BIOTECHNOLOGY

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BIOTECHNOLOGY

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1) INTRODUCTION

Industrial activities based on biological processes have been used for a very long time, but the biotechnology that is today the object of a very considerable policy attention is the result of a series of important advances in molecular biology, which were achieved the early 1970s. As a consequence, since the 1980s many governments started sponsoring the development of biotechnology by means of different policies. Biotechnology is generally perceived as a very pervasive technology, capable of giving rise to innovations in many different industrial sectors and fields of human activity. Many observers predict that the XXIst century will be the century of biotechnology. While the scope of the future developments of biotechnology is immense, the actual rate at which they are achieved is not always comparable to the expectations of policy makers and of economic actors. This is not due to a lack of potential of the technology, but to the nature of scientific and economic evolution. First, pervasive technologies are usually constituted by many interconnected innovations, not all of which can be developed at the same time. Second, pervasive technologies do not develop in a vacuum, but co-evolve with institutions (Nelson, 1994). Thus, even if the early innovations giving rise to a new pervasive technology were to be created without any institutional innovations, the further development of the technology would require the creation of appropriate institutions. As a consequence, the full development of such a technology usually requires a long time, easily reaching a century. It is quite clear that the realizations that we have seen so far constitute only a small part of the potential of biotechnology.

An important characteristic of biotechnology is that it is both the result of a process of structural change in science and that it contributes to structural change in industry. The expression 'the biotechnology sector' is used very often in the literature, although such a sector does not appear in industrial statistics. As a consequence, it is very difficult to find accurate data about biotechnology (Senker, 2000).

In its very early phases the development of modern biotechnology has been mostly based in the United States. EU countries started relatively early to catch up, but their efforts do not seem to have bridged the gap so far. Furthermore, a number of other countries, mostly in South East Asia and in Latin America, have invested in biotechnology and are making rapid progress. The scientific and industrial developments of biotechnology are becoming increasingly competitive and it is very important for all high income countries to acquire best practice capabilities in this technology.

2) THE SOCIO-ECONOMIC CHALLENGES FOR EUROPE.

There are a number of reasons for which countries develop policies and allocate resources to biotechnology. Amongst the most important ones are the increased competitiveness that the mastery of such a technology can give to a country, with the consequent positive impact on the growth of employment and of output, the expected positive impact on human health, on the environment and on national security. While such objectives might be considered common to most countries, the ways in which they are realised are likely to differ. Countries have national innovation systems (NSIs) which are manifested in specific patterns of specialisation and institutional configurations used to achieve even comparable objectives (Freeman, 1987; Lundvall, 1992; Nelson, 1993). Each country is thus caught in between the two competing constraints of adapting to the evolution of the world economic system, for example by learning a new technology invented elsewhere, and of fitting any required resources and new

institutions within its existing institutional structure. Furthermore, technologies can differ for their scope, defined as the range of human activities that they can affect, and for their life cycle, that is for the duration and timing of the sequence of events that lead from the first emergence of a technology to its complete maturity. Whatever its exact definition biotechnology is a pervasive technology of a very wide scope and whose potential can only be realised over a very long period of time. This has profound implications for scientific and industrial policies that countries could develop in order to either establish a leading position in such a technology or to catch up if another country had already established a lead. First, investment in the very early phases is surrounded by a particularly high uncertainty, giving rise to the risk of failure if one is too optimistic and invests too early, or of remaining locked out if one invests too late in presence of first mover advantages linked to increasing returns to adoption. This is precisely the dilemma in which the EU finds itself now, being a second comer with respect to the USA, having attempted with some success to catch up but being still far from this objective.

In what follows of this section the development of biotechnology since the early 1970s will be briefly reviewed in order to establish the relative position of the EU with respect to the USA in this field. This will serve as the basis for the analysis of recent and expected future trends.

2.1) THE DEVELOPMENT OF BIOTECHNOLOGY SINCE THE 1970S.

Modern biotechnology derives from the creation of molecular biology, a new discipline founded in the 1930s with the objective of applying to biology the methods of physics. The discovery of the structure of DNA by Watson and Crick showed that genes contained the information required to produce proteins. Although it became immediately evident that this could have enormous potential implications for medicine as well as for many other fields of human activity, the practical realization of this potential did not begin to happen until the discovery of recombinant DNA and monoclonal antibodies in the early 1970s (McKelvey, 1997; Goujon, 2001; Eliasson, 2000). These two discoveries opened the way to industrial applications that were expected to produce economic returns within relatively short time periods. A wave of investment which gave rise to the creation of many new firms and to a new form of industrial organisation followed. Thus, from its very beginning biotechnology was a very science intensive technology. Subsequent developments depended heavily on technical progress, for example on polymerase chain reaction (PCR), which allowed to magnify the quantities of DNA and of genetic material that could be available to researchers, and on the emergence of bioinformatics (Saviotti et al, 2000), a new discipline at the interface between biology and IT, which led to the automation of the sequencing of DNA and greatly accelerated the Human Genome Project. The Human Genome Project opened the door to a wide range of new potential applications. As a consequence the subsequent development of biotechnology can be characterised as a process of increasing specialisation in which particular diseases become the object of focused attention and emerging technical developments become recognised subsets of biotechnology. There is no consensus about the recognised subsets of biotechnology, although there are some commonalities between different classifications. Two examples are those provided by Biocom and by Nature Biotechnology:

Table 2.1. Specialised fields of biotechnology

Nature Biotechnology web focuses, Jan 2005	Bio.com
Biomanufacturing and bioprocessing	Genomics
Proteomics	Proteomics
RNAi	Biotherapeutics
GM Crops	Bioinformatics
Stem Cells	Bioengineering
Food and the future	Drug discovery
The mouse genome	Immunotech
Proteomics Technology	
The Y chromosome	

Sources: www.nature.com/nbt/index.html (January 2005) ; www.bio.com (March 2005)

Initially molecular biology was a predominantly USA speciality, which gave this country a head start, although some European countries, in particular the UK, achieved some important results already in the 1950s.

To understand the development of biotechnology we have to keep in mind that it is not an industrial sector, but a technology which is based on several scientific disciplines and which can affect a number of industrial sectors. Amongst the sectors that can be affected there are the pharmaceutical, agrochemical, food and chemical sectors and the environment. The adoption of biotechnology in these sectors has not been uniform. The pharmaceutical sector was and still remains dominant. Other sectors, such as agriculture and food, were considered very promising but developments there have been far slower than expected. General industrial applications developed at a slower pace but are gaining momentum. In summary, biotechnology is a component of a system which comprises scientific institutions, industrial firms, financing and regulating institutions.

The various components of this system co-evolve determining its overall dynamics. Although it is not impossible that several system configurations can achieve similar results, a country wishing to develop biotechnology must make sure that all the required components perform well and are well integrated amongst themselves (Eliasson, 2000). In what follows of this section we will review the state of these various components in the EU with respect to the USA. Before embarking on such a comparison it must be brought in mind that we are not really comparing like with like. The EU is far more heterogeneous than the USA for what concerns both scientific or technological performance and institutional structures.

2.1.1) SCIENTIFIC PERFORMANCE.

The performance of scientific institutions can be measured by their publications. EU publications in the life sciences more than doubled during the period 1980-1995 (Quéré et al 2003 pp. 27-30, CEC 1997), keeping the EU share of world publications in this field either constant or slightly increasing. While the situation might be considered satisfactory in this sense, the number of publications is not a definitive measure of the competitiveness of a

country in this field. The quality of publications can vary widely and differentiate countries having a similar number of publications. A study of the citations or impact factors of biotechnology publications is not available at the moment, but the distribution of recent Nobel prizes in medicine and chemistry seems to indicate a USA superiority which goes beyond their relative superiority in numbers.

2.1.2) TECHNOLOGICAL PERFORMANCE.

The technological performance of different countries can be measured by means of the patents they produce. During the period 1980 -1995 the number of patents produced by the USA was considerably above that of the EU (Quéré et al, 2003, pp 31-40). It seems as the relative technological performance of the EU with respect to the USA is worse than the relative scientific performance. It must however be considered that the EU is probably much more heterogeneous than the USA. Some European countries, especially the Scandinavian ones, are virtually best practice while other ones are real laggards in biotechnology. Suffice it to think that Denmark has more biotechnology patents per head of population than the USA while countries like Italy, Spain or Greece have very low R&D expenditures and number of patents. In spite of this qualification, the relatively better scientific vs technological performance of the EU stands. Of course, both scientific and technological performance arise as a consequence of the allocation of resources to search activities, the most common of which is R&D. We will examine the distribution of resources invested in R&D in a subsequent section.

2.1.3) FINANCING INSTITUTIONS.

A very considerable role was played by Venture Capital Firms (VCFs) and by stock markets specialised in high technology firms, such as the NASDAQ, during the evolution of biotechnology in the USA. VCFs are a very special type of institutions, characterised more by their ability to understand the *potential* of new technologies than by their capacity to supply finance. If anything VCFs can be considered as supplying a combination of knowledge and finance (Eliasson, 2000). Both VCFs and new types of stock exchanges were institutional innovations pioneered by the USA. By the late 1980s in the EU there were very few VCFs and the first new stock markets (e.g. Nouveau Marché, Neur Markt) were founded during the 1990s. Of course, both types of institutional innovations had an impact on the creation and development of all high technology firms and not only on biotechnology firms. However, their absence or limited development for a very long time constituted a bottleneck for any European attempt to catch up with the USA in terms of the rate of creation of new firms. It has to be said that the situation of these two types of institutions in the EU improved considerably in the 1990s (Quéré et al, pp. 54-58). In spite of these improvements the supply of venture capital in the EU is still only 21% of that of the USA (Table 2.3).

2.1.4) RESEARCH AND DEVELOPMENT.

Overall expenditures in R&D in biotechnology are difficult to obtain for a number of reasons. First, biotechnology is not a standard category of either scientific activities or of industrial classifications, such as a sector. Biotechnology patents and papers can be distributed over a large number of disciplines or of industrial sectors (biology, medicine, engineering etc in the former case; pharmacy, agro-chemistry, food etc in the latter). Efforts are being made both at the national and at supranational levels to harmonise the collection of statistics, but at present the comparability of data emanating from different sources cannot be expected to be very high. Meetings are being periodically organised by the OECD to provide consistent statistics

on biotechnology (www.oecd.org/sti/biotechnology). The information that is presently available allows us to detect broad patterns of development, but is not necessarily enough to find out about subtle if important trends or to perform accurate inter-country or inter-industry comparisons. Comparable statistics about public funding of biotechnology R&D in European countries, including both EU, other European countries and Canada, are available for 1997 from the OECD (Table 2.2).

Table 2.2. Government funding or outlays for research and development is selected European countries, 1997.

Country	Biotechnology R&D Million PPP $	Total Gov't Budget appropriations or Outlays** for R&D Million PPP $	R&D biotech/R&D overall
Belgium	181.7	1,314.0	13.8
Canada	261.4	2,581.0	10.1
Denmark	45.2	945.6	4.8
Finland*	94.5	1,165.0	8.1
France	560.0	12,683.1	4.4
Germany	1,048.2	15,595.7	6.7
Ireland	15.0	229.9	6.5
Italy	32.1	7,329.6	0.4
Netherlands	78.0	3,069.9	2.5
Norway*	26.8-32.2	880.3	3.0-3.7
Sweden*	65.6	1,795.2	3.7
Switzerland	16.4	1,379.7	1.2
UK	705.1	9,055.7	7.8

Source: Quéré et al, (2003), p 23, based on OECD data, derived from the European Commission (*Inventory of Public Biotechnology R&D Programmes in Europe*, 2000), Eurostat, Statistics Canada, and national sources, OECD Compendium, 3-4 May 2001, p. 37.
Exchange rates based on OECD annual average for 2000.
*National estimates.
**Federal outlays represent the amounts of cheques issued and cash payments made during a given period.

The three largest spenders in biotech R&D in 1997 are Germany, the UK and France in the order although some smaller countries like Belgium, Canada or Finland spend a higher proportion of their GERD on biotechnology. As we previously pointed out, the EU is very heterogeneous, as shown by the spread of biotechnology R&D in different countries: the percentage of R&D allocated to biotechnology ranges from 13.8% of total R&D in Belgium to 0.4% in Italy. In spite of this very skewed distribution of biotechnology R&D in the EU the total EU effort is dwarfed by that of the USA. The NIH budget approved by congress for the year 2002 was 23.4 billion $, to be compared to a total EU public R&D spending of 2.3 billion Euros for the four year period 2002-2006 (Quéré et al, 2003, p. 24).

Table 2.3. Financing of biotechnology. A comparison of the USA and of Europe by category of investor. Source: France Biotech, December (2004)

Type	Total million $	USA	Europe	Europe as % of total
Venture capital	3712	2740	790	21%
IPO	506	483	0	0%
Follow-on	3812	2949	407	11%
Other	11261	9257	1278	11%
Total	19290	15429	2493	13%

By taking into account total investment in biotechnology for the year 2003, the comparison does not become more positive for the EU. In this year the USA invested 17,922 million $, or 92.3% of the total world investment of 19,290 million $ for the whole world. During the same year the EU invested in biotechnology 2,493 million $, or 13% of the USA investment (Source: Biocentury, as cited in France Biotech 2004, p. 16), (Table 2.3).

Table 2.4. World distribution of investment in biotechnology. Source: France Biotech, December (2004)

$ million	world total	US + Europe	US	Europe	Europe as % US
2003	19290	17922	15429	2493	13%
2002	11455	10629	9567	1061	10%
2001	16213	14854	12480	2374	16%
2000	37417	35733	30047	5686	16%

Although further information could allow us to understand the situation in a more subtle or specific way, one conclusion is already abundantly clear: the level of resources allocated to biotechnology both in the public and in the private spheres in the EU is inferior to the corresponding level in the USA by an order of magnitude. In spite of the systemic nature of biotechnology and of innovation systems, it is very doubtful that any economic and innovation system can become competitive by allocating such a relatively low amount of resources.

2.1.5) FIRMS AND INDUSTRIAL ORGANISATION.

The emergence of biotechnology has been accompanied by two very important phenomena: (i) the increasingly important role played by small start-ups created to develop and exploit new knowledge, and (ii) innovation networks, a pattern of inter-firm collaboration to develop innovations, usually involving large diversified firms (LDFs), small new technology start-ups (NTFs), which in the case of biotechnology were called dedicated biotechnology firms (DBFs), and public research institutes (PRIs), a term which includes both universities and non teaching research institutions. This pattern of evolution is by no means unique to biotechnology. Both NTFs and innovation networks can be found in many different fields and industrial sectors, although they are particularly frequent in high technology sectors, typically in ICT and new materials (Freeman, 1991; Hagedoorn, 1993, 1995; Powell et al, 1996). Both of these phenomena are important due to their novelty: until the 1980s economists were generally convinced that the only efficient and stable forms of industrial organisation were the markets and large, vertically integrated firms. Any other form was considered to be only

transient at best. Even when innovation networks started to appear and to grow in numbers many economists thought that they would have only a temporary existence linked to the adaptation to a new paradigm. According to this view industrial organisation would have reverted to markets and hierarchical organisations once this adjustment process had been complete. However, the number of innovation networks kept growing since their inception in the early 1980s (Quéré et al, 2003; Catherine, 2005).

The causes of the emergence of innovation networks are likely to be multiple. A general process of vertical disintegration is under way of which innovation networks could be a component (Langlois, 2003). Yet the factors leading to vertical disintegration are not necessarily the same in different sectors. The reasons for which large firms externalise activities include both efficiency and capability: in the former case an external contractor would perform more efficiently activities that a large firm would have the capability to carry out internally; in the latter case an incumbent large firm would be forced to contract out a given activity because it would not have the capability to carry it out internally. Innovation networks in biotechnology are much more likely to be of the latter than of the former type. Incumbent LDFs in all the sectors that could be affected by biotechnology did not have the absorption capacity required to learn the new biotechnology and were forced to enter into alliances with DBFs. In other words, one of the main factors determining the emergence of innovation networks in biotechnology and in other high technology sectors was the dynamics of creation of new knowledge, involving radical and rapid change (Pyka, Saviotti, 2005).

Since their emergence innovation networks underwent some changes. First, while in the early days most alliances were between LDFs and DBFs, possibly including PRIs, alliances between different DBFs became increasingly frequent during the 1990s. Furthermore, the content of alliances changed in a systematic way. Starting from the late 1970s we can identify two generations of biotechnology alliances, the first based on recombinant DNA and monoclonal antibodies and lasting until the mid 1980s, the second starting from the late 1980s and based on genomics (Catherine, 2005). Within each of these generations the number of alliances grows initially in the early phases of the new technology, reaches a maximum and then falls gradually to zero as the technology matures. Furthermore, for each of these generations the type of alliances changes from R&D based in the early phases to marketing based alliances in the declining phases. We can then describe this phenomenon as constituting a life cycle of innovation networks (Catherine, 2005). A similar transition in innovation networks in biotechnology was found by Orsenigo et al (2001). In their case as well the transition was due to the interplay of the dynamics of new knowledge and of the division of labour that such dynamics generated. Older firms working at a higher level of generality formed alliances with successive generations of entrants who typically embodied increasingly specific hypotheses and techniques. Furthermore, in the post-genome era many alliances are based on “technological platforms”, combinations of firms and scientific institutions that bring together complementary competences to develop knowledge and offer services in the targeted area under investigation (Queré, 2004). Thus, although we can be confident that innovation networks are likely to play an important role in the foreseeable future, their mechanisms of operation are not necessarily going to remain constant.

The comparative evolution of biotechnology in the USA and in the EU can be followed by the rate of creation of DBFs. The phenomenon started earlier in the USA and by the mid 1990s the EU was considerably behind the USA in number of DBFs and in their relative capabilities (Saviotti et al, 1998). During the second half of the 1990s the rate of creation of DBFs accelerated considerably in the EU and by the year 2000 the number of EU DBFs had

overtaken that in the USA (Quéré et al, 2003, p. 21; France Biotech 2004 p. 19). However, the capabilities of EU DBFs were still inferior to those of their USA counterparts, as shown for example by their relative sizes, capitalisation and share of world patents (France Biotech, 2004, p. 19).

2.1.6) SECTORAL DEVELOPMENTS.

As it was previously pointed out, biotechnology can affect a large number of industrial sectors. Two important points have to be borne in mind in this sense: first, the classification of industrial sectors used for statistical purposes is ambiguous and can complicate the analysis of the influence of biotechnology on industrial dynamics; second, the boundaries of industrial sectors are not fixed and biotechnology can exert a profound influence in redefining them, that is, in inducing structural change. The sectors found in industrial statistics are implicitly defined either on the basis of their output (i.e. the products or services they supply) or of the activities they carry out. The automobile industry and the chemical industry are examples of the first and of the second type of definition respectively. Such ambiguity is found in the frequent attribution of DBFs to the biotechnology sector and of incumbent LDFs to the pharmaceutical or agrochemical sectors. We can expect this ambiguity to affect our interpretation of industrial dynamics in the sectors affected by biotechnology. An interesting example involving both of the above points is given by the concept of the life science company. Such a concept emerged during the 1990s, as a firm that could supply products in very different and heterogeneous markets using a common knowledge base linked to biotechnology (Quéré et al., 2003 pp. 40-42). The same firm was expected to profitably supply pharmaceutical products, new plant varieties, new types of food etc. by means of modern biotechnology. The concept of the life science company was the basis of the main strategy pursued by most firms interested in biotechnology during the 1990s although it has now been abandoned by all of them. The reasons for this sudden change of strategy lay more in changes in the selection environment, in particular those linked to the different acceptance of pharmaceutical compounds as opposed to new plant varieties or new types of food, than in intrinsic limitations of the strategy itself. As a consequence of this shift most firms separated their pharmaceutical and agrochemical divisions, in some cases selling off the latter. Thus, although biotechnology still constitutes a horizontal knowledge base that firms in all these sectors can use, firm boundaries are sometimes defined by traditional industrial sectors, especially in the case of LDFs, and in other cases by the activities carried out, as in the case of the so called biotech firms, which are invariably DBFs. Problems of interpretation can arise because some biotech firms work predominantly for the pharmaceutical sector and others for the agrochemical sector. There is no perfect way of compensating these ambiguities in industrial classification, but their potential impact on the interpretation of industrial dynamics must be borne in mind.

Starting from the beginning of modern biotechnology the pharmaceutical sector received most of the investment in the development of innovations. Until the 1970s this sector had been dominated by large multinational firms producing a wide range of drugs. It was already one of the most R&D intensive sectors, but its knowledge base was constituted mostly by organic chemistry. The dominant strategy of pharmaceutical firms was then, and still remains, the so called blockbuster strategy. Blockbusters are drugs capable of curing very common diseases present in a large percentage of the population. Blockbusters were produced in very large quantities and gave the respective firms high profits during the period in which they were covered by patents. At the time the new biotechnology emerged the discovery of new blockbuster candidates was becoming progressively more difficult. Only some pharmaceutical

firms realised immediately the potential of the new biotechnology and even those firms which did could not learn quickly the new biotechnology. This lack of absorption capacity by incumbent pharmaceutical firms was one of the main causes underlying the creation of DBFs. It took incumbent pharmaceutical firms, or Big Pharmas, as they are often called in jargon, the whole of the 1980s to learn the new biotechnology (Grabowsky, Vernon, 1994). As a consequence of the complementarity between Big Pharmas and DBFs, the former having the complementary assets (patenting, testing, marketing, sales etc) and the latter the core scientific and technological competencies, the pharmaceutical sector has since the 1980s been dominated by alliances between these two types of firms.

After the collapse of the life science strategy agrochemical firms became completely separated from pharmaceutical ones. Syngenta was created by the merger of the agrochemical divisions of Novartis and Astra Zeneca, Aventis sold its Crop Science division to Bayer, and even Monsanto, arguably the most successful agrochemical firm in making the transition to biotechnology, became a division of Pharmacia first and of Pfizer later. In spite of these difficulties agrochemical firms are surviving and developing a new strategy, based on the complementarity of the insecticides and herbicides and of the new plant varieties produced by the same firm.

It is possible to classify biotechnology applications into three fields, red or health related, green or agriculture related, and white or industrial biotechnology (www.europabio.org). As previously pointed out these classifications are somewhat inaccurate. Furthermore, the higher the level of aggregation at which a classification is used, the more heterogeneity there will be in each category. For example, green biotechnology includes both agriculture and applications to the food industry. The dynamics of these two sub-sectors of green biotechnology have some similarities but also some differences. The food industry shares competencies and processes both with agriculture and with white or industrial biotechnology. Likewise, the socio-economic barriers to the acceptance of food technology are not identical to those of agriculture. These problems are common to all types of industrial classification. Accordingly when treating one of these sectors the sources of heterogeneity and the implications for different sub-sectors will be indicated.

White biotechnology encompasses applications to many differ sectors and even to the environment. It is possible to conceive a bio-based economy, in which greater efficiency is combined with a reduced environmental impact. This is due to the possibility to recycle by products into bio-resources, which constitute the input for the same or for other industrial processes. We can easily realise that the scope of the bio-based economy is immense. Amongst the products which can be produced in this way there are: fine chemicals, bulk chemicals, bio-plastics, solvents, bio-pesticides, enzymes, bio-fuels (OECD, 2001; UK Task force; 2004; Sotaert, Vandamme, 2004; Guyot, 2005). Clearly, the range of industrial activities that can be switched to the bio-mode is extremely wide, greatly exceeding the scope of the activities which have so far adopted biotechnology. Most of the industries that can be affected by the transition to the bio mode are very important components of the EU industrial system.

In all these sectors the EU has very considerable capabilities inherited from the past. However, the future success of all these pharmaceutical, agrochemical and industrial firms depends crucially on the possibility to exploit the new biotechnology. Although knowledge can in principle flow quite freely across national borders, its adoption and incorporation into new industrial processes is affected by a host of factors, including scientific capabilities,

complementary institutions and a receptive selection environment. All these factors will be discussed in the next section.

3) GLOBAL PERSPECTIVE.

The introduction and diffusion of any new and pervasive technology systematically involves benefits and risks. Institutions are required to make sure that risks are reduced to an acceptable level. For this as well as for other reasons technologies do not evolve in a vacuum but their development path is characterised by the co-evolution of technologies and institutions. Furthermore, for analytical purposes it is possible to separate two types of processes within the development of a given technology. By using a biological metaphor we can call these two stages variation and selection. Variation can be defined as the set of all activities that create new ideas or potential new technologies by means of scientific discoveries, technical inventions etc.. The most important source of variation is today R&D. Selection can be defined as the set of interactions and activities either accepting or rejecting new potential technologies, products etc., thus reducing drastically the number of technologies actually used with respect to those created by variation. These two processes are closely related to those of sponsorship and control, the former being the set of processes aimed at creating new activities and the latter the set of rules and institutions preventing any unwanted consequences of new technologies. It must be borne in mind that while these two processes can usefully be separated conceptually they are hardly ever found alone. The extent and severity of selection can deeply affect variation. Thus, what we will inevitably find in any real life situation is an interacting combination of the two.

Rules, or regulations, need to be created every time new pervasive technologies are created to define adequately both processes of variation and selection. Crucial to the regulatory process is the balance between the benefits and the risks of a new technology. At the beginning of their life pervasive technologies are always surrounded by a very high uncertainty. Nobody can predict accurately the development path of any such technology. As a consequence the benefits and risks of a pervasive new technology are usually based on expectations rather than on objective evidence, and this is especially true in the early phases of the life of the technology. This means that national cultures and existing institutions can be as powerful determinants of the development of a new technology as scientific and technological progress. This accentuates the path dependence that can already be present in a technology due to increasing returns to adoption (Arthur, 1989).

In this section the progress and diffusion of particular fields of biotechnology will be reviewed and particular attention will be paid to institutional and cultural factors that could affect the diffusion of this technology.

3.1) FIELDS OF APPLICATION OF BIOTECHNOLOGY

3.1.1) PHARMACEUTICALS

The pharmaceutical industry has been the first sector to make use of the new biotechnology and still remains its most important user. The adoption of the new biotechnology was expected to induce the transition from random to rational drug discovery (Quéré et al, 2003) and thus to help solve the problem of the increasing cost of creating new drugs. From the viewpoint of incumbent pharmaceutical LDFs the transition to rational drug discovery was expected to save the blockbuster strategy. This strategy, which has been the dominant one for big Pharmas in the last fifty years, is based on the discovery of drugs which can cure very

common and widespread diseases and be sold in very large quantities. Such drugs were protected by patents and in the past they gave large and persistent profits to the firms owning the patents. Yet when the new biotechnology emerged it was becoming increasingly difficult to create new blockbusters, as shown by the increasing R&D budgets of pharmaceutical LDFs. For these firms the expectation of rational drug discovery held the promise of reducing the cost of creation of new blockbusters. This entailed for incumbent pharmaceutical LDFs a considerable change of strategy: while before they had always relied on their own internal R&D laboratories they were now forced to enter into alliances with DBFs. It may still be too early to say whether this strategy has worked, but pharmaceutical LDFs seem to find themselves in a state of crisis at the moment (Economist, 2005). This may not be due purely and simply to the failure of their drug discovery strategy, but to a combination of several factors. However, it is important to discuss this situation given the potential impact it can have on the future development of biotechnology.

The situation of crisis referred to in the previous paragraph can be described as follows. First, the rate of creation of new potential blockbusters so far does not seem to correspond to expectations, although it is not clear whether these difficulties are a permanent obstacle or a temporary bottleneck towards a more prosperous and sustainable future for the industry. A growing number of biotechnology based new candidate drugs are entering the approval pipeline, while some authors (Nightingale, Martin, 2004) maintain that the promises of biotechnology have been exaggerated, that it can only provide a constant stream of incremental innovations and that it cannot cure the ills of the pharmaceutical industry. Considerably diverging opinions exist about this subject (see for example Kean, 2004), but it is not clear whether these difficulties are a transition problem or whether they can sound the death knell for the blockbuster strategy. According to the Economist (2005), while the number of new drugs approved by the FDA declined to 18 in 2002 it rose to 34 in 2004. It is thus not impossible for the number of candidate new drugs to increase as a result of the new biotechnology, but a more fundamental obstacle may be on the way of the continuation of the blockbuster strategy. With the emergence of genomics, and in particular of pharmacogenomics, the possibility to create ‘individual’ drugs became conceivable. In fact, it turns out that blockbusters created to cure every patient with a given type of disease are often unsuitable for a very large percentage of the patients affected by the disease. However, if pharmacogenomics can in principle improve general health, what will it do to scale economies and profits? Will incumbent pharmaceutical LDFs be able to exploit pharmacogenomics or will nimbler DBFs outcompete them?

These uncertainties inherent in the development of biotechnology are compounded by a number of changes taking place in the selection environment. The explosion of health care budgets in developed countries creates cost pressures, with most governments trying to reduce all health related costs, including the cost of drugs. Furthermore, drug firms are increasingly being accused of putting profits before public health, of benefiting from public largesse, either using the results of publicly funded R&D or by tax breaks on their own R&D, without rewarding adequately the public. A further source of strategic uncertainty is constituted by the growing importance of generics, favoured by many governments in order to reduce health care budgets. Generics are important drugs whose patents have expired. Some firms have chosen to exploit generics, but it is only very recently that a large pharmaceutical LDF, Novartis, acquired a generics firm to become the largest world producer of generics. These combined uncertainties will very likely lead to changes in the pharmaceutical industry, although which ones it is not yet clear. The following are examples of possible development paths.

- Some DBFs might grow either internally or by merger and acquisition (M&A) while some of the existing LDFs might disappear.
- A more segmented structure of the industry might emerge, in which LDFs will be accompanied by viable specialist producers and by producers of generics.
- In order to remain LDFs pharmaceutical firms will need to combine the creation of new drugs and the production of generics.

In pharmaceuticals as in other sectors biotechnology is both a source of uncertainty by creating new possibilities and redefining boundaries, and it is itself affected by a series of socio-economic factors that will affect its future development. Different regulatory regimes, with their different emphasis on drug prices and on the ease of introduction of new pharmaceutical compounds, will determine differential rates of growth of pharmaceutical firms and their location decisions.

3.1.2) AGRICULTURE AND FOOD.

These two sectors are treated together because they are affected by similar factors. However, some differences between them and the implications for industrial dynamics and policy will indicated. In a sense the situation here is much more polarised than in the previous case. The first adoption of GM plant varieties took place in the USA 1996 with the planting of GM Soya. In the nine years since the beginning seventeen (17) countries have sown GM seeds. The global area cultivated with GM varieties has grown at double digit rates ever since. In 2004 the GM cultivated area grew by 20% with respect to the previous year. The number of farmers growing GM crops passed from 7 million in 2003 to 8.25 million in 2004. Amongst the users 90% of the beneficiaries were resource poor farmers from developing countries. There are now mega countries, defined as cultivating more than 50,000 hectares of GM varieties, 9 of which are less developed countries (LDCs) and 5 developed countries. The total accumulated land area cultivated with GM crops is now 385 million hectares, equivalent to 40% of the total land area of the USA or China (all the previous information is drawn from James, 2004). By looking only at these figures it would be easy to conclude that the innovation(s) considered have been an outstanding success. In any case, one would tend to exclude the possibility that the early adopters have been persuaded against their will or their interest to adopt these innovations. Yet, while the rate of growth of the cultivated area has been very high in the adopting countries, many other countries, and most notably the EU, refuse steadfastly to allow the cultivation of GM plants and heavily discourage their use in the production of food. The reasons for this extreme divergence of opinion lie in the perceived health and environmental risks that some people attach to these applications of biotechnology, although economic risks may be present as well. Some of the perceived risks are country dependent while others are general.

The uncertainty surrounding a new technology is likely to be higher in the very early phases of the technology life cycle. Nine years after the first commercial adoption of GM crops some evidence begins to be available in a systematic way. First, very few crops have so far been planted in very large acreages. HT (herbicide resistant) Soya has been the first GM crop to be planted and in 2003 accounted for 61% of the area under GM crops. Bt (bacterium tolerant) maize accounts for 13% of the cultivated area while other GM varieties of GM, cotton and canola account each for between 2% and 5% of the area under cultivation (James, 2004). A number of studies have been carried out about the economic benefits of these GM crops (Carpenter, Giannessi, 1999, 2001; Fernandez-Cornejo et al , 2002; Qaim de Janvry, 2003;

Thirtle et al, 2003; Falck-Zepeda et al, 2000). The benefits analysed were possible cost reductions, higher value of the seeds etc. Most of the studies show some advantages from the use of GM varieties both for farmers and for consumers, but these advantages are never so high or so independent of other circumstances to justify the extremely high rates of adoption in some countries. It has to be stressed that the advantages inherent in the adoption of GM varieties would be reduced by the coexistence between GM and conventional crops, due for example to the requirement of buffer zones between them. The results of these studies can explain even less the differences between adopting and non adopting countries. It is not impossible that given the relative youth of this technology not all the relevant variables have been taken into account. Other studies approach the problem from a different angle. For example, Harhoff, Regibeau and Rockett (2001) studied the danger of growing industrial concentration potentially following from the introduction of GM varieties. They found that while the concentration of patents granted on GM crops and food is not as high as to justify antitrust attention, industrial concentration in approved products or in approved and commercialised products is significantly higher. In general, they found that downstream concentration tends to be higher than upstream concentration. Furthermore, they found that the observed integration of seed and agro-chemical manufacturers may bias introduction in undesired directions, for example developing traits which are more useful to producers than to users. The related practice of tie-in contracts between seeds and complementary products, such as herbicides, may have an exclusionary motive. For all these reasons recent developments of biotechnology in these fields warrant anti-trust scrutiny. Thus, in addition to health and environmental risks, the adoption of GM plant varieties may lead to economic costs.

Two other types of consideration are relevant here. First, tests have been carried out to ascertain the risks inherent in the commercial use of GM varieties. The most extended such test has been carried out in the UK ending in 2003. The study compared the results obtained for three conventional varieties and for their herbicide tolerant GM counterparts, GMHT rape, GMHT beet and GMHT maize (GM Science Review Panel, 2004). The use of GMHT varieties generally improved weed control, but had a variable influence on the environment depending on the crop considered. Thus, weeds and other species depending on them, such birds and invertebrates, were more abundant in conventional rape and beet varieties than in the GMHT ones, but they were also more abundant in GMHT maize than in the conventional maize variety. The panel concluded that in the first study, published in 2003, they had found no scientific case ruling out all GM crops and their products, but that they did not give them blanket approval. They emphasised that genetic modification is not a single homogeneous technology and that its applications need to be considered on a case-by-case basis (p. 6). Second, although GM breeding techniques are useful in some situations they are not necessarily the best solution under all circumstances. GM varieties have been developed for crops and conditions of utilisation appropriate to developed countries and they may not be as useful in LDCs. By reducing the allocation of resources to conventional plant breeding, research on GM varieties can impoverish the pool of competencies available to study conventional crop breeding techniques relevant to LDCs. Conventional plant breeding techniques can improve several traits at once while so far GM breeding techniques have improved one trait at a time. Thus, the best solution might be a combination of conventional and GM crop breeding techniques rather than an outright substitution of the former by the latter (Knight, 2003).

In summary, the present diffusion of GM crops and the results obtained in various studies about the benefits and risks involved in their use provide contrasting evidence of an extreme

polarisation between adopters and non adopters accompanied by much more mixed results showing that benefits can be achieved, but that they depend on the crops chosen and on their mode of utilisation. No blanket condemnation of all GM crops is possible but they have to be evaluated on an individual basis. GM and conventional crops do not need to be rivals in all circumstances, but fruitful combinations may exist. These results, which neither absolve not condemn agricultural biotechnology, are not wholly unexpected: it was not always the case that the pervasive new technologies of the past demonstrated immediately their superiority as they were created. Further developments may be required over a period of time to bring out all their potential.

Food technology is affected by very similar socio-economic barriers to adoption. The use of new plant varieties for food production encounters great opposition by the public everywhere but even more so in the EU. However, the applications of biotechnology to food processing are heterogeneous and include (Menrad et al, 1999; Jeffcoat, 1999):

i) The production of novel ingredients
ii) Modified process plant to reduce environmental burden, to improve efficiency and quality
iii) The production of new diagnostic and analytical tools

It is quite likely for public opposition to be greater for the incorporation of GMOs in final foods, affecting (i), than for the use of modern biotechnology in other applications, such as the production of new diagnostic and analytical tools. Furthermore, the competencies and processes used in food biotechnology are more similar to those used in industrial biotechnology than in agriculture. The EU has a large and very active food industry. The adoption of modern biotechnology is going to be of fundamental importance for the future development of this industry and for its continuing competitiveness at an international level. Although the barriers to the adoption of modern biotechnology are likely to be less important for the whole of this industry than for agriculture, they might nevertheless constitute a serious obstacle for its future development.

3.1.3) INDUSTRIAL BIOTECHNOLOGY

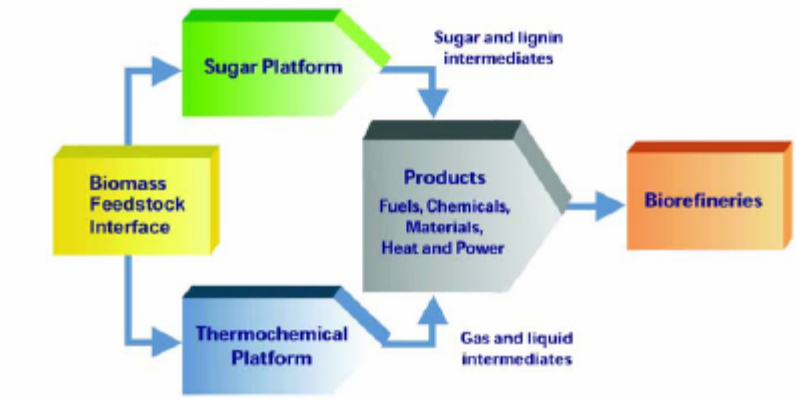
Biotechnology based activities are now often classified as health related, agriculture related, and industrial biotechnologies. The last category is very wide and encompasses many industrial sectors, including the chemical sector, but also food, the environment, energy etc. This is a further example of the capacity of science to induce structural change. Industrial sectors are classification devices. Their boundaries are never perfectly defined and they shift in the course of time. By defining a category of industrial biotechnology which groups together many heterogeneous sectors, as defined according to existing classifications, we emphasize the substantial unity existing amongst these sectors based on the commonality of knowledge bases, of inputs and of procedures that they use. What is at stake here is not a series of unconnected innovations but a general shift away from processes using non renewable resources towards those using biological renewable resources. Not by chance we can talk about the bio-economy, as an economy dominated by the use of biological resources and processes (OECD, 2001; UK Industrial Biotechnology task force, 2004; Sotaert, Vandamme, 2004; Biomass Program USA , 2005). A very considerable stress is placed by all authors and initiatives in this field on sustainability. In the bio-economy it becomes in principle possible to combine a greater economic efficiency with a reduced environmental impact. Given the growing acceptance of the impossibility to continue with the present polluting and wasteful industrial practices it seems clear that such a course will have to be

followed by all industrialised nations. Yet of all the fields surveyed this is the one where the adoption of biotechnology has been the slowest. The awareness of its potential has increased recently, for example with the Economist (2003) stating that 'at the moment biotech's main uses are in medicine and agriculture. But its biggest long term impact may be industrial'.

Example.
Metabolic engineering is a technique which involves genetically engineering a micro-organism to contain all the enzyme steps for a series of reactions leading to a particular product and then uses the cell metabolism to drive the reaction. In effect the cell then becomes a highly efficient mini-reactor for synthesising that product. Hoffman La-Roche (Germany) now uses a metabolically engineered micro-organism to produce Vitamin B_2. This has enabled the company to reduce a six-step chemical process to a one step. As a result, use of non renewable raw materials has decreased by 75%, emissions of volatile organic compounds to air and water have decreased by 50% and operating costs have decreased by 50%.
Source: OECD, (2001) The Application of Biotechnology to Industrial Sustainability – A Primer, Paris, p. 12.

The scope of industrial biotechnology is nicely summarised by the five core R&D areas of the USA Biomass programme (Biomass Program USA, 2005). All the possible processes using biomass to produce energy and finished products are divided into five steps (Fig. 1):

Fig. 1 Biomass Program five core R&D areas.



The biomass feedstock interface provides the necessary large supply of low-cost lignocellulosic biomass to biorefineries that produce fuels, combined power and heat, chemicals and other materials. The sugar platform involves the breakdown of biomass into raw component sugars using a range of chemical and biological processes. The Thermochemical platform emphasis is on converting biomass or biomass-derived biorefinery residues to intermediates such as pyrolisis oil and syngas. These intermediates can be used directly as raw fuels or products, or may be further refined to produce fuels and products that are interchangeable with existing commercial commodities such as oils, gasoline diesel, synthetic natural gas, and high-purity hydrogen. Energy, sugar and lignin intermediates are then converted into final products in integrated biorefineries, which use biomass to make a range of fuels, combined heat and power, chemicals and materials to maximise the value of biomass (www.eere.energy.gov/biomass).

As usual using a very aggregate classification hides many specificities and heterogeneities. For example, the scientific instruments sub-sector of biotechnology is of importance both commercially and an infrastructure for the development of biotechnology. However, its role is not clearly indicated in the previous discussion. A study of this sub-set of biotechnology (Reiss et al, 2002) shows that the EU has biotechnology instruments industry considerably smaller than that of the USA and mostly concentrated in Germany and the UK. Furthermore, important applications to many traditional sectors (textiles, paper, leather, food etc.) could greatly benefit from process-integrated biotechnologies (Wolf et al, 2002).

In summary, although for the time being the collection of sectors that can be found under the label of industrial biotechnology have been less affected by modern biotechnology than either pharmaceuticals or agriculture, the scope of the possible applications there is immense. Biotechnology can not only raise the efficiency of many industrial processes but it can achieve that objective simultaneously with the reduction of the environmental impact of the same processes. Furthermore, by enabling countries to produce energy from renewable raw materials it can reduce the energy import dependence of countries, an objective which seems particularly worthwhile to pursue in countries poor in fossil fuels.

3.2) THE SELECTION ENVIRONMENT.

All pervasive new technologies involving a high degree of novelty and a wide impact on society distributed over a long period of time can be expected to have a life cycle, in which an emergence phase can be separated from other phases, such as growth and maturity. The precise nature of these phases is not important except for the fact that the emergence phase is likely to be ill structured relative to the following phases. The structure to be created consists of institutions which shape and direct the development of the new technology, a process which has already been referred to as the co-evolution technologies and institutions (Nelson, 1994). The required institutions can be of two types, those whose main goal is the sponsorship of the new technology, or the creation of variations about it, and those responsible for the selection, or control, of the risks inherent in the new technology. It is the latter type of institutions that will be discussed in this section.

Any new technology can develop only if there is a demand for its outputs, be they products or services. Usual theories of demand study the relationship between demand and variables such as price or quality. However, during the development of a pervasive new technology, and particularly so for biotechnology, the decision about how much and what type of a new product to buy is preceded by a prior decision about the acceptance of the new technology. This prior decision is often based on non economic criteria, for example on ethical, religious or political criteria. The predominance of economic criteria is likely to come back later on in the life cycle of the technology after the emergence phase is over. The previous considerations imply that the concept of ‘homo economicus’, capable of separating economic decisions from decisions in other spheres of human activities, is limited at best to the post emergence phases of the life cycle, when the new technology has been adequately institutionalised. During the emergence phase we can expect decisions about the new technology to be affected by a variety of factors, many of which can be non economic. Furthermore, non economic factors can be expected to predominate amongst those affecting the general public. The transition to the post emergence phases, leading to the full development of a given technology, can only be expected to occur after laws and other regulatory institutions defining the admissibility and the particular ways in which new goods or services can be produced, sold and consumed have been created.

Two types of problems can be expected to affect the emergence phase of a new technology: first, the construction of institutions based on ethical criteria; second, the construction of general capabilities in the new technology. An example of the first type of problem can be given by the laws regulating therapeutic cloning or research on stem cells. The second type of problem arises when in a given society there is a highly skewed distribution of knowledge about a given technology. This prevents a rational dialogue and constitutes a serious limitation of democracy. The previous statement does not imply that anyone having an adequate amount of knowledge about a technology will converge on the same opinion on whether and how to use that technology. It is clear that differences of opinion exist also within communities of scientists having similar types of knowledge, although there is some evidence that scientists' opinions about biotechnology can, be separated from that of the general public (Salvadori, et al. 2004). Rational dialogue involves communication and there can be no communication when the terms of the problem cannot be understood by one of the parties. A skewed distribution of knowledge arises necessarily as a result of the division of labour in society. The knowledge we receive in the education process becomes increasingly specialised and prevents us from being able to judge on subject matters outside our sphere of competencies. This represents an important challenge for all high income societies, a challenge which may not be overcome by giving people more degrees. It is more likely that open, lifelong learning processes can contribute to reduce the size of the problem. The importance of this barrier can be better understood by referring to the existing evidence that people are generally more prepared to accept a new technology if they are provided with transparent information about it and if they are involved in its implementation (Vilella-Vila et al, 2004).

The previous considerations could be applied to any new technology. However, a unique feature of biotechnology is the ability that it gives to change human nature, a feature which can be the source of both great hopes, for example to cure previously incurable diseases, and of great fears. The objective of medicine is to restore human nature to its healthy state by eliminating the pathological state determined by diseases. To give human beings extra powers so far unimaginable can cause all sorts of fears, both if the extra powers are effectively obtained and if accidents encountered in attempting to achieve the extra powers lead to abnormal outcomes. As Hottois (2004) points out, the objective of all philosophers reflecting in the past on the role of science was always to improve the environment of human beings, by providing more abundant resources of all types, but to leave human beings unchanged. With modern biotechnology for the first time mankind, the purposeful modifier of the external environment, becomes able to radically modify itself. Although this can in principle considerably enhance human power, it is also the source of great uncertainties. Biotechnology has probably been the field of science and technology in which the greatest number of university chairs and departments, and the greatest number of government ethical committees has been created. Some of the uncertainties and fears linked to the emergence of biotechnology are the result of incompatibilities with more traditional beliefs, of a religious or political nature. As a consequence of these considerations we can expect modern biotechnology in its emergence phase to raise even more fears and opposition than any other non biological technology.

As a consequence of the previous considerations we can conclude that:

- Appropriate institutions need to be constructed in the emergence phase of a new technology.

- In this early phase it is particularly important to involve the public in decision making about the future of biotechnology. Delegation will become easier once appropriate institutions have been constructed and are widely recognised.
- It is important that knowledge about the new technologies be diffused amongst the general public during this early emergence phase.

3.2.1) INTELLECTUAL PROPERTY RIGHTS.

Perhaps the most widely studied institutional aspect of modern biotechnology has been that of IPRs. Although the evolution of IPRs since the 1980s has been marked by a number of trends common to all technologies, biotechnology IPRs have some unique features which are worth pointing out. The most important changes which have occurred during this period can be summarised as:

- (i) A general strengthening of IPRs, initiated in the USA and intended to make the leaking out of American knowledge more difficult.
- (ii) An extension of the current and modified IPRs to all countries, including poor less developed countries (LDCs) by means of the TRIPS agreements, liked to international trade.

The first (i) of these trends involved the permission given by the Bayh-Dole act to USA universities and research institutions to apply for patents based on discoveries made by using federal funding. Together with other legislation this has triggered a considerable change in the behaviour of American universities. They have considerably increased their propensity to patent and many of them have developed technology transfer services (Nature Biotechnology, 2005b). Critics have complained that these institutional innovations are endangering the very same fabric of basic research, which was based on the free flow of knowledge between researchers (Mazzoleni, Nelson, 1998). Amongst the other extensions of IPRs introduced after the 1980s there have been those to software and to business methods, both of them still limited to the USA. In general most industrialised countries tended to follow the USA with minor differences about specific points. Strong opposition came instead from LDCs, and in particular from the poorest ones, which saw in the TRIPS agreements an attempt by developed countries (DCs) to unduly extend a monopoly they had on most technologies and to prevent LDCs from using these technologies even in fields crucial to their development, such as health. The TRIPS agreements contain special clauses that allow countries to supersede them for reasons of public health. In spite of these clauses the TRIPS are still the subject of considerable controversy (De Looze et al, 2001; Doern, 2000).

IPRs in biotechnology share with other technologies some general problems. For example, the quality of the patenting process is quite likely to have declined as a result of the rapidly increasing number of patent applications. Patent offices are flooded and tend to approve uncritically rather than to reject. In the USA a partial compensation may come from the Courts, but at a price. Also, IPRs in biotechnology have some specific features which are worth commenting. Although this may happen in other fields, it seems as if the traditional framework of patent law, based on the requirements of originality and industrial application, seems to have been silently abandoned and superseded by a much looser framework in which an invention can be patented. An example of this behaviour was given by the patenting of genetic sequences. This possibility has subsequently been removed, but the patents already awarded stand. The granting of patents on genetic sequences could be criticized on the grounds that (i) the decrypting of a genetic sequence was at best a scientific discovery without

any immediate prospect of industrial applications, and that (ii) with the automation of sequencing no originality was any longer involved in this activity. Furthermore, genes are not usual chemical molecules but they exert an extremely important function in biological organisms. Seen from the viewpoint of an economist patents on genes create a dangerous monopoly in what can be considered a basic infrastructure on biological knowledge, a situation which arises in other fields (e.g. transports, telecommunications) where it is carefully regulated (Henry et al (2003)). Furthermore, as a result of the previously mentioned patent inflation, sometimes many poorly demarcated patents are awarded for interconnected innovations, thus creating unnecessary barriers to any institution requiring access to a technology protected by such a web of patents.

To summarise the situation we could say that IPR system is undergoing a transition, but that such a transition has so far produced a system which is not fully adapted to its intended tasks. In the words of the authors of a recent report (Henry et al, 2003) 'The international IPR system is ill and we are trying to impose it upon LDCs'. This illness is particularly pronounced in biotechnology and we can expect that some reform of the system will be introduced in the near future.

4) EU ACTIVITES IN THE SECTOR AREA.

Biotechnology has been described in the previous sections as a pervasive technology having a very wide potential impact on many sectors of economic activity that will be distributed over along period of time. Clearly, a field like this is characterised by a high uncertainty, especially in its emergence phase. Investment in this phase cannot be based on the same criteria used for more mature technologies, but involves a higher degree of vision or expectation, rather than any extrapolation from past experience. Also, the time path of investment can be crucial: if barriers to entry grow during the process of maturation of a technology early entrants may accumulate an advantage that will make catching up very hard for any later imitators.

As we saw in section 1, biotechnology was initially a largely USA based fields, and that European developments started with a considerable delay. This section will connect the past performance of the EU biotechnology system with recent trends and will develop a more accurate comparison of the EU with the USA, bearing also in mind that other countries are emerging as significant players in the international arena. The comparison for the recent period is complicated by the presence of a situation which could be considered 'anomalous', namely the 1999 bursting of the stock exchange bubble, and the consequent slowdown in economic activity. This phenomenon largely exceeded the boundaries of biotechnology, although it could be argued that biotechnology was one of the factors that led to the creation of the bubble itself. The history of capitalist development has been marked by several waves of investment induced by the emergence of pervasive new technologies. Fairly systematically these waves went through a series of stages leading from the emergence phase to maturity in a period of about fifty years (Perez, 2002; Freeman, Louça, 2001). Biotechnology is likely to have affected the time profile of investment in the 1980s and 1990s, although ITC technologies are likely to have been more important. Whatever its precise role, we cannot expect the situation of biotechnology during the period 1999-2003 to be part of a smooth trend that will continue in future. On the contrary, we should interpret the period 1999-2003 as a crisis that provided a short term shock for biotechnology, as well as for other technologies, but that is unlikely to continue in future.

In order to develop the comparison systematically the biotech system will be divided into the following components:

- The research system
- The industrial system
- The Financial system
- The regulatory system
- The political system/policies.

Such components cannot be considered subsystems in a technical sense. We know that the interactions and feedbacks of the components affect the performance of the biotech system but we do not know exactly how. However, it is useful to use these subsystems as a classification device which makes any comparison more systematic.

4.1) THE RESEARCH SYSTEM.

As we have seen in section 1, the EU research system was performing relatively well in terms of life science publications (Quéré et al, 2003, pp. 27-30). What is not clear is the relative quality of those publications. The recent history of Nobel prizes in medicine and chemistry seems to indicate a distribution of publication quality which is more skewed towards the USA than the number of publications would imply. Quite apart from the relative levels of funding, one could have doubts about the health of the EU research system. It will become clearer later on that the EU is far more heterogeneous than the USA in this as well as in a number of other respects. A study of the contributions of the EU research system to biotechnology would certainly improve our understanding of the situation. Given the constraints of this report it is not possible to carry out such a study. However, a limited search of the organisations applying for and/or awarded patents by the European Patent Office (EPO) or by the USA Patent Office (USPTO) (see Appendix 1) shows that while some EU organisations play a very important role in this field, the vast majority of the organisations holding the majority of the patents belong to the USA.

4.2) THE INDUSTRIAL SYSTEM.

The industrial system relevant for biotechnology is made up by different types of firms distributed over several industrial sectors. Furthermore, the patterns of interaction of these firms amongst themselves and with public research institutions, financing institutions etc are crucial to understanding the workings of the system. Two types of firms are involved in biotechnology, large diversified firms (LDFs) and small dedicated biotechnology firms (DBFs). As previously pointed out, these two types of firms are not substitutes but have mostly collaborative relationships, based on complementary roles, in which DBFs supply mostly competencies about new developments in biotech and LDFs supply mainly the assets required to test and commercialise drugs, to produce products in large scale etc. There is evidence that these collaborative relationships, also called innovation networks (INs), in the course of time have gradually become less asymmetrical. Initially LDFs needed INs to learn what for them was a new and quite foreign technology, but they have now become more competent partners able to collaborate on a more symmetrical basis (E&Y, 2004, p. 19). In order to compare different countries we need to estimate the number, size and other relevant features of the various types of firms and of the INs involved in biotechnology.

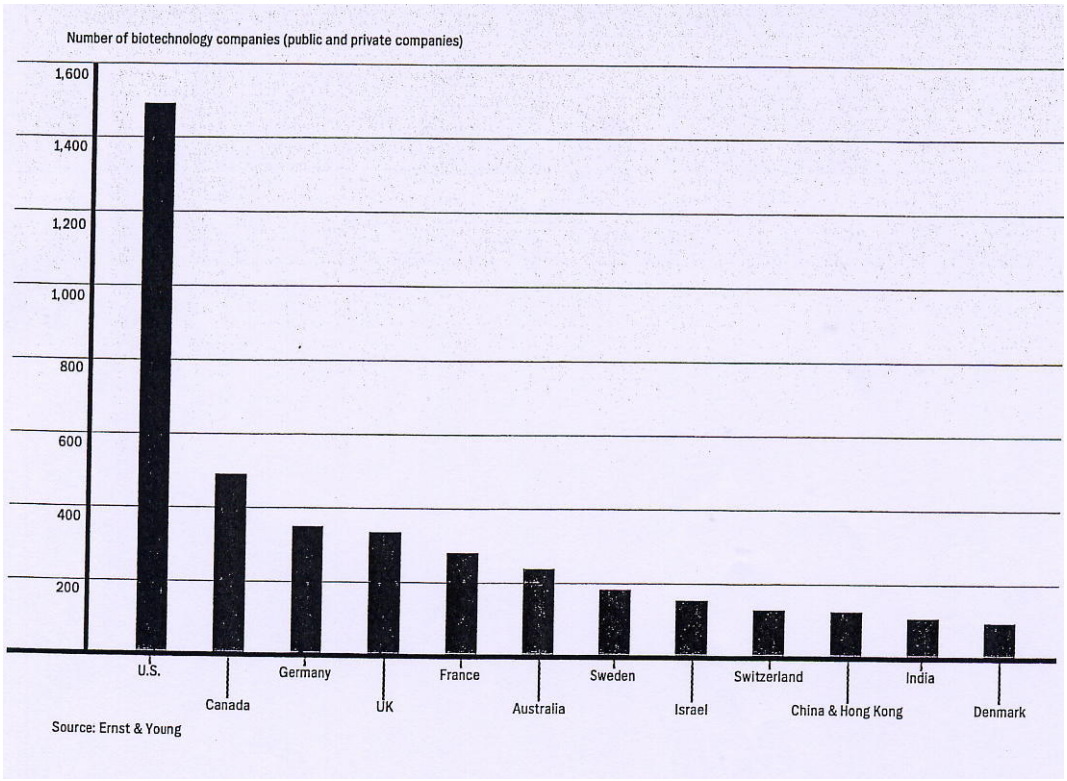


Fig. 2. Number of biotechnology companies by country.

Table 4.1. Global distribution of biotechnology companies in 2003. Source: Ernst & Young.

	Global	US	Europe	Canada	Asia-Pacific
Public company data					
Revenues ($m)	46,553	35,854	7,465	1,729	1,505
R&D expenses	18,636	13,567	4,233	620	217
Net loss ($m)	4,548	3,244	548	586	170
Number of employees	195,820	146,100	32,470	7,440	9,810
Number of companies					
Public companies	611	314	96	81	120
Private companies	3,860	1,159	1,765	389	547
Public and private companies	4,471	1,473	1,861	470	667

From Fig. 2 and Table 4.1. we can notice that the number of biotechnology companies in Europe is now greater than the one in the US. However, we can, also see that the number of public biotechnology companies in Europe is not only substantially smaller than that in the US, but also barely above the number of public companies in Canada and inferior to the number of public biotechnology companies in the Asia-Pacific region. Furthermore, European biotechnology companies are less mature because they have a lower number of products likely to be approved for sale in the foreseeable future. Considering the number of products European firms have in the various phases of clinical trials (Table 4.2) and based on a normal rate of attrition Ernst & Young (2004, p. 43) estimates that fifteen (15) new products are likely to be approved in Europe in the next few years as opposed to an expected rate of

approval of about twenty (20) per year in the US. Clearly, although the process of creation of biotechnology companies in Europe has started, the subsequent growth is still in a very immature phase. Given that the process of creation of biotechnology companies started later in Europe the problem could be simply one of delay. It takes time for firms to grow and one could interpret the situation by saying that European biotechnology firms are now where US firms were a number of years ago. Fazeli (2004) estimates that Europe is five to eight years behind the US.

The performance of European biotechnology firms has been worse than that of the US firms during the slowdown in economic activity following the 1999 stock market bubble. In 2003 the revenues of European biotechnology companies fell by 12%, their R&D expenditure fell by 17%, their employees fell by 5%, VC fund raising fell by 18%. In the same year activity seemed to pick up in both North America and the Asia-Pacific region. The US industry market capitalisation surged by nearly 60% and the Canadian industry by 56%. The market for initial public offerings increased considerably in 2004 (Ernst & Young, 2004; Nature Biotechnology, 2005, p. 164). In Asia-Pacific, which includes Japan, China, India and Australia, total revenues of 120 publicly traded companies increased by 9%, R&D spending increased by 10% and net losses increased by 52%. The total number of public and private biotech companies increased by 11%.

Table 4.2. European public companies: product pipeline 2003. Source Ernst & Young (2004)

Country	Preclinical	Phase 1	Phase II	Phase III	Total
UK	50	37	46	27	160
Switzerland	33	8	14	20	75
France	15	12	8	1	36
Sweden	13	7	8	1	29
Denmark	10	7	7	4	28
Germany	8	3	2	2	15
Norway	6	2	2	3	13
Israel	2	2	3	4	11
Ireland	2	2	2	5	11
The Netherlands	4	1	1	0	6
Finland	2	1	1	1	5
Belgium	2	0	1	0	3
Total	147	82	95	68	392

It would be easy to exaggerate the difficulties of European biotech firms, which might be linked to a particular economic conjuncture, but some problems are clear. First, European biotechnology had been catching up remarkably well during the 1990s, but seems to have lost momentum. Whether this is due to temporary or structural difficulties it is not clear. What is clear though is that, while the process of catching up with the US in the 1990s was very promising it was not complete. In the best of circumstances European biotechnology firms are still behind their US counterparts in size, capitalisation etc, that is in various indicators of maturity. Even assuming that the temporary difficulties experienced in the period 2000-2003 can be rapidly overcome, the process of catching up will have to re-start. Furthermore, even if one does not necessarily agree with Fivez (Ernst & Young, 2004b) who predicts that future competition for the US biotechnology industry will come more from South East Asia than

from Europe, it is clear that the foreseeable future of biotechnology will be characterised by an increasing competition due to the emergence of new players, mostly located in South East Asia.

4.2.1) OTHER SECTORS: AGRICULTURAL AND INDUSTRIAL BIOTECHNOLOGY.

The previous considerations about the situation of European biotechnology in a global context were related mainly to the applications of biotechnology. The relative situation of European biotechnology is different in other sectors. Following the classification previously adopted of biotechnology into three fields, health, agriculture and industry, we can examine in this section the differences arising in the agricultural and industrial fields. For what concerns the former, Europe is clearly in an uncomfortable position. It is home to some of the most important agrochemical firms in the world, but it is the geographical area in the world where the most substantial barriers to the adoption of biotechnology in agriculture have been raised. As we saw in section 2, the adoption of GM crops has proceeded extremely fast in some countries, perhaps surprisingly so given that the studies carried out son far do not seem to find evidence of clear cut advantages for all the GM crops used in actual cultivation rather than infield trials. Discounting the possibility that 8.25 million farmers in 17 countries have been forcibly convinced to adopt GM crops, and consequently assuming that the adopting farmers must find some advantage in GM crops, we can expect their diffusion to continue at a similar pace in the foreseeable future. Of course, this forecast is based on the assumption that in future no catastrophic accident due to the nature of agricultural biotechnology will take place. The development of biotechnology is likely to have path dependent features and this is by no means the only possible scenario (for other possible scenarios see World Business Council for Sustainable Development, 2000). Barring the possibility of such an accident the growing diffusion of agricultural biotechnology might soon provide experimental evidence that the risks involved in this technology are no more serious than those inherent in most technologies in present use, and that the advantages agricultural biotechnology can provide justify its adoption. Recent evidence seems to show that the number of countries willing to adopt agricultural biotechnology is increasing. In early March 2005 the lower house of congress in Brazil approved a law to legalise GM crops (CropBiotech Net, March 4, 2005). It is to be noticed that Brazil was already considered a GM using country, even if this practice was still legally forbidden there. Also, China will soon seek commercial planting of biotech rice (CropBiotech Net, March 4, 2005). The continued adoption of GM crops and the persistent lack of any serious shortcoming could convince a number of sceptical people that previous objections to agricultural biotechnology were excessive and could constitute a de facto transition to a world where such a technology is generally accepted. If this scenario were to occur Europe would find itself in an uncomfortable situation, having made a choice that severely limits the building up of competencies of both producers and users in agricultural biotechnology without any return to such a choice. To avoid this outcome it seems desirable for the EU to improve communications and to involve people in processes of decision making about biotechnology.

Industrial biotechnology is likely to raise less fundamental objections than applications to agriculture. In fact, there is a clear possibility that it can be perceived as making a positive contribution to the environment. As previously pointed out, the use of biological processes to replace others based on fossil fuels or on non renewable resources can in principle reduce both the quantity of inputs required and the wastes produced by a process. In other words, it can be an example of what environmental economists call the win-win theory, that is, the possibility to improve simultaneously efficiency and environmental impact. From a similar point of view, industrial biotechnology represents a systematic approach to a technology

which is clean by design, rather than an end-of-pipe technology whose environmental impact is improved by attaching a device to clean wastes at the end of the process. We can expect that the positive influence of industrial biotechnology on the environment will cause a more positive acceptance by the general public.

It has to be stressed that this category is very broadly defined and that it does not correspond to any existing industrial sector. For example, it includes the chemical industry, energy, environmental activities, mining, parts of the agrochemical and pharmaceutical industries. The lack of correspondence of industrial biotechnology with established industrial sectors is clearly shown by the concept of biorefinery. A biorefinery can be defined as an integrated cluster of bio-industries, using efficient technology to produce chemicals, biofuel, food ingredients, and power from biomass raw materials (Soetaert, Vandamme, 2004). This broad definition is further example of the capacity of science to induce structural change in industry. The previous considerations mean that the scope of industrial biotechnology is immense and may be greater than that of either health or agricultural biotechnology. However, it is clear that for the time being this is not the sector which has received the highest investment in biotechnology. The situation could be described by saying that the diffusion of biotechnology started in health related activities, it proceeded later and with considerable hesitations to agricultural biotechnology, and it is picking up in industrial biotechnology.

There are at least three types of reasons for which industrial biotechnology is very important for Europe: first, European industry has considerable strengths in the sectors closest to industrial biotechnology; second, Europe is very poor in fossil fuels and very dependent on imports; third, Europe is very densely populated and has a greater need than other countries to protect its environment. Let us take for example the chemical industry. World chemicals production in 2002 was estimated at 1921 billion Euros, of which the EU accounts for 27.5%. The EU is thus the region of the world having the highest share of chemical output (Soetaert, Vandamme, 2004). For what concerns energy production, a IIASA scenario predicts that biomass will account for a rapidly growing share of total energy production during the XXIst century. For the time being Europe is only the fifth world producer of bio-ethanol and of other bio-fuels, behind Brazil, the US, China and India (Soetaert, Vandamme, 2004).

Existing reports on industrial biotechnology (UK Industrial Biotechnology Task Force, 2004; Soetaert, Vandamme, 2004) recommend measures such as enhanced support for R&D, fiscal support measures such as de-taxation of bio-energy, promotion of knowledge and awareness of industrial biotechnology, and the development of a European policy in this field. However, it has to be borne in mind that this is new technology affected by a high uncertainty. The criteria used to construct policies have to be different from those of a mature technology. The 2004 report of the UK industrial biotechnology includes amongst its recommendations to focus first on improving the analysis of the technology and to identify companies capable of exploiting this technology. Although the desirability of using industrial biotechnology may be very high for the EU the introduction of process-integrated biotechnology cannot be expected to occur rapidly. Most companies potentially affected do not invest in R&D, lack biotech competences and are reluctant to make large investments in new process plant when the existing plant still works well (Wolff et al., 2002). The adoption of biological processes may require incentives, demonstration projects or education of consulting engineers who advise on installing new plant.

In summary, we can consider industrial biotechnology as a technology of immense scope, in which Europe has both considerable strengths and very strong inducements to participate.

However, this is a new technology that requires investment, vision, coordination and commitment. National and European initiatives are going to be required.

4.3) EUROPE, A HIGHLY HETEROGENEOUS CONTINENT.

The previous section treated the EU as a unit, but, relative to the US, the EU is much more heterogeneous. A recent EU funded study called EPOHITE (Reiss et al, 2003) tried to compare the policies of 14 different European countries based on the inventory made in a previous study (Enzing et al , 1999-2000). The results of the EPOHITE project allowed the 14 countries considered to be grouped according to their performance into four clusters (Zechendorf, 2004):

- The best performing countries, Denmark, Sweden and Finland. These countries have a long tradition of industry-academia collaboration, invest adequately in biotechnology, recognise scientific excellence and have suitable measures to support industry.
- The second cluster is more heterogeneous. It includes countries which have adopted effective policies for biotechnology, but which have been less successful than the first group. Two of the countries in this group are large (the UK and Germany) and two are small (Belgium and the Netherlands). In general they have allocated relatively large budgets to biotechnology with generally positive results, but with some problems still persisting.
- The third cluster of intermediate performers includes Austria, France and Ireland.
- The fourth cluster includes the weak performers Greece, Italy, Portugal and Spain. These countries are weak in all relevant aspects of biotechnology, ranging from biotechnology budgets to policy instruments to support for commercialisation to regulations to the protection of intellectual property.

Some more detailed comments will be presented here about the three largest EU countries, the UK, Germany and France. The UK was an early starter and still remains number one. Today the UK has the largest and most profitable biotech companies in Europe (about 400 in 2003, employing over 18,700 people); the largest number of public companies (43); the strongest financial market; the best research environment; the second highest R&D funding; it accounts for 49 percent of products in the pipeline of European companies and for 62 percent of products in late-stage development. Few problems persist, like relatively unattractive careers in biotechnology, with a consequent brain drain to the USA, and the unpopularity of GM crops and food products. Germany started later than the UK but has been successful in creating new biotechnology firms: now it has the greatest number in the EU. However, it is still considerably behind the UK for what concerns firms size, number of public firms and products in late stage development. France invests adequately in R&D, and has managed to create a considerable number of SMEs and technology clusters with incubator facilities. In summary, one can consider the UK the leader who is slowing down in performance somewhat; Germany a competitor with strong capacities coming from behind and aiming for first place in Europe; France an underachiever not realising her full potential and continuously catching up (Zechendorf, 2004).

The considerable heterogeneity documented by the previously cited studies implies that there cannot be any policy common to the whole EU. For example, the objective of raising R&D intensity to 3% of GDP has already been achieved or could easily be achieved by some countries while it might be an impossible task for other countries. The only possible role for a high level coordinating agent could be to identify relevant subsets of the biotechnology

system and to create differential inducements for countries to improve their performance in the subsystems where they are weak. Great attention should be paid to the effect of policies on the heterogeneity of EU countries. Given that the best European performers are slightly behind the US, policies and support are required in all countries. However, if such policies were to increase the difference between top and bottom performers both industrial and social problems could follow. It is unlikely that the Lisbon objective of Making Europe the most competitive knowledge intensive economy in the world can be achieved by preserving the current levels and distribution of competencies in any of the technologies that are keys to the futures of Europe.

5) SWOT

Biotechnology is a pervasive technology likely to affect many sectors and to provide competitive advantage over a wide range of economic activities for a long time. In addition biotechnology can contribute to social value because it can positively influence employment and growth and because it is expected to contribute to the improvement of human health. Furthermore, by gradually replacing many electrical, mechanical or chemical processes based on the use of non renewable inputs it can simultaneously improve economic efficiency and reduce environmental impact. Lastly, given the potential impact of biomass on energy production, biotechnology can improve the energy mix in an energy poor region like the EU. Given the previous opportunities biotechnology is highly compatible with the highest level EU objectives and it is a true key technology for Europe.

Considerable threats to the EU ability to develop successfully biotechnology come from the competition of a number of countries. The USA pioneered biotechnology and still are the leading country. The EU started late and considerably improved its position but without catching up. Lagging behind might not only delay the potential growth effects of this technology but lead to growing entry barriers which might prevent a full process of catching up. In addition to the USA other emerging countries, such as Canada, Australia and Israel, are providing increasing competition.

The EU has considerable strengths in the pharmaceutical and chemical industries and it has a good R&D and higher education system. Furthermore, given its high population density and its relative poverty of energy sources it should have a strong inducement to develop biotechnology as quickly as possible.

Unfortunately these strengths are accompanied by weaknesses. Biotechnology is highly science dependent and the EU has R&D and higher education systems which include best practice institutions and very low performance institutions. This situation is reflected in the low R&D intensity and in the very large variance of R&D expenditures in EU countries. Furthermore, the EU Venture Capital industry, in spite of considerable improvements obtained in the 1990s, is still behind that of the USA. In addition to the previous ones, a distinctive EU weakness comes from the very strong opposition to the use of modern biotechnology in the agricultural and food sectors.

Although each of the strengths, weaknesses, opportunities and threats previously described could be declined in far greater detail, the ones chosen here are the main determinants of the EU ability to develop successfully biotechnology.

Table: SWOT of EU biotechnology

Opportunities	Employment creation Competitiveness Environmental improvement Health care Better energy mix	Strong pharmaceutical and chemical industries Strong R&D and higher education systems	Strengths
Threats	First comer advantage by USA Other emerging countries, increased competition.	Low average resource level in R&D & higher education systems Very uneven distribution of capabilities in EU Still weak venture capital industry Strong opposition to agricultural and food applications	Weaknesses

6) FORWARD LOOK

This section is obviously very speculative in the sense that no one can successfully predict the future and that this is particularly difficult in an emerging technology. What can normally be done is some form of extrapolation of existing trends combined with an analysis of the conditions that could make such trends stable or unstable. Such analysis will be carried out separately for different subsets of biotechnology.

6.1) SCIENTIFIC DEVELOPMENTS.

During the Human Genome Project one had often the impression that the final objective of biology was within sight. Although this may have been due to the enthusiasm and to the rhetorical skills of the authors of various articles, the situation was not new. A scientific objective passionately pursued as a final step turned out to be an intermediate, albeit very important step. By mapping the human genome the HG project showed clearly that in very few cases the expression of proteins by genes was due uniquely to the nature of the gene. The environmental conditions under which protein expression takes place are equally important. This growing awareness has given rise to a post-genomics era, in which specialities like functional genomics, proteomics etc. emerge. Thus, we are witnessing a process of differentiation and specialisation in biotechnology. This process of differentiation has at least three components: the one described above and consisting of the internal differentiation of the discipline, another one due to the specialisation by target application, and a third one due to the emergence of new disciplines from the merger of previously separate ones. An example of the second component in the health field would be specialisation by disease. An example of the third component would be the emergence of bioinformatics from the merger of biology and information technology. In a technology which is still in flux we cannot expect any partition of biotechnology into consensually agreed specialities and sub-disciplines to exist. Any classification will mix the internal, applications and merger criteria described above. For

example the classification given in Table 2.1 as well as the more extended list provided by Nature Biotechnology (2000) in a special issue about Industry Trends, include proteomics and pharmacogenomics together with bioinformatics, cardiovascular disease and cancer. Thus, while the process of differentiation is clearly occurring, its nature is not precisely defined. The only possible generalisations are the transition from genomics to post-genomics and the gradual transformation of biological research into an application area of physics and chemistry. The former trend involves the focusing of attention on levels of aggregation either lower (proteins) or higher (cells) than that of the gene, accompanied by a selective targeting of the relevant technological developments on particular diseases. Passing to a higher level of aggregation, for example moving from the gene to the cell, involves a more systemic approach. Cells are complex systems depending on the interactions of many components and variables. Furthermore, the human genome project clearly demonstrated that biological traits and organism behaviour rarely depend on a single gene and are considerably influenced by the environment in which genes operate. Also, it is quite clear that the future development of biotechnology will involve considerable interactions and strong commonalities with nanotechnology. It could be said that the initial programme of molecular biology and that of nanotechnology coincide, except for the fact that the latter has a wider field of application, including non biological systems. In both cases all macroscopic phenomena have to be explained by means of entities at the atomic or molecular level. However, an important change induced by nanotechnology consists of the possibility to produce molecular size 'machines', which could be used for the precise delivery of drugs only to the cells affected by a particular disease. Although nanotechnology is undoubtedly going to interact very closely with biotechnology, the analysis of this interaction is outside the scope of this report.

In spite of the uncertainties inherent in the present state of biotechnology some more specific predictions can be attempted. The fields covered in the main articles of Biotechnology International (BTi) appeared during 2004 are amongst the most important expected developments in biotechnology.

- Gene silencing, in particular by means of RNAi, is one of the most important techniques now widely used in functional genomics (Samarsky, Taylor, 2004).
- Antibody engineering, involving the humanisation of antibodies, seems to be considerably improving the performance of antibodies in the treatment of a series of diseases. Production of these improved antibodies, now very expensive, might in future benefit from the use of transgenic animals or plants (Lowe, 2004).
- Macromolecular structure determination, using both new and more established techniques, such as Sidec Electron Tomography and Protein Crystallography respectively, are very important techniques which determine the rate of progress in proteomics and in functional genomics (Savage, Barker, 2004)
- Embryonic stem cells, endowed with the properties of self–renewal and pluripotency, have the potential of serving both as an inexhaustible source of various types of cells for transplantation purposes and of being an invaluable tool for studying the initial stages of embryonic development (Urbach, 2004).

Although this list is by no means complete it gives an idea of the some of the most promising fields in biotechnology in which work is likely to continue in the next ten to fifteen years. Summarising, we can expect future work to focus on (i) internal specialisation of biotechnology, (ii) contributions from other disciplines (IT, Physics, Chemistry), (iii) targeting particular diseases.

6.2) INDUSTRIAL DEVELOPMENTS.

As it was done previously, the applications of biotechnology will be classified into three fields: health, agriculture and industry.

6.2.1) HEALTH

The present industrial structure constituted by LDFs and DBFs collaborating to create new drugs can be expected to survive over the next ten-fifteen years, possibly with some modifications. LDFs, which were initially completely dependent on DBFs for access to the new biotechnology, have become more competent partners. They will still rely largely on DBFs and collaborate with them not because they are incapable to discover novelty but because the trend towards an increasing differentiation continuously creates new niches in which for a while DBFs have a comparative advantage. This phenomenon is exemplified by the changing composition of innovation networks, which have changed from the first generation based on recombinant DNA and monoclonal antibodies to the second generation based on genomics (Catherine, 2005). We can then expect new generations of DBFs and of innovation networks to emerge as new specialities are created by the progress of biological knowledge. In this sense the emergence of new generations of DBFs will depend on regulatory activities as well as from scientific progress. For example, the legislation on Stem cells could exert an important influence on both research and industrial applications in this field. Of course, this means that the DBFs creating the new innovation networks will not be the same that created the old ones. A further cause of the persistence of innovation networks can be the extremely high rate of growth of new knowledge, which would make it impossible for LDFs to cover all new developments. In this case DBFs would help LDFs to explore new emerging knowledge. Furthermore, innovation networks involving exclusively DBFs started emerging recently. The prosecution of this trend could create some medium firms, either by internal growth or by mergers and acquisitions amongst DBFs. These firms would not initially be competitors of LDFs, since they would not have a comparable range of competencies and products, but they could specialise in high tech products which require limited complementary assets, for example by selling to hospitals. In spite of these DBFs mergers the process of growth of DBFs and the possibility for them to replace LFDs is very limited. Barriers to the growth of DBFs include their extremely specialised knowledge base (Orsenigo et al, 2001) and their inability to acquire complementary assets. Thus, we can expect most DBFs to remain small. However, since the number of LDFs is likely to fall by mergers and acquisitions, this fall in numbers might be compensated by the consolidation and growth of the very small number DBFs which are capable to grow. At least some LDFs might adopt a two pronged strategy, combining the creation of new drugs with the production and distribution of generics. This would be a response to the growing cost pressures faced by health care systems, which would be accompanied by a growing collaboration between hospitals and pharmaceutical producers, a situation that Ernst & Young (2004) calls the New Health Economy.

6.2.2) AGRICULTURAL BIOTECHNOLOGY.

Barring a catastrophic accident, the diffusion of the first generation of GM crops will continue at a rate comparable to that of the recent past. The number of adopting countries is likely to increase because in absence of adverse effects previous adoption is interpreted as evidence of benefits for farmers and consumers. Based on the prosecution of present trends some GM crops, namely Soya, will virtually take over the market. It has to be borne in mind

that, for all their impressive rates of diffusion, GM crops are very few and that their diffusion is still limited to a small number of countries. Even taking these limitations into account, the selective but very fast rate of diffusion of GM crops is likely to provide legitimation for a more generalised use of GM crops.

The previous considerations are relative to the first generation of GM varieties. This generation is constituted by a limited number of crops grown in very large quantities and in which one trait per crop was modified. Quite often the desirability of this trait was due to the desire of companies to sell plant varieties requiring the use of the use of the herbicides they were producing. The identification of this trait may not be considered optimal taking into account the welfare of the users of the technology (Harhoff et al, 2001). However, this can be considered a path dependent feature likely to affect only the first generation of GM crops. Subsequent generations can be expected to contain a wider range of more appealing traits, making their diffusion easier. For example, new plant varieties providing food with improved nutritional value or plant varieties capable of producing substances of pharmaceutical interest are likely to be perceived as more beneficial than those of the first generation.

The development of new GM plant varieties is going to require some time. For the foreseeable future most cultivated plant varieties will be obtained by means of traditional breeding techniques. These techniques still have some advantages with respect to GM based ones, for example the ability to modify simultaneously several traits. Furthermore, conventional plant breeding can be used in conjunction with modern biotechnology as a quick way to identify the specific traits of the hybrids produced. It is possible to conceive a combination of GM ad traditional breeding techniques, giving rise to synergistic effects. This could be useful in the development of new plant varieties adapted to the condition of LDCs, which for the moment do not receive the lion's share of investment (Knight, 2003).

The simultaneous cultivation of GM and of traditional plant varieties will survive not only due to the time and resources required to develop a sufficiently wide range of GM plants with useful traits, but to the need to give citizens choice. Even if it could be demonstrated that GM varieties provide clear benefits, some people might still not want to use them, and they must be given the freedom to do so. Present European regulations, requiring all products containing more than a given percentage of GMOs to be labelled, are aimed exactly at this objective. Although costly such a regulation is a basic requirement of democratic countries. It is more difficult to imagine the persistence of an attitude which completely and systematically excludes the use of any GM plant variety in a country or group of countries when the rest of the world has become an adopter. For example, if the EU were to persist in its present attitude of effective outright banning of GM crops and plant varieties, it would create problems for EU based producers and users, who would miss relevant competencies and markets. It is not difficult to imagine that, if these conditions were to persist, EU based agrochemical producers would have a strong inducement to move part of their activities elsewhere.

6.2.3) INDUSTRIAL BIOTECHNOLOGY.

So far the impact of biotechnology has been concentrated on the pharmaceutical sector, with agriculture coming a distant second. In general industrial activities did not attract a comparable amount of attention and of investment. This is likely to change in the next ten to fifteen years as a consequence of a number of factors. The combination of rising energy prices and of a growing need to reduce the environmental impact of all technologies can be expected to induce a considerable amount of R&D aimed at replacing fossil fuels and non renewable

inputs with renewable biological ones. In some cases even physical equipment will be replaced by biological organisms, such as bacteria or yeasts. The scope of industrial biotechnology is extremely wide, to the extent that it can be described as a bio-economy, an economy in which non biological processes will be replaced by biological ones. The transition to a bio-economy will not consist of the replacement of biological processes with biological ones which produce the same outputs just reducing costs and environmental. The input-output relationships of different sectors are likely to be changed. The concept of a bio-refinery exemplifies clearly this point. A bio-refinery is an integrated cluster of bio-industries, using efficient technology to produce chemicals, bio-fuels, food ingredients and power from biomass raw materials. What firms will use bio-refineries? In what sector will they be classified? Or, is the concept of bio-refinery too integrated? Will the transition to the bio-economy be more gradual than that, with firms adopting new processes in a piecemeal fashion? What will happen of the industrial sectors whose activities will be replaced by bio-based activities? Clearly, a large number of questions can be raised about the structure of the emerging bio-economy, questions to which for the moment no precise answer can be given. Yet the time to provide operational answers to these questions may not be all that large. By 2050 oil and gas reserves will be almost exhausted (Stodaert, Vandamme, 2004). The transition of a large part of our economies to a bio-economy will have to take place before that. McKinsey (cited in Stodaert, Vandamme, 2004) forecasts that by the year 2010 biomass will account for 20% of chemicals production, up from 5% now. The percentage of energy produced from biomass is expected to grow from 5.8% in 2002 to 14% in 2010. If these forecasts are going to be realised, answers to the previous questions will have to be provided on the run. It is unlikely that a transition of this magnitude, if it takes place, will occur without a high level of coordination within countries and across countries. This higher level of coordination will not necessarily involve governments, but it unlikely that firms and industrial associations by themselves will be up to the task of developing a bio-economy. For example of the United States, certainly not the country where the government enjoys the highest reputation, has seen the creation and subsequent direction of a very ambitious biomass program by the American government. The Biomass program is guided by (Biomass Program USA, 2005):

- the President's National Energy Policy
- The Biomass R&D act of 2000
- U.S Department of Energy and Office of Energy Efficiency and Renewable Energy strategic plans.
- The biomass R&D Technical Advisory Committee.
- Technical Peer Reviews.

Clearly, this is not a limited initiative arising 'spontaneously' in a corner of the economy, but a concerted national plan with a long term vision.

The EU has probably stronger inducements than the US to innovate towards a bio-economy: (i) a greater scarcity of fossil fuels and of raw materials; (ii) a higher share of the world chemical industry, the industry which is more likely to benefit from the transition to the bio-economy if it manages it effectively or to be heavily harmed by the same transition if it fails to anticipate the relevant technological changes and to interpret them innovatively.

6.3) THE SOCIO-ECONOMIC ENVIRONMENT.

Biotechnology is a pervasive technology, having a very wide scope that can only be realised over a long period of time. Like all technologies it can provide both benefits and risks and it needs adequate institutions to make sure that the benefits outweigh the risks and that in any case the risks accepted are tolerable for everyone. The institutions that have to co-evolve with biotechnology require the development of ethical and legal foundations. Biotechnology creates particular ethical and legal dilemmas more difficult than those of most other technologies. However, the general environment in which it evolves can have an important influence on its development. The image and understanding that people have of science could be a crucial factor in this sense. On the one hand a negative image of science is likely to constitute an obstacle to any new technology; on the other hand too limited an understanding of science and technology constitutes an obstacle to a rational dialogue about new technologies. Of course, this does not imply that the same answer will be given about questions in a given field by people having the same level of knowledge in that field. It is important to point out that modern science, while being much more powerful that the one of the XIXth century, has abandoned the dream of a complete and certain knowledge that was then formulated. In a democratic society technologies cannot be imposed upon people, but they can only diffuse and provide all their benefits if they are generally accepted. This implies communication and participation, the former to make knowledge distribution in society less skewed and to allow a rational dialogue, the latter to involve people in consultation and decision making. It might be thought that an authoritarian society would not have to face these problems and that it would have a comparative advantage in adopting new technologies. This is at best likely in the very short run. In general democratic societies have a greater capacity for error making and for learning from errors, or a greater capacity for experimentation, at the condition that they do not lose the taste for learning and discovering. The future of biotechnology will depend greatly on the ability to create a receptive and supportive socio-economic environment, a task which seems to be more difficult in the EU than in other countries.

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Appendix 1
Biotechnology organisations applying for or being awarded patents by the European Patent Office (EPO) or by the US Patent Office (USPTO)

This appendix describes the organisations applying for or being awarded patents by the European Patent Office (EPO) or by the US Patent Office (USPTO). The results presented in the following tables were obtained using the search equations described in each case. The search equations used contain very general key words, such as Biotech, Genome, Proteome, RNA or DNA. Also, the period studied varies in each case and it is indicated near the corresponding table.

Patent applications to the European Patent Office (EPO)

Research equation used

AB=biotech* **OU** **AB** = "GENOM*****" **OU AB**="proteom*****" **OU AB**=ARN **OU AB**=ADN **ET SAUF NO**=*

Between 1978 and December 2004, 4331 patent applications have been made to EPO in the fields covered by this equation.

The main organisations applying for at least 10 patents

Patents are assigned to the country of priority. In some cases this implies that patents applied for by an organisation from a given country (for example France) are assigned to the country of priority. In other cases the patents are assigned to a foreign subsidiary of a given organisation.

N° patents	ORGANISATION	COUNTRY
157	PE CORPORATION (NY)	US
64	INSTITUT PASTEUR	FR
54	EPIGENOMICS AG	DE
53	The Regents of The University of California	US
51	APPLERA CORPORATION	US
38	CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE (CNRS)	FR
37	GENSET	US
30	INCYTE PHARMACEUTICALS, INC.	US
30	TRANSGENE S.A.	FR
30	INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE – INSERM	FR
28	INSTITUT NATIONAL DE LA RECHERCHE AGRONOMIQUE	FR
27	GENENTECH INC.	US
26	CHIRON CORPORATION	US
26	CORNELL RESEARCH FOUNDATION, INC.	US
25	THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY	US
22	WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH	US
22	SIRNA THERAPEUTICS, INC.	US
21	ZENECA LIMITED	GB
20	E. I. DU PONT DE NEMOURS AND COMPANY	US
19	AMERICAN CYANAMID COMPANY	US
19	BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM	US
19	COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION	AU
18	AFFYMETRIX, INC.	US
18	PIONEER HI-BRED INTERNATIONAL, INC.	US
17	JAPAN SCIENCE AND TECHNOLOGY CORPORATION	JP
17	MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V.	DE
17	THE JOHNS HOPKINS UNIVERSITY	US
17	THE GENERAL HOSPITAL CORPORATION	US
16	OXFORD BIOMEDICA (UK) LIMITED	GB
15	YALE UNIVERSITY	US
15	SARTORIUS AG	DE
15	INSTITUT PASTEUR	US
15	ZYMOGENETICS, INC.	US
14	SYNGENTA PARTICIPATIONS AG	US
14	MERCK & CO. INC.	US

14	THE SCRIPPS RESEARCH INSTITUTE	US
14	GENELABS TECHNOLOGIES, INC.	US
13	METAGEN GESELLSCHAFT FÜR GENOMFORSCHUNG MBH	DE
13	RIBOZYME PHARMACEUTICALS, INC.	US
13	WISCONSIN ALUMNI RESEARCH FOUNDATION	US
13	ABBOTT LABORATORIES	US
12	PLANT GENETIC SYSTEMS N.V.	GB
12	AKZO NOBEL N.V.	EP
12	BAYLOR COLLEGE OF MEDICINE	US
12	CENTRO DE INGENIERIA GENETICA Y BIOTECNOLOGIA (CIGB)	CU
12	MASSACHUSETTS INSTITUTE OF TECHNOLOGY	US
12	IMPERIAL CHEMICAL INDUSTRIES PLC	GB
11	UNIVERSITY OF UTAH RESEARCH FOUNDATION	US
10	BIO MERIEUX	FR
10	AGILENT TECHNOLOGIES INC.	US
10	BASF AKTIENGESELLSCHAFT	DE
10	SYNTRO CORPORATION	US
10	BEHRINGWERKE Aktiengesellschaft	DE
10	DUKE UNIVERSITY	US
10	NOVARTIS AG	US
10	MONSANTO TECHNOLOGY LLC	US
10	MONSANTO COMPANY	US

Patents awarded by the US Patent Office (USPTO)

Equation used

((biotech$).TIAB.) OR ((genom$).TIAB.) OR ((proteom$).TIAB.) OR ((rna).TIAB.) OR ((dna).TIAB.)

The total number of patents for the period September 1988 to February 2005 is 15833.

The main organisations having obtained at least 10 patents

Given the information supplied by the data base patents are assigned to the country of the first inventor. 298 organisations are contained in this table.

N° pat.	Assignee	Country
282	UNIVERSITY OF CALIFORNIA, THE REGENTS OF	US
276	UNITED STATES OF AMERICA, HEALTH & HUMAN SERVICES	US
257	SMITHKLINE BEECHAM CORPORATION	US
205	HUMAN GENOME SCIENCES, INC.	US
154	GENENTECH, INC.	US
150	INSTITUT PASTEUR	FR
131	UNIVERSITY OF TEXAS	US
126	GENERAL HOSPITAL CORPORATION	US
126	CHIRON CORPORATION	US
116	APPLERA CORPORATION	US
110	ELI LILLY AND COMPANY	US
109	ISIS PHARMACEUTICALS, INC.	US
104	IMMUNEX CORPORATION	US
102	MERCK + CO., INC.	US
90	COLUMBIA UNIVERSITY	US
89	SALK INSTITUTE FOR BIOLOGICAL STUDIES	US
87	CORNELL RESEARCH FOUNDATION INC.	US
87	NOVO NORDISK A/S	DK
84	HARVARD COLLEGE, PRESIDENT AND FELLOWS	US
83	MONSANTO COMPANY, INC.	US
82	JOHNS HOPKINS UNIVERSITY	US
81	PIONEER HI BRED INTERNATIONAL, INC.	US
80	THE SCRIPPS RESEARCH INSTITUTE	US
79	INCYTE PHARMACEUTICALS, INC.	US
79	WISCONSIN ALUMNI RESEARCH FOUNDATION	US
74	GENETICS INSTITUTE, INC.	US
74	ZYMOGENETICS, INC.	US
74	TAKEDA CHEMICAL INDUSTRIES LTD.	JP
74	AMGEN, INC.	US
73	NEW ENGLAND BIOLABS, INC.	US
71	WASHINGTON UNIVERSITY	US
70	STANFORD UNIVERSITY, LELAND JUNIOR, THE BOARD OF TRUSTEES OF	US
68	BECTON, DICKINSON AND COMPANY	US
64	UNITED STATES OF AMERICA, DEPARTMENT OF AGRICULTURE	US
63	AJINOMOTO COMPANY INCORPORATED	JP
63	AMERICAN CYANAMID COMPANY	US
63	SYNAPTIC PHARMACEUTICAL CORPORATION	US
63	MASSACHUSETTS INSTITUTE OF TECHNOLOGY	US
60	HITACHI, LTD	JP
58	ABBOTT LABORATORIES	US
58	ROCKEFELLER UNIVERSITY	US

58	HOFFMANN LA ROCHE INC.	US
57	RIBOZYME PHARMACEUTICALS, INC.	US
56	YALE UNIVERSITY	US
55	RESEARCH FOUNDATION OF STATE UNIVERSITY OF NEW YORK	US
54	DANA FARBER CANCER INSTITUTE, INC.	US
54	GENENCOR INTERNATIONAL, INC.	US
53	KYOWA HAKKO KOGYO CO., LTD	JP
52	E. I. DU PONT DE NEMOURS AND COMPANY	US
52	CALIFORNIA INSTITUTE OF TECHNOLOGY	US
52	BAYLOR COLLEGE OF MEDICINE	US
52	NEW YORK UNIVERSITY	US
51	GENZYME CORPORATION	US
51	UNIVERSITY OF NORTH CAROLINA	US
50	DUKE UNIVERSITY INC.	US
50	STRATAGENE	US
49	CORIXA CORPORATION	US
47	BOEHRINGER MANNHEIM G.M.B.H.	DE
47	LIFE TECHNOLOGIES, INC.	US
46	NOVARTIS FINANCE CORPORATION	US
46	ARCH DEVELOPMENT CORP.	US
46	UNIVERSITY OF MICHIGAN	US
45	NEXSTAR PHARMACEUTICALS, INC.	US
44	SMITHKLINE BEECHAM PLC	US
44	PE CORPORATION	US
43	MAXYGEN, INC.	US
43	ZENECA LIMITED	GB
41	PLANT GENETIC SYSTEMS N.V.	BE
41	CALGENE, INC.	US
41	CITY OF HOPE	US
40	UNIVERSITY OF MINNESOTA, THE REGENTS OF	US
39	MYCOGEN CORPORATION	US
39	MICHIGAN STATE UNIVERSITY	US
39	OREGON HEALTH SCIENCES UNIVERSITY	US
38	NORTH CAROLINA STATE UNIVERSITY	US
38	ROCHE DIAGNOSTICS GMBH	DE
37	PROMEGA CORPORATION	US
37	BIOGEN, INC.	US
37	GEN PROBE INCORPORATED	US
36	UNIVERSITY OF GEORGIA RESEARCH FOUNDATION, INC.	US
35	UNIVERSITY OF PENNSYLVANIA	US
35	HEALTH RESEARCH, INCORPORATED	US
34	HOECHST AKTIENGESELLSCHAFT	DE
34	YEDA RESEARCH AND DEVELOPMENT CO., LTD.	IL
34	HAYASHIBARA BIOCHEMICAL LABORATORIES INCORPORATED	JP
33	WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH	US
33	AFFYMETRIX, INC.	US
33	UNIVERSITY OF UTAH RESEARCH FOUNDATION	US
33	UNIVERSITY OF WASHINGTON	US
32	UNIVERSITY OF NEBRASKA, THE BOARD OF REGENTS OF	US
31	UNIVERSITY OF IOWA RESEARCH FOUNDATION	US
31	TAKARA SHUZO CO., LTD.	JP
30	DEKALB GENETICS CORPORATION	US
30	UAB RESEARCH FOUNDATION	US
30	RESEARCH DEVELOPMENT FOUNDATION	US
29	MAX PLANCK GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V	DE
29	VIROGENETICS CORPORATION	US
29	GENELABS TECHNOLOGIES, INC.	US
28	TRANSKARYOTIC THERAPIES, INC.	US

28	UNIVERSITY OF MEDICINE AND DENTISTRY OF NEW JERSEY	US
28	CETUS CORPORATION	US
28	SCHERING CORP.	US
27	ICOS CORPORATION OF AMERICA	US
27	BRISTOL MYERS SQUIBB COMPANY	US
27	COLD SPRING HARBOR LABORATORY	US
27	FUJI PHOTO FILM CO., LTD	JP
27	BRIGHAM AND WOMEN'S HOSPITAL	US
27	SEQUENOM, INC.	US
26	COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANIZATION	AU
26	MONSANTO TECHNOLOGY, LLC	US
26	UNIVERSITY OF MARYLAND	US
26	AMOCO CORPORATION	US
25	TOYO BOSEKI KABUSHIKI KAISHA	JP
25	RESEARCH CORPORATION TECHNOLOGIES, INC.	US
25	WASHINGTON STATE UNIVERSITY RESEARCH FOUNDATION, INC.	US
25	PERKIN ELMER CORPORATION	US
25	UNIVERSITY OF PITTSBURGH	US
25	BIO TECHNOLOGY GENERAL CORP.	IL
24	SYNTRO CORPORATION	US
24	ALBERT EINSTEIN COLLEGE OF MEDICINE OF YESHIVA UNIVERSITY	US
24	INVITROGEN CORPORATION	US
24	NOVOZYMES A/S	DK
24	MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK	US
24	GILEAD SCIENCES, INC.	US
24	AKZO NOBEL NV	NL
24	SUNTORY LTD.	JP
23	MYCOGEN PLANT SCIENCES, INC.	US
23	TEXAS A&M UNIVERSITY SYSTEM	US
23	BAYER AKTIENGESELLSCHAFT	DE
23	THOMAS JEFFERSON UNIVERSITY	US
23	DIVERSA CORPORATION	US
23	DNA PLANT TECHNOLOGY CORPORATION	US
23	UNITED STATES OF AMERICA, ARMY	US
23	COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH	IN
23	CALGENE LLC	US
23	HOECHST SCHERING AGREVO GMBH	DE
22	UNIVERSITY OF SOUTHERN CALIFORNIA	US
22	TRANSGENE S.A.	FR
22	CREATIVE BIOMOLECULES, INC.	US
22	MEDICAL RESEARCH COUNCIL	GB
21	NANOGEN, INC.	US
21	RUTGERS UNIVERSITY	US
21	SLOAN KETTERING INSTITUTE FOR CANCER RESEARCH	US
20	KIRIN BEER KABUSHIKI KAISHA	JP
20	IOWA STATE UNIVERSITY RESEARCH FOUNDATION INC.	US
20	CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE CNRS	FR
20	EMORY UNIVERSITY	US
20	INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE	FR
19	CURAGEN CORPORATION	US
19	ROCHE MOLECULAR SYSTEMS, INC.	US
19	ST. JUDE CHILDREN'S RESEARCH HOSPITAL	US
19	PFIZER INC.	US
19	GENE SHEARS PTY. LIMITED	AU
18	LYNX THERAPEUTICS, INC.	US
18	SMITHKLINE BECKMAN CORPORATION	US
18	UNIVERSITY OF FLORIDA BOARD OF REGENTS	US
18	INSTITUT PASTEUR	US

18	IMPERIAL CHEMICAL INDUSTRIES PLC	GB
18	BAYER CORPORATION	US
18	CALIPER TECHNOLOGIES CORP.	US
17	GENESIS RESEARCH & DEVELOPMENT CORPORATION, LTD.	NZ
17	CARNEGIE MELLON UNIVERSITY	US
17	UNIVERSITY OF ARKANSAS	US
17	CIBA GEIGY CORPORATION	CH
17	BIOMERIEUX SA	FR
17	NATIONAL RESEARCH COUNCIL OF CANADA	CA
17	VISIBLE GENETICS INC.	CA
17	MILLENNIUM PHARMACEUTICALS, INC.	US
16	XOMA CORPORATION	US
16	UNIVERSITY OF KENTUCKY RESEARCH FOUNDATION	US
16	FUJISAWA PHARMACEUTICAL CO., LTD.	JP
16	SHIONOGI + CO. LTD.	JP
16	KIKKOMAN CORPORATION	JP
16	PURDUE RESEARCH FOUNDATION	US
16	UNIVERSITY OF CONNECTICUT	US
16	AMERICAN HOME PRODUCTS CORPORATION	US
16	TRANSGENOMIC INCORPORATED	US
16	MCGILL UNIVERSITY	CA
16	PHARMACIA & UPJOHN COMPANY	US
15	SYNGENTA PARTICIPATIONS AG	US
15	UNIVERSITY OF BRITISH COLUMBIA	CA
15	YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM	IL
15	EASTMAN KODAK COMPANY	US
15	ALLELIX BIOPHARMACEUTICALS INC.	CA
15	THE WISTAR INSTITUTE OF ANATOMY AND BIOLOGY	US
15	PHILLIPS PETROLEUM COMPANY	US
15	AMBION, INC.	US
15	CLEVELAND CLINIC FOUNDATION	US
15	STRYKER CORPORATION	US
15	AGENCY OF INDUSTRIAL SCIENCE & TECHNOLOGY	JP
15	OHIO STATE RESEARCH FOUNDATION	US
15	BOARD OF REGENTS OF THE UNIVERSITY OF OKLAHOMA	US
15	DARTMOUTH COLLEGE	US
15	AFFYMAX TECHNOLOGIES N.V.	US
15	BOEHRINGER INGELHEIM INTERNATIONAL GMBH	AT
15	RHONE POULENC RORER, S.A.	FR
14	AVENTIS PHARMA DEUTSCHLAND GMBH	DE
14	SEIKAGAKU CORPORATION	JP
14	DEUTSCHES KREBSFORSCHUNGSZENTRUM STIFTUNG DES OEFFENTLICHEN RECHTS	DE
14	NESTEC, S.A.	CH
14	UNIVERSITY OF MASSACHUSETTS MEDICAL CENTER	US
14	LI COR, INC.	US
14	ACADEMIA SINICA	TW
14	BEHRINGWERKE AKTIENGESELLSCHAFT	DE
14	MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH	US
14	RESEARCH FOUNDATION FOR MICROBIAL DISEASES OF OSAKA UNIVERSI	JP
14	VANDERBILT UNIVERSITY	US
14	GENSET, S.A.	FR
14	BOSTON UNIVERSITY	US
14	GERON CORPORATION	US
14	KYOWA HAKKO KOGYO CO., LTD	US
14	JURIDICAL FOUNDATION, THE CHEMO SERO THERAPEUTIC RESEARCH IN	JP
13	AVIGEN INCORPORATED	US

13	UPJOHN COMPANY	US
13	CURATORS OF THE UNIVERSITY OF MISSOURI	US
13	UNIVERSITY OF SASKATCHEWAN	CA
13	CIBA GEIGY CORPORATION	US
13	NOVARTIS AG (FORMERLY SANDOZ LTD.)	US
13	NEW ENGLAND MEDICAL CENTER HOSPITALS, INC.	US
13	AVENTIS PASTEUR LIMITED	CA
13	SIBIA NEUROSCIENCES, INC.	US
13	APPLIED BIOSYSTEMS, INC.	US
13	LARGE SCALE BIOLOGY CORPORATION	US
13	MOCHIDA PHARMACEUTICAL CO., LTD.	JP
13	FRED HUTCHINSON CANCER RESEARCH CENTER	US
13	HOFFMANN LA ROCHE INC.	CH
13	LOUISIANA STATE UNIVERSITY, AGRICULTURAL AND MECHANICAL COLLEGE	US
13	PENN STATE RESEARCH FOUNDATION, INC.	US
12	HYBRIDON, INC.	US
12	UNITED STATES OF AMERICA	US
12	INSTITUT NATIONAL DE LA RECHERCHE AGRONOMIQUE	FR
12	SYNTEX (U.S.A) INC.	US
12	CHUGAI SEIYAKU KABUSHIKI KAISHA	JP
12	BETH ISRAEL HOSPITAL ASSOCIATION	US
12	CELLTECH LIMITED	GB
12	LUBRIZOL GENETICS, INC.	US
12	MOGEN INTERNATIONAL N.V.	NL
12	ACLARA BIOSCIENCES, INC.	US
12	KOREA KUMHO PETROCHEMICAL CO., LTD.	KR
12	JOHNSON & JOHNSON CLINICAL DIAGNOSTICS, INC.	US
12	GEORGETOWN UNIVERSITY	US
12	LA JOLLA CANCER RESEARCH FOUNDATION	US
12	WASHINGTON RESEARCH FOUNDATION	US
12	AVENTIS PHARMA SA	FR
12	CORVAS INTERNATIONAL, INC.	US
12	JAPAN SCIENCE AND TECHNOLOGY CORPORATION	JP
12	ONCOGEN	US
12	MITSUBISHI CHEMICAL CORPORATION	JP
12	UNIVERSITY OF ROCHESTER	US
12	CHILDREN'S MEDICAL CENTER CORPORATION	US
11	TOSOH CORPORATION	JP
11	UNITED STATES OF AMERICA, DEPARTMENT OF ENERGY	US
11	LYNX THERAPEUTICS, INC.	GB
11	UNITED STATES OF AMERICA, NAVY	US
11	GENPHARM INTERNATIONAL, INC.	US
11	AGILENT TECHNOLOGIES, INC.	US
11	KOSAN BIOSCIENCES, INC.	US
11	ASAHI KASEI KOGYO KABUSHIKI KAISHA	JP
11	APPLIED RESEARCH SYSTEMS ARS HOLDING N.V.	US
11	NATIONAL SCIENCE COUNCIL	TW
11	AVENTIS CROPSCIENCE N.V.	BE
11	COR THERAPEUTICS, INC.	US
11	DADE BEHRING MARBURG GMBH	DE
11	UNIVERSITY OF ILLINOIS	US
11	ORTHO MCNEIL PHARMACEUTICAL, INC.	US
11	UNIVERSITY OF VIRGINIA ALUMNI PATENTS FOUNDATION	US
11	AKZO NOBEL NV	GB
11	AKZO NOBEL NV	US
11	CELL GENESYS, INC.	US
11	HOWARD FLOREY INSTITUTE OF EXPERIMENTAL PHYSIOLOGY AND MEDIC	AU
11	MOLECULAR STAGING INC.	US

11	UNIVERSITY OF MARYLAND BIOTECHNOLOGY INSTITUTE	US
11	UNIVERSITY OF MASSACHUSETTS	US
10	CELLTECH THERAPEUTICS LIMITED	GB
10	CLONTECH LABORATORIES, INC.	US
10	SOMATOGEN, INC.	US
10	NATIONAL INSTITUTE OF AGROBIOLOGICAL SCIENCES	JP
10	JAPAN TOBACCO INC.	JP
10	UNILEVER PATENT HOLDINGS B.V.	NL
10	SYMBICOM AKTIEBOLAG	US
10	TROPIX, INC.	US
10	CANCER INSTITUTE	JP
10	RHONE POULENC RORER PHARMACEUTICALS INC.	US
10	BOYCE THOMPSON INSTITUTE FOR PLANT RESEARCH, INC.	US
10	FMC CORPORATION	US
10	NITTO CHEMICAL INDUSTRY CO., LTD.	JP
10	RIGEL PHARMACEUTICALS, INC.	US
10	EPICENTRE TECHNOLOGIES CORP.	US
10	ZENECA LIMITED	BE
10	INSTITUTE OF PHYSICAL AND CHEMICAL RESEARCH	JP
10	AVIRON, INC.	US
10	MERCK FROSST CANADA, INC.	CA
10	UNIVERSITY OF UTAH	US
10	INNOVIR LABORATORIES, INC.	US
10	OKLAHOMA MEDICAL RESEARCH FOUNDATION	US

Patents applied for at the US Patent Office (USPTO)

Equation used

((biotech$).TIAB.) OR ((genom$).TIAB.) OR ((proteom$).TIAB.) OR ((rna).TIAB.) OR ((dna).TIAB.)

The total number of patents applied for between March 2001 and February 2005 is 8190.

Main applying organisations (>=10 applications)

N°	ASSIGNEE	Country
171	APPLERA CORPORATION	US
85	HUMAN GENOME SCIENCES, INC.	US
51	PE CORPORATION	US
49	AFFYMETRIX, INC.	US
44	UNIVERSITY OF CALIFORNIA, THE REGENTS OF	US
35	GENENTECH, INC.	US
32	INVITROGEN CORPORATION	US
30	AJINOMOTO COMPANY INCORPORATED	JP
27	HITACHI, LTD	JP
23	INSTITUT PASTEUR	FR
23	IMMUNEX CORPORATION	US
22	SYNAPTIC PHARMACEUTICAL CORPORATION	US
21	NOVOZYMES A/S	DK
20	AMGEN, INC.	US
19	PIONEER HI BRED INTERNATIONAL, INC.	US
19	UNIVERSITY OF TEXAS	US
14	JOHNS HOPKINS UNIVERSITY	US
14	MONSANTO TECHNOLOGY, LLC	US
14	PERLEGEN SCIENCES, INC.	US
13	COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH	IN
13	STRATAGENE	US
13	PFIZER INC.	US
13	MERCK + CO., INC.	US
13	CORIXA CORPORATION	US
12	NEW ENGLAND BIOLABS, INC.	US
12	MAX PLANCK GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V	DE
12	AVENTIS PASTEUR LIMITED	CA
12	GENVEC, INC.	US
11	THE SCRIPPS RESEARCH INSTITUTE	US
11	SMITHKLINE BEECHAM CORPORATION	US
11	YEDA RESEARCH AND DEVELOPMENT CO., LTD.	IL
11	LARGE SCALE BIOLOGY CORPORATION	US
11	ZYMOGENETICS, INC.	US
11	CHIRON CORPORATION	US
10	TOSOH CORPORATION	JP
10	ISIS PHARMACEUTICALS, INC.	US
10	ROCHE DIAGNOSTICS GMBH	DE
10	RIBOZYME PHARMACEUTICALS, INC.	US
10	WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH	US