6	5.6

The academic activities of centres were assessed in terms of research training, publications and prestige activities. Table A1-12 shows the average productivity of centres in training students. Although students per centre and students per member of research staff are remarkably similar in the EU and US, EU centres have double the productivity of US centres in both the award of PhDs per centre and in PhDs awarded per member of research staff.

Table A1-12: Centres' training activities (averages for 1999)

	Students per centre	PhDs awarded per centre	Students per research staff	PhDs awarded per research staff
EU	33.97	10.59	0.83	0.36
US	33.33	5.22	0.86	0.17

Details of the publications and citations of centres are presented in Table A1-13. This shows that the US and the EU have a similar share of total scientific publications in biotechnology. Both regions contributed about 42% of all biotech publications. Publications which gave author addresses of centres in this study accounted for 7.1% of European and 0.3% of US

Table A1-13: Centres' biotech publications and citations, by country 1994-99

	No. biotech pubs	% total biotech pubs	Sum centres' pubs	Share national Pubs (%)	Sum centre cites	Sum centre cites (no self-cites)	CPP** (self-cites incl)	CPP (self cites excl)
Total Publications	**824816**	100						
Austria	7589	0.9	513	6.8	6295	5978	12.3	11.7
Belgium	11647	1.4	1003	8.6	13746	13226	13.7	13.2
Denmark	9007	1.1	329	3.7	3645	3456	11.1	10.5
Finland	8402	1.0	957	11.4	12649	12173	13.2	12.7
France	58490	7.1	2421	4.1	33772	32442	13.9	13.4
Germany	71007	8.6	7426	10.5	97426	93349	13.1	12.6
Greece	3365	0.4	264	7.8	2884	2766	10.9	10.5
Ireland	2429	0.3	113	4.7	834	787	7.4	7.0
Italy	34021	4.1	1017	3.0	15498	14951	15.2	14.7
Luxembourg	118	0.0		0.0				
Netherlands	23697	2.9	1775	7.5	20344	19411	11.5	10.9
Portugal	2241	0.3	630	28.1	3762	3489	6.0	5.5
Spain	20677	2.5	2417	11.7	22515	21069	9.3	8.7
Sweden	19415	2.4	154	0.8	928	877	6.0	5.7
Switzerland	18128	2.2	321	1.8	3413	3221	10.6	10.0
UK	76830	9.3	5880	7.7	80849	77367	13.7	13.2
Sum EU (excl. CH)	348935	42.3	24899	7.1	315147	301341	11.2*	10.7*
Sum EU (incl. CH)	**367063**	**44.5**	25220	6.9	318560	304562	11.2*	10.7*
USA	345206	41.9	1072	0.3	19999	19487	18.7	18.2
Sum EU (incl. CH) + USA	**712269**	**86.4**	26292	3.7				

* average value **CPP = citations per publication

Source: SCI, Online via Host STN

publications. The tendency for authors to provide departmental or university addresses, rather than that of a centre, tends to under-represent the publications output of centres.

Citation analysis shows that there are national differences in the impact made by biotechnology centres' publications. A European centre's paper in biotechnology received on average 10.7 citations while for the US the value is 18.2 citations. This is an indication that the impact of the scientific activities of US centres is higher than that of their European counterparts.

The external academic activities undertaken by centre research staff which reflect a centre's prestige are shown in Table A1-14.

Table A1-14: "Prestige" activities for centres

	EU average	US average
Member of editorial committee/research staff	0.13	0.07
Member of scientific committee/research staff	0.25	0.12
EU conferences/research staff	0.68	0.22
US conferences/research staff	0.30	1.30

The commercialisation activities of centres were assessed in terms of industrial research collaborations and the number of spin-off firms established. 78% of European centres had industrial collaborations and an average of 7.91 collaborations per centre.

Table A1-15 shows that a slightly higher proportion of US centres (65%) indicated that they had launched spin-off firms than EU centres (52%). The US centres involved also appear to have a higher launch rate than the EU ones. This may indicate that commercialisation activities in the EU put more emphasis on industrial collaboration and in the US on launching spin-off firms. In regard to commercialisation, it is also interesting to note that 56% of US centres have a technology transfer office compared to 48% of EU centres.

Table A1-15: Proportion of centres launching spin-off firms

Number of Firms	% EU centres	% US centres
1-2	36	34
3-5	12	19
6-10	2	6
11-20	2	3
Over 20	0	3

Further analysis was undertaken to assess the factors affecting the academic, prestige, industry and networking performance of centres. It was found that age has a relationship with high performance industrial centres, which are likely to be 12-20 years old and with high performance networking centres, which were formed between 1991 and 2000. High performance academic, prestige and industrial centres are likely to be small, with 25 or less staff. High performance networking centres are more likely to specialise in a single area and not be multi-focus.

An assessment of the factors affecting the relative efficiency of centres in research excellence, research training and knowledge production found that a single research focus is closely related to efficiency. We could find no factors associated with efficiency in fostering commercialisation. The US centres – "second movers and emerging actors" – represent a high proportion of centres efficient at knowledge production and at fostering commercialisation.

The main results to emerge from the benchmark of biotech research centres is that centres which concentrate most of their activities in a single research area are more efficient than centres that spread their research activities over many areas. Secondly, small research centres produce the highest performance. The findings also suggest that there is no "best practice" to achieve either high performance or efficiency, and research centres should not all be forced into one mould. Small centres which mainly focus on a single area of research can achieve success in a short period of time. In addition, the fact that US latecomer centres at non-prestigious institutions are achieving high performance and efficiency gives hope to peripheral regions.

Appendix II: An International Benchmark of Biotech Research Centres – Detailed Methodological Review

This appendix provides details of the various methodological approaches adopted for the international benchmark, including discussion of the problems encountered. It reviews each of the following steps of the methodology

i. developing criteria for identifying "biotech research centre";
ii. selecting potential candidate centres for the exercise;
iii. determining the characteristics of centres and the input and output indicators for which to gather data;
iv. preparing a questionnaire and mailing it to identified centres;
v. screening the responses to eliminate centres which did not fully meet the criteria for "biotech research centre";
vi. conducting bibliometric and patent searches for centres which did meet the criteria;
vii. designing and entering data about centres on a biotech research centre database;
viii. analysing the database, including an assessment of how far the biotech research centres in the study represent the total public biotech research effort in Europe and the US.

A1. The definition of "biotech research centre"

An initial definition of biotech centre was proposed for the study, based on the following four criteria:

Focus of research	50% of researchers in centre would focus mainly on biotech as outlined in the taxonomy of biotech areas
Financing	50% of funding would come from public[27] sources, excluding centres wholly funded by charities.
Organisation	research centres must be separate accounting units, and have an appointed Director with a salary. 'Single unit' centres would be differentiated from 'co-operative research centres'. The first consists of one research institution while the latter may consist of different institutions or parts thereof. Both categories will be covered if they are situated in one geographic location
Geographic location	A city or town

During the initial process of identifying biotech centres it was discovered that some of the organisational criteria were too restrictive. In particular, the use of criteria for research centres to be separate accounting units, have an appointed Director with a salary and be situated in one geographic location, would have led to the omission of some important centres and limited the number included in the study. These two criteria were abandoned in favour of the following criteria:

Mission	centres had been established deliberately, or evolved, to fulfil a specific mission related to biotechnology.

[27] "Public" funding excludes funds from charities.

A2. Selection of potential centres for the benchmarking exercise

The approach to selecting centres for the benchmarking exercise was to provide a broad range of centres in the preliminary stages of the project. We anticipated that questionnaire responses might lead to the elimination of some of these centres at a later stage. We identified European centres through the European Commission *Inventory of Public Biotechnology R&D Programmes in Europe* (Enzing *et al* 1999), supplemented by the database of all biotechnology groups which had approached the EC's QoL and BIOTECH programmes. National funding agencies and national experts were asked to check the list of centres for each country. In response, several funding agencies sent lists of all university departments in their country that had any connection with biotechnology. Others expressed interest in the project but gave no further information. A few agencies made additions, deletions and corrections to our list. The US sub-contractor identified US biotech research centres by first using information from the US Council of Biotechnology Centres, and then following leads mentioned by people in the initial sample ("snowball" effect) and by tracing web-links from one centre to another. In total, 714 centres were selected (see Table A2-1). The internet was used to gather contact details for each centre (name of Director, address, email information, etc).

A3. Determining the factors for which to gather data

It was agreed that the benchmarking exercise should consider any differences between EU and US biotech centres in terms of their characteristics as well as comparing performance in terms of input and output indicators. The factors for which information and data was gathered include the following:

i. affiliation of centre (eg, belonging to a university, government research organisation, independent, other);
ii. area of specialisation (according to taxonomy of areas of biotechnology);
iii. key personnel (to be assessed by patent and publication activity);
iv. number of researchers (FTEs) both senior and junior; doctoral students; and technicians;
v. total funding (both core funds and project grants) and proportion contributed by the following sources: national or regional government, European grants, industry, university, other;
vi. expenditure (proportion spent on salaries for contract researchers, faculty and students), administration including overheads, equipment and supplies, workshops and travel, etc;
vii. number of publications in internationally peer reviewed journals per annum (1994-1999);
viii. number of European, US and Japanese patents per annum (1994-1999);
ix. number of research projects (average for 1998 and 1999);
x. industrial research collaborations/consultancy;
xi. involvement in external activities reflecting prestige on centre (eg, membership of scientific committees, government "expert", journal editor);
xii. presence of technology transfer office support;
xiii. number of spin-off firms launched since 1990;
xiv. number of PhDs awarded;
xv. number of doctoral students being trained;

Budgetary and expenditure income was collected in national currencies and converted to Euros using Eurostat conversion rates. Data was collected for the two years 1998 and 1999, except where otherwise indicated above. Data for the majority of these indicators were collected by a postal questionnaire (see Annex to this appendix for EU and US versions of the questionnaire). The questionnaire also asked centres to indicate from a selection of graphs which best

described its development between 1994 and 1999 (or since its creation). The questionnaire was supplemented with bibliometric and patent database searches for the 226 centres which responded to the questionnaire and met the criteria for biotech research centre.

A4. Preparing and mailing the questionnaire

A first draft of the questionnaire was designed to collect the required information and data. It was piloted in a small number of centres and was slightly amended to cope with ambiguities which were revealed. The EU version of the questionnaire was amended slightly for the US centres (eg, removing from Question 12 about sources of funding "funds for projects from the EU Framework Programme").

The questionnaire was mailed to the 714 centres identified and two electronic versions of the questionnaire were mounted on a website (one for European and one for US centres). Centres were given the option of completing the paper or electronic versions. Personalised emails were also sent to the Directors of all the centres to encourage them to complete the questionnaire. We followed-up non-responding centres with two reminder emails and telephone calls. A second copy of the questionnaire was mailed to some centres when requested.

Table A2-1 shows the number of biotech centres identified and response rate for each country. It shows that response rates for the EU were excellent (averaging 57%), but less satisfactory for the US (25%). We believe the US response partially reflects lack of vested interest in the results but also "questionnaire fatigue".

Table A2-1: Questionnaire response rate by country

Country	Sent out	Received	% Received
Austria	11	6	55
Belgium	27	18	67
Denmark	23	14	61
Finland	14	10	71
France	53	25	47
Germany	139	71	51
Greece	7	4	57
Ireland	5	3	60
Italy	38	9	24
Netherlands	27	17	63
Portugal	20	14	70
Spain	38	18	47
Sweden	30	19	63
Switzerland	21	10	48
UK	51	34	67
Total EU	*504*	*272*	*57*
USA	210	52	25
Total	714	324	45

The answers to the questionnaires were entered on a database of biotech research centres. The process for deciding which centres should be included in the final biotech centres database was based on questionnaire responses. We excluded the 390 centres that did not respond to the questionnaire. A further 98 centres were excluded because they did not meet the criteria developed to define "biotech research centre". This included the 41 centres that said they did *not* have a specific mission related to biotechnology. None of these centres completed the rest of the questionnaire.

We also excluded those centres that allocated less than 50% of their budget to biotechnology (response to question 2). We double-checked the results with answers to question 5 (where the proportion of the centre's total budget spent on biotechnology was indicated). The two approaches yielded similar results. We included those centres that did not specify the proportion of their budget spent on any area. Of the 37 centres that were excluded according to research focus, 18 of them spent over 50% of their budget in an 'other' area which fell outside the categories in the taxonomy. Comparing these results to the centres' responses to Question 5 demonstrated that the centres were treating this area as a non-biotech area. The rest allocated less than 50% of their funds to all the areas in the taxonomy.

Funding criteria led to the exclusion of a further 20 centres, including those centres receiving less than 50% of their funding from public sources (responses to question 12). 'Public' included the three categories: 'Core funding from government', 'Public funds for individual research projects from national sources' and 'Funds for projects from the EU Framework programme'. We included those centres that did not specify the proportion of funds that came from any source.

Of the centres that were excluded by the funding criteria:

- 6 received 50% or more of their funds from industrial contracts;
- 6 (different ones) received 50% or more funds from foundations and charities;
- 4 (different ones) received funds from 'other' sources including "income from services", "own capital of our company" and "facility rental income";
- 1 had most of its funding from a combination of industrial sources and licenses;
- 3 accounted for less than 100% of their funding.

Table A2-2 shows the number of questionnaires received from each country, and those excluded because they failed to meet specific identification criteria. It shows that 98 responding centres did not meet the criteria developed to define "biotech research centre". The results of the study are therefore based on 226 centres in total (194 in the EU and 32 in the US).

The postal questionnaire was generally preferred by the centres that responded, although 39% of the total responses were made via the electronic questionnaire. Questionnaires were quite well completed as illustrated in the Table A2-3 below.[28] This table includes responses to individual questions by centres which were subsequently excluded because they failed to meet the criteria for biotech centre. This table shows that questions about the current year were better completed than those for the previous year.

[28] Yes/No questions have been excluded because a default 'No' appeared in the database when there was no response.

Table A2-2: Breakdown of steps involved in excluding centres, by country

		Reasons for excluding centres			*Result of exclusions*		
Country	***Received***	***Mission***	***Focus***	***Funding***	**Total excl.**	**% excluded**	**Remaining**
Austria	6	2	0	0	2	33	4
Belgium	18	0	3	0	3	17	15
Denmark	14	1	0	0	1	7	13
Finland	10	1	0	0	1	10	9
France	25	4	3	2	9	36	16
Germany	71	11	12	4	27	38	44
Greece	4	0	0	0	0	0	4
Ireland	3	0	0	0	0	0	3
Italy	9	3	0	0	3	33	6
Netherlands	17	1	2	2	5	29	12
Portugal	14	0	1	2	3	21	11
Spain	18	2	2	0	4	22	14
Sweden	19	1	1	5	7	37	12
Switzerland	10	1	1	1	3	30	7
UK	34	4	5	1	10	29	24
USA	52	10	7	3	20	38	32
Total	324	41	37	20	98	30	226

Experience of responses to the questionnaire and analysis of the results suggests that it could be improved by the following minor modifications.

a) Question 6 was originally related to the criteria for defining a "centre". As these criteria were subsequently dropped, the question should be deleted.
b) Question 7 about affiliation to other organisations should include companies in the list of organisations, and allow respondents to tick more than one box so as to assess any increasing "hybridisation" of centres.
c) Question 11 (a detailed breakdown of centre expenditure) should be eliminated. It was not well answered and was not used in the analysis. It is obvious from those who provided information that the answers are not easily available and demand a great deal of time to calculate.
d) Question 13 about number of projects was relatively well answered, but it is difficult to understand the results. Information about the trend in the number of projects may not indicate any change in the overall activity of a centre. For instance, a constant number of researchers could be involved in a shift from many small to a few large projects. Therefore information is required for a single year only.
e) Question 15 about spin-off firms should include a category "Nil". The lack of this category meant we could not distinguish between respondents who had not answered the question and centres which had not launched any firms.
f) A question should be added to obtain information about the number of patents applied for by the centre and the patent office the application was directed to. Furthermore the number of patents granted should be asked for. If might also be appropriate to include questions about other forms of intellectual output. These could be identified by detailed interviews with a few potential recipients of the questionnaire, to ascertain the variety of outputs produced (eg, reports published by sponsors, media coverage, etc)

Table A2-3: Response rates to individual questions (%)

Question	US and EU centres	EU centres only	US centres only	Centres excluded by focus	Centres excluded by funding
2. Focus of research	96	96	91	100	90
3. Date when research centre created	95	96	85	97	100
4. Development form	98	98	97	92	100
8. Organised form	96	97	94	95	100
9. Composition of centre 1999	94	96	79	89	90
9. Composition of centre 1998	81	85	**58**	76	71
10. Total budget 1999	88	90	85	89	81
10. Total budget 1998	80	82	76	76	76
11. Centre's expenditure 1999	73	75	67	70	67
11. Centre's expenditure 1998	**62**	**64**	**52**	**57**	**62**
12. Sources of funding	92	93	88	86	100
13. Research projects 1999 and 1998	87	90	76	89	90
13. Trend in number of projects	85	84	76	89	86
14. Networking	85	80	82	89	95
15. Industrial collaborations 1999	77	80	67	70	81
15. Industrial collaborations 1998	69	70	**61**	**65**	76
15. Biotech spin-off firms	**54**	**52**	67	**43**	**38**
16. Prestige activities	77	84	**33**	89	90
17. Post-graduate training activities	73	78	**48**	76	76

Bold = less than 66% response rate

A5. Representativeness of biotech research centres in database

The initial method for assessing the representativeness of centres was based on centres' 1999 budgets as a proportion of annual national biotech research funding estimated from the inventory report (Enzing *et al*, 1998). The results, shown in Table A2-4, proved inappropriate.

We cannot fully explain the results of the analysis in Table A2-4, but suggest that they are related both to the different methods employed for funding biotechnology research in each country and to the limitations of data collection for the inventory report. An example of the former is disparity in national biotechnology expenditure caused by the type of institution in which biotechnology research is performed. Research in institutes covers core costs of the institution including all staff costs, but project grants for universities normally cover only the direct costs of the project. Countries whose centres are mainly located in universities may therefore account for a lower proportion of total biotech research budgets than those with a majority of centres located in institutes. In addition, the results may also reflect whether or not countries choose to fund the majority of biotechnology research through centres. Two examples of the latter problem (limitations in inventory data on national budgets) are provided by Germany and Spain. In Germany, core financing of universities is provided by the "länder". Since there is no breakdown of these core funds into biotechnology and other areas, it was not possible for the inventory to identify which part of this core funding was related to biotechnology. The core budgets of university based biotech research centres are therefore not covered by the inventory, leading to under-estimates for centre budgets. In Spain, the regions fund a high proportion of biotechnology research, but data on regional

Table A2-4: Centre budgets as percentage of total biotech funding 1994-98

Country	Total centre budget 1999 (Mio. €)	Total biotech funding 1994-98 (Mio. €)	Total biotech funding/year (Mio. €)	Centre budget as % total
Spain	54.87	47	9.4	584
Netherlands	178.56	314	62.8	284
Ireland	20.87	46	9.2	227
Greece	6.75	20	4	169
Switzerland	14.47	50	10	145
Denmark	33.60	138	27.6	122
Portugal	13.38	73	14.6	92
Austria	8.76	49	9.8	89
Finland	41.36	248	49.6	83
Germany	481.47	3021	604.2	80
Belgium	81.80	551	110.2	74
Italy	22.16	207	41.4	54
Sweden	27.18	271	54.2	50
UK	247.18	2572	514.4	48
France	50.07	2115	423	12

funds were not included in the inventory report, leading to an underestimate for national expenditure.

A third problem relates to funds for biotech research centres associated with institutions that rely to a great extent on contract research (eg, FhG in Germany, TNO in The Netherlands). Their aggregate budgets may exceed national public expenditure. The results may also reflect whether or not countries choose to fund the majority of biotechnology research through centres.

To deal with some of these problems, we next compared representativeness based on centres' national project funds as a proportion of national project funding (provided in the national studies of the inventory report.[29] As shown by Table A2-5, this approach also failed to assess representativeness; we do not know the reasons for the results. Despite the limitations discussed in Section A8 below, we concluded that centres' publication data as a proportion of national publications is the most reliable method for assessing representativeness.

[29] National project funding was only available for 12 of the 15 countries.

Table A2-5: Centres' national project funds as a percentage of total project funding

Country	Total project funding 1994-98 (Mio. €)	Total project funding per year (Mio. €)	Centres' project funding 1999 (Mio. €)	Centres' project funding as % of total
Belgium	189.0	37.8	17.53	46.38
Denmark	42.4	8.48	8.58	101.13
Finland	72.5	14.5	13.12	90.47
France	114.0	22.8	4.15	18.19
Germany	1385	277	60.50	21.84
Ireland	14.5	2.9	3.30	113.65
Italy	77.9	15.58	4.60	29.55
Netherlands	11.0	2.2	46.76	2125.61
Spain	34.0	6.8	14.02	206.19
Sweden	50.6	10.12	7.70	76.04
Switzerland	47.1	9.42	2.36	25.06
UK	687.8	137.56	70.39	51.17

A6. Bibliometric searches

Bibliometric data was collected using the online version of the Science Citation Index (SCI), produced by the Institute of Scientific Information in Philadelphia and offered by the host STN. The SCI covers a broad range of scientific disciplines. Its specific advantage for institutional analysis or data gathering based on institutional affiliation is that the addresses of all the authors that contributed to the publication and their institutional affiliation are searchable in the database. The majority of databases only contain data on the first author. Publication data was collected for the period 1994-1999.

The starting point for the bibliometric work was the definition of the field under analysis. A set of keywords as well as subject codes, which are provided by the SCI, were used for the delimiting the field 'biotechnology'. In the next step it was necessary to identify individual centres. This was complicated because the database does not give names in a standardised form. To ensure that the publications list identified for each centre was as complete as possible it was necessary to "clean" the data by finding all the different name variations used for each individual centre. We used a search strategy to ensure comprehensive coverage which combined the city or postcode of the centre with word combinations representing centre names. The identified name variations were then checked for correctness. (Information about name variations also informed the patent searches.) The publications identified for each centre were added to the centre database.

Another task tackled by bibliometrics was the identification of key personnel. It is impossible to construct an author–address relationship from the bibliometric database for publications with more than one author and more than one author address. When papers gave more than one author address, it was impossible to identify the institutional affiliation of each author. In order to solve this problem we introduced a threshold. We selected all publications that contain each centre's address and determined the distribution of papers per author for this set of papers. The list of authors identified included all authors from co-authoring institutions. From those publication lists we selected those authors that contributed at least 20 papers to the centres' overall publication output. Those authors selected were traced back to their institutional affiliation in order to identify highly active researchers for each centre. The internet was used as the main source of for this task.

A7. Patent searches

Initial searches for patents held by the centres which fulfilled the criteria were made by searching the entire list of assignee names for patents granted at the European Patent Office (EPO) between 1994 and 1999. After identifying several centres we looked at the most commonly occurring IPC code (CN12N15) and extracted all those patents which had that code. These patents were then searched to find our 226 centres. However, this produced a few "hits" only. We next made lists of the top 20 assignees in the database and the top 20 European publicly-funded assignees. The former were mainly companies and the latter were large organisations (universities or research funders) or generic institutions encompassing many research entities (eg, Max Planck in Germany and INSERM in France).

Further patent searches were carried out using an extended search strategy based on additional IPC codes related to biotech (from the ISI definition of biotech) to extract records from the EPO database. A search of these records resulted in 18 specific centres and 49 generic organisations (such as 'Medical Research Council' in the UK) being identified.

We contacted generic centres to ask for help in identifying patents from our specific centres. Very few replies were received. A typical response was:

> It is really difficult to respond to your request. The [name of centre] is not a unit to which we track patents. Many of the faculty associated with the Center have patent activity with us, but we credit those patents to the respective home departments of these faculty. I don't have any good way of telling which (if any) of these patents are the result of Center activity.

Further searches were conducted using name and address variations for centres in Austria and Belgium revealed by bibliometric analysis. Alternative addresses resulted in the same generic centres being found again, rather than more specific centres being identified. Lack of identifiable patents for centres may also have been caused by country-specific regulations for 'university' patents. For instance, in some countries such as Germany, the individual professor had the right to apply for patents until recently, but not the universities or centres belonging to a university. This rule was changed only recently. In order to account for any such patents, we attempted some patent searches based on the names of key personnel revealed by bibliometric analysis. This failed because many key personnel had "common" names, impossible to distinguish among the many instances of patentees with the same name.

We then searched US Patent Office (USPTO) for our US centres, but found only *generic* names of large organisational entities, mainly universities.

As so little data was found in the EPO or USPTO databases, it was not thought worth searching Japanese patent data. The failure to identify patents for the centres in our database, means that it is not possible to include such output data in the centre database.

A8. Bibliometric and patent counts and representativeness

Using bibliometric analysis to the check the representativeness of the centres in our database gave rise to several problems. On the one hand there was a problem of assigning publications to some of the centres due to their organisational set up (see Section A6 above). On the other hand, it is important to recognise the fact that universities are significant players in European biotechnology, contributing significantly to publication output and also increasingly to patents. For example, German universities applied for about 2% of German patents in pharmaceutical biotechnology between 1990-1992, and during 1996-1998 they contributed 5% of total patent applications. In the first period about 9% of the patents in this area were applied for by

individuals. This share increased to about 21% between 1996 and 1999. Due to specific regulations in Germany (see Section A7 above) a considerable share of patents taken out by professors actually reflect university research output. These data lead to the assumption that universities are important players in pharmaceutical biotechnology (contributing up to about 25% of all patent applications). It is appropriate to assume that this would be the same for biotechnology in general.

The proportion of the contribution of individual actor groups to total output – either patents or publications – is unknown for each country, and could differ significantly. Therefore using the publication output collected for the biotech research centres and its comparison with the total output of a country in order to determine the degree of representativeness could be misleading, because the extent of the contribution of the centres to knowledge generation may differ between countries. The organisational form of centres differ significantly between countries (see Figure 9). Countries with significant numbers of 'virtual' and 'co-operative' centres could have lower than actual publication counts for centres due to the problem mentioned above. These lower counts distort any assessments of representativeness.

A9. Research specialisation

As Table A2-6 illustrates, the majority of centres are involved in more than one focus area, as defined by the taxonomy of biotechnology.

Table A2-6: Research focus of biotech research centres

Number of focus areas	Number of centres
8	1
7	11
6	15
5	31
4	45
3	45
2	42
1	24
No information	12
Total	**226**

Only 24 centres indicated that they specialised in one area only. Their area of specialisation was:

- 7 focused on basic only
- 6 focused on plant only
- 5 focused on human only
- 3 focused on animal only
- 2 focused on environmental only
- 1 focused on cell factory only

Of the 42 centres that were involved in 2 focus areas only, the most common combination was human and basic (15 centres), but we were unable to find significant numbers of combinations of other areas. We therefore divided centres into those that focused predominantly on one area only (single focus centres) and those allocating similar amounts of their budgets to several areas (multi-focus centres).

A10. Constructing performance indices

The construction of indices for centres' academic, industrial, prestige and networking activities draws on Larédo (1999). The approach considers the relative performance of individual centres before constructing indices. The aim was to position centres against each other, rather than against some pre-determined norm. The factors included in each index are given below. Research staff are based on aggregating the full-time equivalent of full- and part-time professors, lecturers and researchers. The average for 1998 and 1999 were used when we had data for both years. Otherwise data for 1999 only was used.

i) Academic Index

- Ratio of doctoral students to research staff.
- Number of PhDs awarded – internal and external PhDs – per member of research staff.
- Publications per member of research staff.

ii) Industrial Index

- % of funds from industrial contracts.
- Number industrial research collaborations per member of research staff.
- Number spin-off firms launched.
- If researchers sit on Scientific Advisory Boards of firms (add 1 point).

iii) Networking Index

- Proportion of research projects with EU researchers to all research projects.
- Proportion of research projects with US researchers to all research projects.
- Proportion of research projects with national researchers outside centre to all research projects.
- Number EU conferences/workshops attended by researchers per member of research staff.
- Number of US conferences/workshops attended by researchers per member of research staff.

iv) Prestige Index

- Highly active researchers (from bibliometric analysis) as proportion of research staff.
- Number researchers with scientific awards as proportion of research staff.
- Number researchers who are members of scientific committee as proportion of research staff.
- Number researchers who are members of research program committee as proportion of research staff.
- Number researchers who are members of other international committees as proportion of research staff.

A11. Calculating performance indices

In order to determine the indices for each factor quartiles were calculated.[30] The calculation of quartiles omits all blanks and zeros. Index calculation and the formulas applied are explained in the following example:

[30] The statistical package SPSS was used.

Example: Prestige Index

Factors to be included:

- Highly active researchers (from bibliometric analysis) as proportion of research staff: key personnel/research staff
- Number researchers with scientific awards as proportion of research staff: scientific awards/research staff
- Number researchers who are members of scientific committee as proportion of research staff: scientific committees/research staff
- Number researchers who are members of research program committee as proportion of research staff: funding committees/research staff
- Number researchers who are members of other international committees as proportion of research staff: representative other international committees/research staff

§ Step One: Calculation of the quartiles for the distribution of indicators:

- key personnel/research staff;
- scientific awards/research staff;
- scientific committees/research staff;
- funding committees/research staff;
- representative other international/research staff

§ Step Two: Assignment of points:

- If the relevant data for the centre is greater than zero and less than the first quartile (0<x<1st quartile) = 1 point
- If the relevant data for the centre is greater than or equal to the first quartile and less than the third quartile (1st quartile<=x<3rd quartile) = 2 points
- If the relevant data for the centre is greater than or equal to the third quartile (x>=3rd quartile) = 3 points

§ Step Three: Calculation of index:

- Sum all points assigned to each factor included in index definition (see above for example concerning prestige index)
- Division of total points calculated for each centre by the total number of indicators available for the specific index, which means that only when the indicator value, eg, key personnel/research staff is >0 is the indicator counted as "being available".

Indicator value for a centre = $\sum_{i=1}^{5} w(i) / \sum_{i=1}^{5} n(i)$

with: w(i) = indicator value per factor
n(i) = 1 if w(i) >1 or
= 0 if w(i)=0

When indices are constructed of less or more than five factors the relevant number is changed in the formula given above.

Step Four: Classification of index values:

- The scores for each index, which result from the above calculation are used to allocate centres to low, medium or high performing categories according to the following scale:

  Low performing >=1.5
  Medium performing 1.5>=2
  High performing 2>=3

A12. DEA analysis

Data Envelopment Analysis (DEA) is a methodology which can be used to evaluate the efficiency of various entities including organisations such as research centres. For a basic introduction into the method see for instance Charnes *et al* (1994) and Bowlin (1998). Examples for the application of the method can be found in Grupp (1998), Wörner (1998) and Kocher *et al* (2001). It is widely used when there are multiple inputs and outputs, without a clear relationship between them, which usually makes it difficult to compare different units. Another advantage of DEA is that inputs and outputs using different measurements (scales) can be used, eg, budgets in Euros, numbers of publications. The method calculates the relative efficiency of all the units in the dataset against each other and therefore makes it possible to differentiate between efficient and inefficient units. The analysis used a program, EMS, developed by Holger Scheel of the University of Dortmund (Scheel 2000). The program has a number of choices for analysis, including an input or output oriented analysis. The input oriented model calculates the achievement of efficiency in terms of how much a centre should reduce its input in order to produce the same output. The output oriented model calculates how much output should be increased, keeping input constant, for a centre to be considered efficient. The output-oriented model was used for this study, because we assumed that it would be easier for centres to increase output than to increase size. Secondly, the analysis assumes that there are variable returns to scale, and that an increase or decrease in inputs does not lead to a proportionate increase or decrease in outputs.

The inputs were defined as R&D budgets and aggregate research staff. The outputs were grouped in four clusters to consider efficiency related to the various missions aimed for by centres:

Education and Training
Number PhDs awarded

Knowledge Base
Number scientific publications
Number citations received

Research Excellence
Number scientific awards
Number key personnel
Membership of “international” advisory, funding and other committees
Membership of editorial boards

Fostering Commercialisation
Number industrial collaborations
Number spin-offs

ANNEX – QUESTIONNAIRES

EUROPEAN COMMISSION
RESEARCH DIRECTORATE-GENERAL

Life Sciences – Coordination
The Director

Brussels,
6 November 2000

Dear Colleague

An International Benchmark of Biotech Research Centres

Biotechnology creates expectations about its potential to improve the quality of life. It is also key to the competitiveness of important economic sectors. European policies must be responsive to these challenges. To this end, it is crucial for the European Commission to understand the focus of European research, the resources being used and how Europe's biotech centres compare to those in the United States. That is why the Directorate General for Research of the European Commission has commissioned a study on key indicators for biotech research centres. The results of this study will contribute to the reflection on the establishment of the European Research Area (Communication of the European Commission of 18 January 2000).

The attached questionnaire has been developed to collect data both on the resources provided for your centre (human and financial) and the activities performed with those resources (research, doctoral training, interaction with industry and other external activities). By completing it, you can help contribute to EC research policy for biotechnology. It does not require any search for information since it refers to basic data and, when this is not the case, orders of magnitude will be sufficient.

Your centre has been identified as a significant biotechnology research performer. We therefore hope that you will be ready to devote time to help in our quest to develop an overview of the key indicators of biotech research centres, and to compare the resources and activities of centres in Europe and the United States. Completed questionnaires will be treated as strictly confidential and used only in aggregate form. Thanking you in advance for your cooperation.

Yours sincerely
BRUNO HANSEN
Director

The questionnaire may also be completed at
http://qmhost.central.sussex.ac.uk/qm/perception.dll?spru **If you want any further information, feel free to contact the following researcher, who is carrying out this study.**

- Contact details for SPRU or Fraunhofer researcher

The questionnaire addresses the following elements: identification; key elements in the development of your centre; resources (personnel and finance); and activities (research, doctoral training, contacts with industry and other external activities).

IDENTIFICATION

1. Does your centre have a specific mission related to biotechnology?
(see definition of biotechnology in question 2)
If you answered "No", please return the questionnaire. Thank you for your time.

Yes ☐ No ☐

If you answered "Yes", indicate the nature of the mission (multiple answers allowed)

To provide education and training	☐
To build up the knowledge base in biotechnology	☐
To be a national centre of research excellence	☐
To foster commercialisation and economic development of industry	☐

2. Focus of research: We define biotechnology in terms of the categories in following table. Please check the main field(s) in which your centre carried out research in 1999, and the proportion of your budget allocated to each area. Under "other" indicate if your centre is involved in research fields not in the table, and the proportion of your budget allocated to this other research.

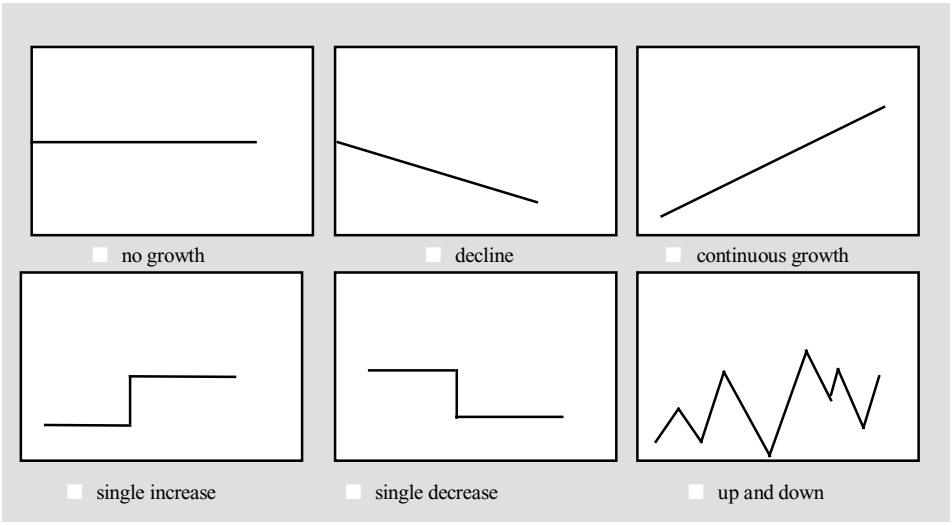
	B.1	B.2	B.3	B.4	B.5	B.6	B.7	Other
Research in:	☐	☐	☐	☐	☐	☐	☐	☐
% budget to each area								

B.1	**Plant biotechnology (crops, trees, shrubs, etc), including**
1.1	reproduction and propagation
1.2	genetic modification introducing new/excluding existing genes (mono- and polygenic traits)
1.3	growth conditions
1.4	plant protection
1.5	plant pathogen diagnosis
1.6	genome mapping
1.7	biodiversity of plants in agriculture/horticulture
B.2	**Animal biotechnology, including**
2.1	reproduction
2.2	production
2.3	breeding, including genetic engineering in animals (creation of transgenics)
2.4	animal health care,
2.5	genome mapping
2.6	biodiversity of farm animals
B.3	**Environmental biotechnology, including**
3.1	microbial ecology
3.2	biosafety
3.3	microbial functions for degradation/transformation of pollutants
3.4	isolation, breeding and genetic engineering of micro-organisms to degrade pollutants
3.5	biotechnological processes for soil and land treatment
3.6	biotechnological processes for water treatment
3.7	biotechnological processes for air and off-gas treatment
B.4	**Industrial biotechnology: food/feed, paper, textile, and pharmaceutical and chemical production**
4.1	enzymatic processes
4.2	development of bioprocessing techniques (fermentation, immobilisation of biocatalysts, quality control, etc)
4.3	downstream processing
B.5	**Industrial biotechnology: Cell factory, including all biotechnology research focused on the cell as producer of all sorts of (food and non-food) products**
5.1	plant cell biotechnology: plant cell biology
5.2	animal cell biotechnology: animal cell biology
5.3	bacteria as cell factories: microbiology
5.4	genetic engineering and production of enzymes
5.5	genetic engineering of micro-organisms and yeast
5.6	cell culture techniques
5.7	genome mapping of specific bacterial and yeast genomes
5.8	biodiversity of micro-organisms in production processes

B.6	Developments of human/veterinary diagnostic, therapeutic systems
6.1	immunology, therapeutic and diagnostic antibodies
6.2	vaccinology
6.3	human genome mapping
6.4	human gene transfer techniques
6.5	therapeutic proteins and oligonucleotides (substitutes for pharmaceuticals)
6.6	tissue engineering
6.7	genomics in drug discovery (substitutes for pharmaceuticals)
6.8	DNA diagnostics
6.9	forensics (genetic fingerprinting)
B.7	**Development of basic biotechnology**
7.1	techniques to determine the structure of biomolecules and study the structure-function relationship
7.2	techniques to build biomolecules (nanotechnologies)
7.3	interaction of biomolecules with micro-electronic devices, incl. biosensors, biomonitoring
7.4	techniques of genome analysis
7.5	bio-data-informatics (set of tools, which is applied to solve data handling and processing problems in biological research, eg, genome sequencing)
7.6	bio-informatics (application of biological principles to information processing for technical applications)

3. Date when your biotech research centre was created .....

4. Which of the following graphs best describe the development of your biotech centre in terms of research manpower in the period 1994-1999 (or since its creation)?



5. Type of biotech research centre

Is your centre part of a larger Research Institute Yes ☐ No ☐

If "yes", indicate the proportion of your budget allocated to biotechnology and ***complete the remainder of the questionnaire for the biotechnology-related parts of your Institute.***

Share of total budget devoted to biotechnology ____ %

6. Characteristics of your biotech research centre:

Is your centre a separate accounting unit? Yes ☐ No ☐

Has a Director been appointed to lead the centre Yes ☐ No ☐

Is the Director's post salaried? Yes ☐ No ☐

7. Is your centre affiliated or associated with another organisation? Yes ☐ No ☐

If yes, tick only one box in the following list

University ☐

Government research organisation ☐

Private non-profit organisation ☐

Foundation, charity or voluntary organisation ☐

Other. Please specify. _____

Contact details for SPRU or Fraunhofer researcher

8. How is your centre organised?

Tick one box only

Co-operative centre consisting of different institutions or parts thereof in the same town or city	
Co-operative centre consisting of different institutions or parts thereof not within the same city	
A unitary centre consisting of a single institution	

RESOURCES

9. Indicate the composition of your centre (measured in full-time equivalent (FTE) posts)

Please indicate the number of the following types of staff in your research centre in the past two years

	1999		1998	
Type of post	*Long-term Positions*[1]	*Short-term Positions*[2]	*Long-term positions*	*Short-term positions*
Professors, lecturers				
Full time researchers (including post-doctoral fellows)				
Doctoral students				
Technicians				
Total				

[1]Permanent positions or contracts for a minimum of 5 years [2] Fixed term positions for less than 5 years

10. The centre's budget

	1999	1998	Currency
Total budget for your centre			

11. The centre's expenditure

	1999	1998
Expenditure on	*Approx. share of expenditure on category*	*Approx. share of expenditure on category*
- long-term staff	%	%
- short-term staff	%	%
- doctoral students	%	%
- funds for renewal/acquisition of equipment	%	%
- overheads paid to your parent organisation*	%	%
- conferences and travel	%	%
- professional research training**	%	%
- consumables	%	%
- Other. Specify	%	%
Total	100%	100%

*for providing, maintaining and running the centre's infrastructure (eg, rent, heating, general administration...).

** for providing short courses and sending researchers on external courses)

12. Sources of funding

Estimate the share of each source of funds in your total budget in 1999.

Type of funds	*Share in total budget*
Core funding from government*	%
Public funds for individual research projects from national sources	%
Funds for projects from the EU Framework programme	%
Funds from foundations and charities	%
Funds from industrial contracts	%
Income from licenses	%
Other. Specify:	%
Total	100 %

* This covers funds allocated to the research centre on a pluri-annual basis by its institution (eg, CNRS in France), or by the national or regional government

ACTIVITIES

13. Research projects

No. of projects 1999		No. of projects 1998	
Indicate trend in number of projects since 1995. Use (I) for increasing (S) for stable and (D) for decreasing			

14. Networking

Indicate how far your centre networked with external researchers in 1999

Activity	*No.*
No. of research projects with European researchers	
No. of research projects with US researchers	
No. of research projects with national researchers outside your centre	
No. of researchers attending European conferences/workshops	
No. of researchers attending US conferences/workshops	

15. Activities to promote industrial exploitation of the centre's research

Activity	*Information Required*
No. of industrial research collaborations	1999 ☐ 1998 ☐
No. of biotech spin off firms launched since 1990 or since centre's foundation (if later)	1-2 ☐ 3-5 ☐ 6-10 ☐ 11-20 ☐ over 20 ☐
Do any of your researchers sit on scientific advisory boards of firms?	Yes ☐ No ☐
Are the services of your centre promoted by a technology transfer office?	Yes ☐ No ☐

16. Activities conferring prestige and scientific recognition on a research centre

Could you tick the activities in which your researchers were involved during 1998-99 (multiple answers allowed)

List of activities	*Tick if Involved*	*No. researchers involved*
Scientific awards for centre researchers	☐	
Journal editor or member of editorial committee	☐	
Member of scientific advisory committees – at national level	☐	
– in the EC	☐	
– other international	☐	
Member of research programme funding committee:		
- at national level	☐	
– in the EC	☐	
– other international	☐	
National representative on other international committee	☐	

17. Tell us about your centre's post-graduate training activities

Is your centre permitted to award PhDs Yes ☐ No ☐

If "Yes"

How many PhDs were awarded to your graduate students in 1999 ☐ 1998 ☐

If "No"

How many of your graduate students were awarded external PhDs in 1999 ☐ 1998 ☐

Thank you very much for taking the time to complete this form. We are most grateful for you help. All information will remain confidential and only appear in aggregated form. Please check the following box and give us your email address if you wish to receive a summary of the results ¤

Name……Position…..……email…….….

Name of Centre…….……...

Address ……

COVERING LETTER FOR US QUESTIONNAIRES

North Carolina Biotechnology Center

15 T.W. Alexander Drive

Post Office Box 13547

Research Triangle Park

North Carolina 27709-3547

USA

919-541-9366

main fax 919-549-9710

28 November 2000

Dear Biotechnology Colleague,

Many places worldwide have targeted biotechnology for economic and societal gain. As a result, biotechnology has triggered a phenomenon not seen in development of earlier comparably important sectors: a large number of deliberately constituted biotechnology centers, agencies, or initiatives. These entities vary in nature and programs. All, however, share a common premise: that research, development, and commercialization of biotechnology requires purposeful attention and capabilities.

Research centers are particularly important within this grouping, because biotechnology – like all technologies – springs from scientific curiosity, research, and resources. While such centers are likely to share certain goals and structures, they are also inevitably different in varied ways. Resources, emphases, and strategies vary, as does the balance between research, education, and commercial exploration. In addition, the commitment to fund science, as well as underlying cultural or national predispositions, shapes the nature and capabilities of centers.

Persons and institutions involved in biotechnology benefit from understanding the range and nature of other research centers and endeavors worldwide. After all, the entities in total constitute our shared community. In addition, they offer possibilities for partnership, learning, and sharing of experience.

Understanding international biotechnology resources and centers is particularly important in this enormously global endeavor. Accordingly, the Directorate General for Research of the European Commission has initiated a study on key indicators for biotechnology research centers. Your attention to the attached questionnaire will be valuable to the project and to its American director, Henry Etzkowitz, of State University of New York at Purchase. Mr. Etzkowitz will treat responses confidentially, using data only in aggregate form. Upon completion of the study in mid-2001, all respondents will be furnished a summary of the useful and interesting final report.

I am pleased to encourage participation in this project by colleagues, and share your expectation that it will increase understanding of our shared biotechnology endeavor.

Best wishes,

Steven Burke

W. Steven Burke
Senior Vice President, Corporate Affairs and External Relations
Past Chair, Council of Biotechnology Centers, BIO

If you prefer, the questionnaire can be completed at
http://qmhost.central.sussex.ac.uk/qm/perception.dll?name=usa

If you want any further information, feel free to contact the following researchers, who is carrying out this study.

- Henry Etzkowitz, SPI, State University of New York at Purchase, NY, USA (phone 212 864 4183; email HenryEtzkowitz@earthlink.net)

Please complete online at http://qmhost.central.sussex.ac.uk/qm/perception.dll?name=usa

OR return this questionnaire
Before February 10 2001 to:

Henry Etzkowitz
State University of New York at Purchase
730 Anderson Hill Road
Purchase, NY 10577-1400
Henryetzkowitz@earthlink.net

Respondent Name:
_____

The questionnaire addresses the following elements**: identification; key elements in the development of your centre; resources (personnel and finance); and activities (research, doctoral training, contacts with industry and other external activities).**

IDENTIFICATION

1. Does your centre have a specific mission related to biotechnology?
(see definition of biotechnology in question 2)
If you answered "No", please return the questionnaire. Thank you for your time.

Yes n No n

If you answered "Yes", indicate the nature of the mission (multiple answers allowed)

To provide education and training	n
To build up the knowledge base in biotechnology	n
To be a national centre of research excellence	n
To foster commercialisation and economic development of industry	n

2. Focus of research: We define biotechnology in terms of the categories in following table. Please check the main field(s) in which your centre carried out research in 1999, and the proportion of your budget allocated to each area. Under "other" indicate if your centre is involved in research fields not in the table, and the proportion of your budget allocated to this other research.

	B.1	B.2	B.3	B.4	B.5	B.6	B.7	Other
Research in:	n	n	n	n	n	n	n	n
% budget to each area								

B.1	**Plant biotechnology (crops, trees, shrubs, etc), including**
1.1	reproduction and propagation
1.2	genetic modification introducing new/excluding existing genes (mono- and polygenic traits)
1.3	growth conditions
1.4	plant protection
1.5	plant pathogen diagnosis
1.6	genome mapping
1.7	biodiversity of plants in agriculture/horticulture
B.2	**Animal biotechnology, including**
2.1	reproduction
2.2	production
2.3	breeding, including genetic engineering in animals (creation of transgenics)
2.4	animal health care,
2.5	genome mapping
2.6	biodiversity of farm animals
B.3	**Environmental biotechnology, including**
3.1	microbial ecology
3.2	biosafety
3.3	microbial functions for degradation/transformation of pollutants
3.4	isolation, breeding and genetic engineering of micro-organisms to degrade pollutants
3.5	biotechnological processes for soil and land treatment
3.6	biotechnological processes for water treatment
3.7	biotechnological processes for air and off-gas treatment

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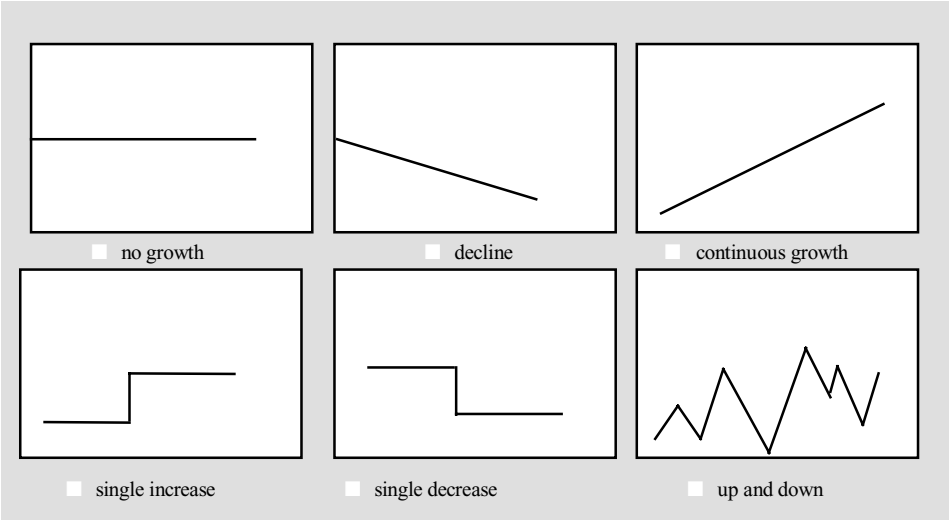
Henry Etzkowitz, State University of New York at Purchase, N.Y.,
730 Anderson Hill Road, Purchase, NY 10577-1400

B.4	**Industrial biotechnology: food/feed, paper, textile, and pharmaceutical and chemical production**
4.1	enzymatic processes
4.2	development of bioprocessing techniques (fermentation, immobilisation of biocatalysts, quality control, etc)
4.3	downstream processing
B.5	**Industrial biotechnology: Cell factory, including all biotechnology research focused on the cell as producer of all sorts of (food and non-food) products**
5.1	plant cell biotechnology: plant cell biology
5.2	animal cell biotechnology: animal cell biology
5.3	bacteria as cell factories: microbiology
5.4	genetic engineering and production of enzymes
5.5	genetic engineering of micro-organisms and yeast
5.6	cell culture techniques
5.7	genome mapping of specific bacterial and yeast genomes
5.8	biodiversity of micro-organisms in production processes
B.6	**Developments of human/veterinary diagnostic, therapeutic systems**
6.1	immunology, therapeutic and diagnostic antibodies
6.2	vaccinology
6.3	human genome mapping
6.4	human gene transfer techniques
6.5	therapeutic proteins and oligonucleotides (substitutes for pharmaceuticals)
6.6	tissue engineering
6.7	genomics in drug discovery (substitutes for pharmaceuticals)
6.8	DNA diagnostics
6.9	forensics (genetic fingerprinting)
B.7	**Development of basic biotechnology**
7.1	techniques to determine the structure of biomolecules and study the structure-function relationship
7.2	techniques to build biomolecules (nanotechnologies)
7.3	interaction of biomolecules with micro-electronic devices, including biosensors, biomonitoring
7.4	techniques of genome analysis
7.5	bio-data-informatics (set of tools, which is applied to solve data handling and processing problems in biological research, eg, genome sequencing)
7.6	bio-informatics (application of biological principles to information processing for technical applications)

Please return this questionnaire before February 10, 2001 to :
Henry Etzkowitz, State University of New York at Purchase, N.Y.,
730 Anderson Hill Road, Purchase, NY 10577-1400

3. Date when your biotech research centre was created .....

4. Which of the following graphs best describe the development of your biotech centre in terms of research manpower in the period 1994-1999 (or since its creation)?



5. Type of biotech research centre

Is your centre part of a larger Research Institute	Yes	n	No	n

If "yes", indicate the proportion of your budget allocated to biotechnology and ***complete the remainder of the questionnaire for the biotechnology-related parts of your Institute.***

Share of total budget devoted to biotechnology		%

6. Characteristics of your biotech research centre:

Is your centre a separate accounting unit?	Yes	n	No	n
Has a Director been appointed to lead the centre	Yes	n	No	n
Is the Director's post salaried?	Yes	n	No	n

7. Is your centre affiliated or associated with another organisation? Yes n No n

If yes, tick only one box in the following list

University	n
Government research organisation	n
Private non-profit organisation	n
Foundation, charity or voluntary organisation	n
Other. Please specify.	

8. How is your centre organised?

Tick one box only

Co-operative centre consisting of different institutions or parts thereof in the same town or city	n
Co-operative centre consisting of different institutions or parts thereof not within the same city	n
A unitary centre consisting of a single institution	n

Please return this questionnaire before February 10, 2001 to :

Henry Etzkowitz, State University of New York at Purchase, N.Y.,
730 Anderson Hill Road, Purchase, NY 10577-1400

RESOURCES

9. Indicate the composition of your centre (measured in full-time equivalent (FTE) posts)

Please indicate the number of the following types of staff in your research centre in the past two years

	1999		1998	
Type of post	*Long-term Positions*[1]	*Short-term Positions*[2]	*Long-term positions*	*Short-term positions*
Professors, lecturers				
Full time researchers (including post-doctoral fellows)				
Doctoral students				
Technicians				
Total				

[1]Permanent positions or contracts for a minimum of 5 years [2] Fixed term positions for less than 5 years

10. The centre's budget

	1999	1998	Currency
Total budget for your centre			

11. The centre's expenditure

	1999	1998
Expenditure on	*Approx. share of expenditure on category*	*Approx. share of expenditure on category*
- long-term staff	%	%
- short-term staff	%	%
- doctoral students	%	%
- funds for renewal/acquisition of equipment	%	%
- overheads paid to your parent organisation*	%	%
- conferences and travel	%	%
- professional research training**	%	%
- consumables	%	%
- Other. Specify	%	%
Total	100%	100%

*for providing, maintaining and running the centre's infrastructure (eg, rent, heating, general administration...).
** for providing short courses and sending researchers on external courses)

12. Sources of funding

Estimate the share of each source of funds in your total budget in 1999.

Type of funds	*Share in total budget*
Core funding from government*	%
Public funds for individual research projects from national sources	%
Funds from foundations and charities	%
Funds from industrial contracts	%
Income from licenses	%
Other. Specify:	%
Total	100 %

* This covers funds allocated to the research centre on a pluri-annual basis by its institution (eg, CNRS in France), or by the Federal or state government

Please return this questionnaire before February 10, 2001 to :

Henry Etzkowitz, State University of New York at Purchase, N.Y.,
730 Anderson Hill Road, Purchase, NY 10577-1400

ACTIVITIES

13. Research projects

No. of projects 1999	No. of projects 1998
Indicate trend in number of projects since 1995. Use (I) for increasing (S) for stable and (D) for decreasing	

14. Networking

Indicate how far your centre networked with external researchers in 1999

Activity	*No.*
No. of research projects with European researchers	
No. of research projects with national researchers outside your center	
No. of researchers attending European conferences/workshops	
No. of researchers attending US conferences	

15. Activities to promote industrial exploitation of the centre's research

Activity	*Information Required*
No. of industrial research collaborations	1999 1998
No. of biotech spin off firms launched since 1990 or since centre's foundation (if later)	1-2 n 3-5 n 6-10 n 11-20 n over 20 n
Do any of your researchers sit on scientific advisory boards of firms?	Yes n No n
Are the services of your centre promoted by a technology transfer office?	Yes n No n

16. Activities conferring prestige and scientific recognition on a research centre

Could you tick the activities in which your researchers were involved during 1998-99 (multiple answers allowed)

List of activities	*Tick if involved*	*No. researchers involved*
Scientific awards for centre researchers	n	
Journal editor or member of editorial committee	n	
Member of scientific advisory committees - at federal level	n	
- at the state level	n	
- other international	n	
Member of research programme funding committee:		
- at federal level	n	
- at the state level	n	
- international	n	
National representative on other international committee	n	

Please return this questionnaire before February 10, 2001 to :

Henry Etzkowitz, State University of New York at Purchase, N.Y.,
730 Anderson Hill Road, Purchase, NY 10577-1400

17. Tell us about your centres' post-graduate training activities

Is your centre permitted to award PhDs	Yes n	No n		
If "Yes"				
How many PhDs were awarded to your graduate students in	1999		1998	
If "No"				
How many of your graduate students were awarded external PhDs in	1999		1998	

Thank you very much for taking the time to complete this form. We are most grateful for you help. All information will remain confidential and only appear in aggregated form. Please check the following box and give us your email address if you wish to receive a summary of the results ¤

Name……Position….……email…….….

Name of Centre…….……...

Address ……

Please return this questionnaire before 30 November 2000 to :
Henry Etzkowitz, Science Policy Institute, State University of New York at Purchase, N.Y., 730 Anderson Hill Road, Purchase, NY 10577-1400

Please return this questionnaire before February 10, 2001 to :
Henry Etzkowitz, State University of New York at Purchase, N.Y.,
730 Anderson Hill Road, Purchase, NY 10577-1400