EIB SECTOR PAPERS

BIOTECHNOLOGY : AN OVERVIEW

European Investment Bank

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BIOTECHNOLOGY
AN OVERVIEW

EXECUTIVE SUMMARY

Biotechnology *is defined as "any technical application that uses biological systems, living organisms or derivatives thereof, to make or modify products or processes for specific use"[1]. As such, biotechnology has existed since the human race first used fermentation to make bread, cheese and wine.*

Modern or "new" biotechnology *refers to the understanding and application of genetic information of animal and plant species. Genetic engineering modifies the functioning of genes in the same species or moves genes across species resulting in Genetically Modified Organisms (GMOs)*

Starting with the discovery, in 1953, of the way genetic information is passed from generation to generation[2], modern biotechnology developed at an accelerating pace in the second half of the 20th century. The recently accomplished mapping of the ***human genome***, i.e. the identification of the about 30,000 genes that ultimately encode the hereditary characteristics of a human being, has been described as a quantum leap in biology.

In the course of its short history, modern biotechnology has given rise to a multitude of products and processes in the life sciences fields. In the ***health sector*** *human insulin* was the first product to meet with commercial success. Among processes, *gene therapy* still has to be proven but holds much promise for treating genetic disorders and chronic diseases. Whilst *cloning* of mammals is unlikely, given its complexity, to be viable from a breeding point of view, it has a potential for the production of proteins with therapeutic value.

In ***agriculture***, applications of biotechnology concentrate on the *genetic modification* of existing plant and animal species, by means of genetic material implantation from one species to another, where "natural" crossbreeding does not function. In terms of commercial importance, gene-modified (GM) crops, corn, soya and other oilseeds are, so far, the main applications.

In recent years, the worldwide biotechnology-based products market has grown at an annual average rate of 15% to reach a value of about € 30 bn in 2000. Biopharmaceuticals dominate this market (€ 20 bn), with agriculture related products making-up the balance. Biopharmaceuticals account for less than 5% of the total pharmaceuticals market but are growing at 2.5 times its overall growth rate.

There is little doubt that biotechnology presents a significant potential for growth and creation of wealth. Eventually, a substantial part of Europe's GDP could be generated by and spent on biotechnology products. Recognising this, both Member States and the Commission have, over the years, been

[1] Definition by the 1992 Convention on Biological Diversity (CBD)

[2] when Crick and Watson developed the double helix model for the molecular structure of DNA, where genetic information is encoded.

dedicating significant funds and resources to stimulating the development of biotechnology. More recently, the biotechnology sector received public endorsement at EU level at both the Lisbon 2000 and Stockholm 2001 Council meetings, to draw attention to the sector's importance and encourage a concerted effort to ensure Europe does not trail its competitors.

Similar to all "new" technologies, biotechnology is based on knowledge, from the discovery and understanding of the underlying basic science, through the accumulation of scientific data and the elucidation of mechanisms to the subsequent development of commercially viable products and processes. In this aspect, public actions to stimulate biotechnology should essentially be no different from those required for the development of other technologies; such as, providing an ***environment conducive to R&D***, ensuring the ***protection of Intellectual Property***, developing the ***necessary skills*** in the workforce, supplying a ***proper level and type of funding***, etc. However, biotechnology does have a number of particularities, which must be addressed for Europe to secure its place as a leading developer, producer and user of biotechnology products and processes.

1. Modern biotechnology raises ***ethical issues*** by interfering with the genetic code of plant and animal, including human, species. As such, it may be perceived as 'unnatural' or even sacrilegious. Additionally, GM food (and feed) products and plant species can be viewed with mistrust, either because of ***health concerns*** arising from their direct consumption or because of longer-term environmental disruption arising from their uncontrolled release in nature.

   The Commission's White Paper[3] contributes to a necessary debate between public authorities and civil society to define a broadly accepted biotechnology policy in the full respect of moral or religious convictions and incorporating fundamental ethical considerations. In the process, it must be recognised that concepts such as naturalness and health and environmental concerns will change as science advances and expands our knowledge of, and ability to influence, our physical circumstances, whilst understanding the consequences thereof. In practice, ethical concerns will vary according to the perceived risk/reward balance. The need for GM crops is less clear to a well-fed society than the need for a cure for AIDS to someone who is HIV positive.

2. A consequence of these ethical issues and health concerns is the substantial and ***relatively complex regulation*** the Member States have put in place addressing topics such as:
   - Genetic manipulation and the right to perform certain research activities;
   - Biopharmaceutical (drug) development, medical procedures and privacy – the balance between the availability of an individual's

[3] "Towards a strategic vision of life sciences and biotechnology", COM (2002) 27 final

genetic data to assist drug development/medical diagnosis/ treatment and the protection of the individual's privacy;
- Controls/restrictions for the release/disposal of GM species in nature (bio-safety);
- Intellectual property rights (patentability) of products and processes that are admissible for patent protection.

The complex regulatory framework, with the occasional significant differences (fragmentation) from one Member State to another, whilst designed to alleviate the public's concerns with biotechnology also acts as a disincentive for its balanced development. Developers, producers and users will tend to migrate to those regions (including outside the EU) where regulation is most conducive for the proliferation of biotechnology related activities.

3. Finally, modern biotechnology has the particularity of ***long R&D lead times***. Compared to other "new" technologies, where a piece of software or an IT hardware will typically be developed in a period of months, a biotechnology product or process will normally require a number of years to reach patenting stage, let alone commercial launch. In part, this is attributable to the complex regulations.

The particularities of biotechnology - the ethical issues and health and environmental concerns; the complex (and fragmented) regulation; the long R&D lead times - make the perception of risk higher than generally associated with the "new" technology sectors and combine to make sufficient and timely ***funding difficult to obtain***. This can be more acute for start-up companies striving to complete a research project and patent a product to serve as an asset for securing further funding, but also for companies at a later stage of growth, faced with long periods of product development and testing, which can have difficulty obtaining "top-up" funding in the first steps of commercialisation.

Since the 1980s, realising the potential of biotechnology for generating growth and creating of wealth, the Bank has been financing infrastructure provision and production projects in this sector under its "International Competitiveness of European Industry" eligibility. The recently launched "Innovation 2000 Initiative" (i2i) provided the opportunity for the Bank, and its venture capital arm, the EIF, to address, in a more focused manner, R&D and companies in their early development stages. The i2i framework covers the biotechnology sector as well, where the Bank, as the EU public policy Bank, will follow relevant EU policy and national legislation (in particular for ethical related issues).

The EIB Group, based on experience gained from operations to date and taking into account the particularities of the biotechnology sector, can support and catalyse its development in a number of conventional and more focused, innovative ways, including:

- by ***funding in infrastructure projects*** which have the right characteristics to support the development of clusters (centres of research, development and commercialisation for the biotechnology industry);
- by ***lending to industry, including the larger corporates,*** to support biotechnology based R & D and product launches;
- by investing in education projects aimed at ***developing the skills*** necessary to support the biotechnology sector;
- by ***developing financial instruments*** appropriate to the needs of the emerging biotechnology sector, in particular, to support public investment in the sector, to support the early stages in the life of start-up companies and to provide financial support as these companies grow;
- by ***providing venture capital*** to help "young" companies take their ideas and develop them into likely commercial products before going to the public equity markets.

This study analyses the achievements and perspectives of biotechnology, the structure and evolution of the markets for the products and processes and the availability of financial resources. In order to make the "correct" decisions about which actions and projects to support, the Bank needs to continue to keep itself informed of developments in the sector and to maintain a dialogue with the Commission and other relevant parties.

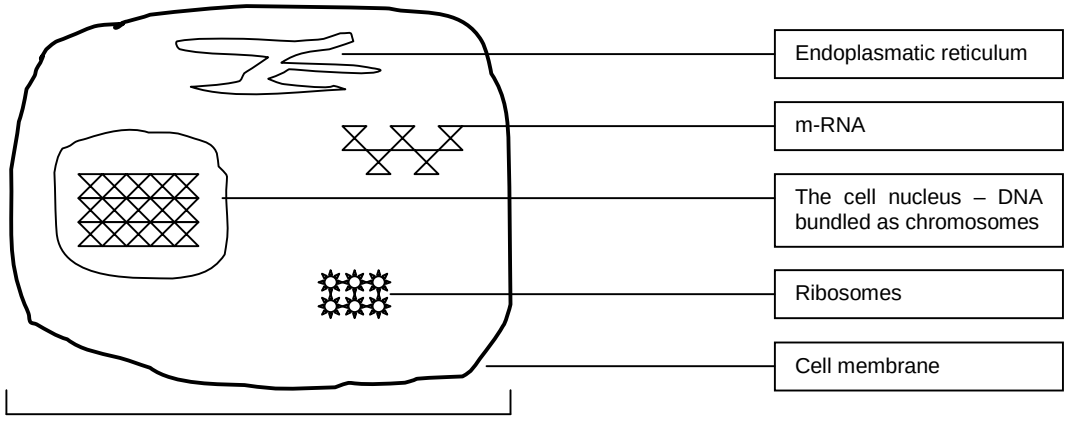
1. ACHIEVEMENTS AND PERSPECTIVES

A Primer on the 'Cell Factory'

Cell Organisation

All living matter – except viruses and prions[4] – consists of cells. Some organisms are single cells, e.g. bacteria, yeast, amoeba and some other parasites, while others consist of from several (e.g. fungi) to several billions of cells. While, in principle, cells are similar in a number of ways irrespective of their origin, in humans and other higher animals they are, in fact, also highly specialised. Fig. 1 presents a diagrammatic, highly simplified cross section of a cell containing a nucleus, m-RNA (ribonucleic acid), ribosomes, and endoplasmatic reticulum. All this is enveloped by the cell membrane. The structures shown here are those directly concerned with the cell's production of proteins. Real cells contain several other structures, the most important of which are the systems that provide energy for the intracellular processes and those involved in maintaining an appropriate intracellular environment.

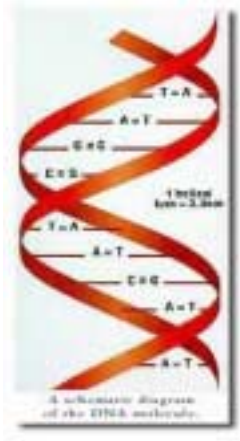
Fig. 1



Size of a human cell: 7-20 μ

The Genome

Recently accomplished, the mapping of the human genome, i.e. the identification of the about



30,000 genes that ultimately encode for the biochemical processes that constitute a living, human being - as well as their localisation on our 23 chromosome pairs, has rightly been touted as the equivalent of a quantum leap in biology. The strands of DNA in the cell nucleus hold the genes, i.e. the sets of base pairs that code the basic genetic information enabling the cell to produce identical proteins throughout its life, as well as let 'daughter cells' inherit identical instructions in the case of cell division. The bases individually convey no message. Instead, they act in strings of three, with a total of sixty-four such combinations. In turn, these codons can be ordered in innumerable ways on the DNA molecule. Their function is to give instructions for specifying and ordering amino acids - the structural elements of proteins. There are twenty amino acids found in proteins, and the codes for ordering them are universal - the sequence of bases to specify an amino acid is the same for a gnu, a geranium, or a grouse. However,

[4] Viruses consist of a section of DNA (or RNA) wrapped in a protein envelope. They have no metabolism of their own and can only multiply using the intracellular apparatus of animal or plant cells, or even bacteria, to replicate their DNA and proteins. In the process, some viruses cause considerable injury to their host. Prions, i.e. the entities involved in causing Bovine Spongiform Encephalitis (BSE) and its human variant Creutzfelt-Jacob, are 'misshaped' proteins – not on its own living matter.

the amino acids can be combined in many ways to make millions of proteins with distinct functions.

Transcription and Translation - from Instruction to Product

Transcription is the process in which a gene on the DNA molecule is used as a template to generate a corresponding strand of messenger-RNA (mRNA), a molecule the structure of which is related to that of DNA. The function of mRNA is to carry the coded messages from the nuclear DNA to the ribosomes. Ribosomes may be 'free' in the cell plasma or attached to the endoplasmatic reticulum (ER). Reading the sequence of base triplets, the ribosome moves along the mRNA adding amino acids one by one, translating the original DNA code into protein sequences. The ER is a 3-dimensional maze of connecting and branching channels involved in the synthesis of proteins destined for secretion or storage, e.g. digestive enzymes, hormones or antibodies, or the structural proteins for incorporation e.g. into cell membranes. Proteins may also be modified in the ER by the addition of carbohydrate, removal of a signal sequence or other modifications.

Plant cells are organised, in principle, along the lines of animal cells. However, they are generally larger and often specialised to the production of carbohydrates rather than proteins.

The Proteome

However complex the structure of the genome, it pales against that of the human proteome, i.e. the total of proteins produced by various cells to sustain life; the number of different proteins[5] is enormous - perhaps as many as 1,000,000 in humans - and while the DNA essentially is composed of four different building blocks, the 20 different amino acids of proteins can be linked together in occasionally extremely large molecules which - unlike the consistently helical structure of DNA - come in a variety of three-dimensional structures. The function – or malfunction - of proteins may be as dependent on structure as on chemical sequence. Protein variations are very significant among species; even within the same species, variations are substantial enough to make e.g. blood or tissue from one person potentially incompatible with that of another – hence the basis of blood types and the need to ensure as high a degree of tissue compatibility as possible between donor and recipient of organs for transplant.

Applications of Biotechnology in Human Health

Recombinant DNA Technology

Combining DNA through natural sexual reproduction can occur only between individuals of the same species. Since 1972 technology has, however, been available that allows the identification of genes for specific, desirable traits and the transfer of these, often using a virus as the vector, into another organism. Comparable to a word-processor's 'cut-and-paste', this process is called recombinant DNA technology or gene splicing. Virtually any desirable trait found in nature can, in principle, be transferred into any chosen organism. An organism modified by gene splicing is called transgenic or genetically modified (GM). Specific applications of this type of genetic engineering are rapidly increasing in number - in the production of pharmaceuticals, gene therapy, development of transgenic plants and animals, and in several other fields.

Pharmaceutical Production

The first major healthcare application of recombinant technology was in the production of human insulin, a hormone substantially involved in the regulation of metabolism, particularly

[5] Proteus – in Greek mythology a god who knew all things past, present, and future but disliked telling what he knew. From his power of assuming whatever shape he pleased, Proteus came to be regarded as a symbol of the original matter from which all is created.

of carbohydrates and fats, and the relative lack of which leads to the clinical condition called diabetes mellitus. Insulin is a relatively small protein consisting of 51 amino acids.

While the bovine or porcine insulin that had been used to treat human diabetes since the 1920s had become increasingly pure, side effects did occur due to its originating from a different species. In 1978, however, scientists succeeded in inserting the gene for human insulin into an E. coli bacterium. Once inside the bacterial cell, the gene could turn on its bacterial host's protein making machine to make – human insulin. Bacterial cells divide rapidly to make billions of copies of themselves, each modified bacterium carrying in its DNA an accurate replica of the gene for insulin production. Thus, given the necessary environmental factors, the bacteria would produce significant quantities of insulin, which can then be extracted from the 'soup' in which the process takes place and purified for use in humans. Today, most commercially available insulin is produced in this manner, using e.g. yeast cells as hosts.

A perhaps more famous example is recombinant erythropoietin, a hormone that regulates the production of red blood cells. The clinical conditions for which erythropoietin is indicated are relatively rare, but the bio-engineered product has gained enormous popularity in professional sports – as EPO – because it enables athletes to add 15-20 per cent to their oxygen carrying capacity.

Using micro-organisms or human cell cultures, similarly modified, in the production of highly complex molecules which would otherwise be impossible, or extremely difficult, to synthesise, is now employed extensively by the pharmaceutical industry. Increasingly, higher animals - "bioreactors" – modified by recombinant technology and able to express high value pharmaceutical proteins in their milk are also gaining use in reducing the cost of creating and producing new medical products.

Vaccines; Recombinant Technology and the Immune System

A vaccine is an antigen, e.g. the surface proteins of a pathogenic micro-organism. By exposing the immune system to an antigen previously 'unknown' to it, it primes the system so that on later contact with the antigen, a swift and effective defence will be mounted to prevent disease. The substances involved in this defence are called antibodies, proteins specific to, and able to deactivate the germs that carry, the particular antigen 'remembered' from previous contact, e.g. from vaccination. Immunological memory, including the ability to produce specific antibodies, is held by specialised white blood cells, making use of their 'cell factory' as described above. Obviously, an antigen used as a vaccine should be unable to cause disease, or at the least be much less a threat than the organism against which it is intended to protect. The classic example is Jenner's use 200 years ago of cowpox (vaccinia)[6] virus to immunize his son. While cowpox virus is almost a-pathogenic to humans, it has antigenic characteristics akin to those of the human smallpox virus – a close 'relative' – or close enough to induce an immune response sufficient to fight off 'real' smallpox. Immunisation is a cornerstone of preventive medicine, having provided some of the most cost-effective health interventions known.

Traditionally, vaccines are live attenuated (weakened virus or bacteria) or inactivated; the latter either whole, killed micro-organisms or e.g. selected cell surface proteins. While technological limitations remain and, for example, an effective AIDS/HIV vaccine has not yet been found, recombinant technology constitutes a powerful tool for the production of purer and safer vaccines. For example, the insertion of a hepatitis B virus gene into the genome of a yeast cell allows the production of pure hepatitis B surface antigen - a very effective vaccine, biologically equivalent of an inactivated vaccine. A live attenuated typhoid vaccine is now being produced from a *Salmonella typhi* bacterium cell line modified by recombinant technology so as not to cause typhoid. Several new vaccines using genetically weakened

[6] At the time, in 1798 viruses were not known to exist and the knowledge of micro-organisms and their role in pathogenesis was in its earliest infancy. Jenner, a British country medical practitioner, had observed, however, that milk maids would occasionally suffer a minor, short illness accompanied by a skin rash (i.e. cowpox), and that these maids would never be sick from smallpox, an otherwise often deadly disease eradicated from the world only in 1977.

versions of micro-organisms for which vaccines have either not existed before or been only marginally effective, are now making their way through the testing process. Thus, in a few years we are likely to have at our disposal vaccines against rotavirus, malaria, cholera and, hopefully, HIV.

Separately, recombinant technology is now being used to modify plants, rather than animal cell lines or micro-organisms, to produce vaccines. Likely to gain increased use in the future, this will enable many vaccines to be made for oral administration, thus overcoming many vaccine logistics constraints and the need for medically qualified or veterinary personnel and other costly elements currently necessary to carry out effective immunisations. The first potato-produced, edible hepatitis B vaccine is in clinical trial.

In addition to vaccines to *prevent* against micro-organisms, others – so-called therapeutic vaccines - based on combining immune pathology and genetic modification may soon revolutionise the *treatment* of many diseases – infectious as well as non-infectious. Some of these will stimulate an impaired immune response in an individual who is already infected with that organism and has mounted an inadequate immune response to that organism. The aim of administering a therapeutic vaccine may be to increase the individual's immunity to an organism that, for instance, is unable to provoke an appropriate response on its own. A vaccine against Helicobactor pylori, the causative agent of duodenal ulcers is being tested. Other vaccine approaches under development modulate the immune response in rheumatoid arthritis and related disorders, the pathological mechanisms of which involve an inappropriate, so-called autoimmune process. Similarly, vaccines are being developed for use in the treatment of diseases, such as asthma, hypertension, atherosclerosis, Alzheimer's disease and others, in which so-called endogenous[7] substances, are known to play a role. Also, and perhaps at an even more advanced stage, there are vaccines against specific cancers, e.g. melanoma, breast cancer, colon cancer[8], or even one that may offer more universal protection against cancer.[9]

Not related to vaccines, but nevertheless at the epistemological intersection of immunology and recombinant technology, attempts are underway to modify the coding – by cut-and-paste recombinant technology – for the so-called immunomodulators. These are naturally occurring molecules (cytokines, interleukins, interferons) with broader, regulatory effects on the immune system, as well as on several other biological functions, such as wound healing, nerve cell repair, blood cell formation. While the use of interferon – as a drug - in multiple sclerosis has been the topic of a recent debate, the ability to adjust 'own' production of these modulators may have important applications in a majority of the diseases currently plagueing mankind.

Monoclonal antibodies

While vaccines are antigens which, when inoculated, cause the immune system to produce antibodies, recombinant technology is being used, as well, to produce antibodies directly. In this variation on the immune/genetics theme, single cell lines, i.e. cloned, wholly identical, specialised cells that can be grown indefinitely are used to produce antibodies of singular specificity - monoclonal antibodies. These are used in a number of diagnostic applications, as well as to prevent acute transplant rejection, and treat leukaemias and lymphomas. Some show promise against auto-immune diseases.

Gene Therapies

While the above applications mostly rely on using modified organisms or cell lines to produce substances *in vitro* that can then be used to treat or prevent human disease, gene therapy is distinctly different in that it essentially modifies the patient's own genetic setup. In other words, while the aim remains the manipulation of a specific gene into a designated host cell,

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[7] These are biologically active chemicals produced by the body; in the case of these disorders for reasons not well understood.

[8] SCRIP, March 16th 2001: Therapeutic vaccines on the horizon.

[9] Duke University Medical Center: Universal cancer vaccine shows promise in lab. 29 August 2000 at:http://www.dukenews.duke.edu/Med/vaccine1.htm

the ‘host’ is a ‘population’ of cells in situ in the human body. In contrast to the above technologies, gene therapy takes place *in vivo*[10].

Technical details differ, but gene therapy essentially makes use of an approach similar to recombinant technology. An isolated gene encoding for the desired characteristic is spliced into the genome of a virus[11], often itself modified so as not to cause disease. Infecting the host organism, the virus introduces the gene into the target cells to 'appropriate' the cells' protein-making apparatus. Gene treatment is likely to involve one of the following:

- Gene replacement, a substitution of a non-active or defective gene by a "new" (or additional), functional copy of the gene, to restore the production of a required protein. This technique is used in e.g. the treatment of cystic fibrosis and certain cancers;
- Gene addition, the insertion into the cell of a *new* gene, to enable the production of a protein not normally expressed by that cell. For example, the code for a stimulatory protein may be inserted to enhance an immune response to cancer cells;
- Gene control, the alteration of expression of a gene used, for example, to suppress a mutated onco-gene in tumour cells so as to prevent specific protein production.

Gene therapy was first used in 1990, for an enzyme deficiency. Since then, more than 100 clinical gene-therapy trials have been initiated world-wide. Most of the trials have been for the treatment of tumours (predominantly malignant melanoma and haematological disorders), but there have also been trials of gene therapies for genetic disorders, AIDS, and cardiovascular disease. While many technical problems are yet unsolved, in relation to vector design as well as to clinical safety and efficacy, gene therapy appears likely to become an important part of the armoury with which disease will be fought in the future.

Other Medical Biotechnology Applications

Stem cell research and cloning share technological approaches and are occasionally combined with recombinant technologies. However, rather than the ‘cut-and-paste’ approach to DNA in recombinant technology, the central premise of stem cell and cloning is to preserve the entirety of the genome and guide its ability to express itself for novel therapeutic applications.

Stem Cell Research and its Potential

Upon fertilisation, an egg cell initially starts dividing into undifferentiated cells from which, later, cells of increasing specialisation develop and from which eventually the highly differentiated cells in tissues of different organs stem. In human embryos, the potential for giving rise to cells of any specialisation is held only by very early, primitive, so-called *totipotent* stem cells, at the most up to the 16 cell stage. Identical twins (triplets etc.) originate from totipotent cells, i.e. the result of a cleavage of the embryo within a few days after fertilisation.

At the next stage of development, the now *pluripotent* stem cells have already acquired some degree of specialisation. While they are no longer individually able to give rise to a foetus, they are still able to differentiate into any cells of an adult human being. *Multipotent* stem cells can be derived from foetuses or umbilical cord blood, and are even present throughout life, although in progressively decreasing numbers in adults. Unless 'reprogrammed', the latter cells are probably only able to develop into specialised tissues or organs. Common to stem cells is their ability - under given circumstances - to multiply almost indefinitely and be stimulated to grow into a variety of specialised tissues, opening up vast possibilities of tissue repair.

Much of the controversy over stem cell research relates to the ethics of using cells deriving from aborted foetuses, seen by many as a violation of the respect for human life. In

[10] In vitro and in vivo are expressions designating that a process takes place in the test tube or in the living organism, repsectively.

[11] other vectors are used as well.

recognition of this, the debate has partly centred on the possibility of allowing stem cell research to be carried out on early embryos no longer needed for infertility treatment ("spare embryos") or resulting from in vitro fertilisation specifically for research. However, ethical concerns also arise from the potential of creating stem cells by cell nuclear replacement.

This technique involves removing the nucleus, i.e. the DNA, of an egg and replacing it with the nucleus of a cell from a given individual. This would enable the cultivation of pluripotent cells genetically almost identical to the person from which the nucleus was derived. Such cells would therefore not evoke an immune rejection, and transplant medicine would offer entirely new therapies. The problem, in moral terms, with nuclear transfer is its likeness - technically - to cloning, the creation of a true copy of an existing individual. However, while cloning and this particular pursuit of stem cell research largely share the technique of nuclear replacement, they differ significantly in that the latter involves the extraction of stem cells for the purpose of developing the tissue of a single organ - the heart, nerve cells etc.

The potential scope of stem cell research and derived applications is enormous. Improved transplantation therapy with tissue grown from stem cells in a laboratory would open the possibility of renewing heart muscle in congestive heart failure; replacing blood-forming stem cells to produce healthy red and white blood cells to treat e.g. AIDS and leukaemias; relining blood vessels with new cells as treatment for atherosclerosis, angina, or stroke; restoring islet cells in the pancreas to produce natural insulin in diabetics; or renewing of nerve cells in patients with Parkinson's disease or paralysis. Stem cell therapy may also bring a host of rare congenital disorders within therapeutic reach.

Cloning

Human cloning has become a highly emotive issue. However, unsensational and far from uncommon in nature, a clone is essentially the result of asexual reproduction, leaving clones with no choice but to accept a genome identical to that of their ancestor. Microbes reproduce by cloning; the chrysanthemum plants available at the local supermarket are clones of a long dead plant, as are the high-yielding vines in a Bordeaux vineyard. And one of a pair of identical twins is a clone of the other.

Cloning in modern biotechnology is based on cell nucleus transfer, and Dolly, the first mammal to be cloned, is the result of a transfer of the nucleus of an udder cell to an enucleated egg cell. Following this, the egg was implanted in the mother's uterus and went through a normal gestation. Contrary to public expectation, Dolly may not have made the cloning of a human being any likelier to happen; it simply may not be possible - other than in fiction. For while the principle would be the same as in sheep, 'switching' the genetic complement in the nucleus of, say, a skin cell from performing its rather specialised functions to taking on the highly complex role of orchestrating embryonic differentiation and development may not be feasible in some species, given a very limited 'window of opportunity'. Cloning a mouse, a mammal far better known as a laboratory animal than sheep, was tried unsuccesfully for a long time[12] and, after all, Dolly was the only success among about 300 attempts.

Even if human cloning were possible, its appeal may well be more fictional than real - partly a result of literary and cinematic hype. Aside from 'vanity cloning', a real demand for which remains dubious, cloning of humans may be of little value other than to those who are childless as a result of genetic disease. With a success rate of less than one per cent, however, this option hardly looks interesting. Add the many unknown factors related to the resulting child's genetic predisposition and the attractiveness of human cloning remains dubious. Thus, with no demonstrable benefits - and few supporters - prohibiting human reproductive cloning would appear to be straightforward.

Emphasising this point, the cloning of mammals has no value from the point of view of breeding of farm animals; for that, it remains far too risky and costly. Most, if not all, of its attraction derives from its potential in pharmaceutical production. Of particular allure is the

[12] Mice, cattle, goats, and pigs have now been cloned.

potential of having animals express proteins of therapeutic value in their milk. Interestingly though, this will be achieved through recombinant technology, i.e. insertion of the appropriate gene, as earlier described, rather than of cloning *per se*. In the context, however, cloning, is intended to enable the breeding of animals with a genetic setup that facilitates, or impedes least, the production of the required pharmaceuticals.

Applications in agriculture

The use of traditional plant protection agents, fertilizers and breeding will only be able to provide limited help for the world's continually growing population with its increasing demand for food. Biotechnology methods promise to have the power to lower the cost of food production, to increase yield and to produce food of higher nutritional value.

Applications of biotechnology in agriculture concentrate on the genetic modification of existing plant species. In this sense, genetic modification means the implantation of genetic material from other species into the DNA as described above where “natural” cross-breeding does not function. In terms of commercial importance, gene-manipulated (GM) crops corn, soya and other oilseeds are the main applications. Some others concern vegetables, such as tomatoes, and cotton. Strictly speaking, they fall within one of two broad categories: One group of applications focus on changing plant traits which are aiming at facilitating the treatment for the farmer. In the other group, biotechnology is used to change plant traits which benefit the final consumer.

Facilitating plant treatment

Currently, efforts to facilitate plant treatment for the farmer concentrate on pesticide resistance, pathogen or stress tolerance. Resistance to pesticides is the most widespread form of biotechnological applications in plants. Pesticides are commonly used to kill weeds, insects or fungi which threaten the normal growth of crops and, thereby, reduce their potential yield. Among all pesticides, herbicides against weeds stand out in importance. Weeds compete with the crop for minerals, water or light. Conventional herbicides, so-called “selective herbicides” kill only the weed and leave the crop intact. The effectiveness of herbicides is based on suppressing the production of specific “growth proteins” in the weed. The destruction of reproduction mechanisms for these specific proteins then quickly leads to the death, or, at least, to a slow-down of growth of the weed. As selective herbicides are aiming at the growth proteins of different weeds but not of the crop, biotechnology is used in identifying the relevant proteins and in tailoring the herbicide to a particular crop-weed system. It should be noted, however, that in this case neither the plants nor the herbicide are genetically modified.

Genetic engineering comes into play in the case of so-called “non-selective” herbicides. These are chemicals which do not differentiate between weed and crop but kill all plants – except for those with an in-built protection mechanism. GM crops dispose of this in-built protection as one or a number of genes in their DNA have been changed. The modified genes trigger the production of proteins which prevent the non-selective herbicide stopping the production of the vital growth proteins of the crop. The inserted gene is normally transferred from another plant species. Herbicide resistance is the gene-instigated reversal of the working mechanism of conventional selective herbicides.

Resistance to pests rather than to pesticides is another variant of in-built resistance. The most important form – soon to be commercialised - is crop resistance to insects. Instead of spraying insecticides on the plant, the modified plant DNA produces a protein which kills insect larvae. The genetic manipulation of crops requires both the identification of the essential gene in the donor organism and the subsequent isolation and transfer of the gene to the crop DNA. One example of a donor organism is the bacterium *Bacillus thuringiensis*. Insect resistant cotton might be one of the first products of this type commercially launched.

A third way to reduce treatment time for the farmer is to modify the crop DNA through activating the immune system of plants. Although not comparable to the animal immune system, plant cells which have been infected with, e.g. a virus, produce an immune reaction

which prevents the cell from being infected a second time. It has been discovered that this immune reaction is triggered by a particular viral protein. Inserting such a viral protein into the DNA of a crop makes the plant "feel" infected which stirs the immune reaction fighting the potential pest.

Current research focuses on another element of resistance, the so-called "stress tolerance". Hostile climate conditions in most parts of the developing world, including drought, cold temperatures or salty soil, severely hamper agriculture through high costs or low yields. Gene modification aims at "immunising" crops against those environmental conditions while keeping yields at normal levels. Up to now, there are no applications for commercial use.

For the farmer, pest or pesticide resistance or stress tolerance of crops is supposed to mean less and cheaper pesticides, less treatment time and higher yields. In addition, the environment is thought to benefit in terms of lower pesticide volumes and faster decomposition. However, it is still unclear whether resistance instigated by gene modification will not lead – e.g. through cross-breeding - to the creation of pesticide-resistant weeds and pests. In addition the farmer's dependancy on a small number of seed producers will increase.

Enhancing the nutritional value of crops

The second aim of biotechnological applications in agriculture aims at enhancing the nutritional value of crops. Whereas in the case of many GM crops, as described above, the farmer is supposed to be the beneficiary, enhanced nutritional value will be mainly an advantage for the consumer. The development of so-called "novel food", if safe and accepted by consumers, may not only help to alleviate the problem of malnutrition in some parts of the world but also contribute to improving the health of consumers. Food with a therapeutic effect has been coined "nutraceuticals".

The first genetically modified food product was the "FlavrSavr" tomato which was developed by Zeneca of the UK (today part of Syngenta) and commercially launched in 1994. The gene modification consisted in the de-activation of a gene resposnsible for decay. The lack of the protein, responsible for initiating the process of decay and produced by the de-activated gene, extended the shelf life of the vegetable and allowed the farmer a later harvest. The consumer benefitted from a fresher and more tasty tomato. After consumer restraint and protests, however, the GM tomato was withdrawn from the market.

Another string of research concentrates on increasing the concentration of vital ingredients in food. The most common examples are vitamins, mainly vitamin A necessary to prevent blindness, and the so-called "essential" amino acids lysine, methionine and threonine[13]. An example of vitamin-enriched plants is the so-called "golden" rice which got its name from the yellow colour. The golden rice DNA is altered to produce proteins which entail higher quantities of vitamin A. It is hoped that the rice, currently under field trial in Asia, will help to effectively address the problem of widespread blindness related to vitamin A deficiency.

Nevertheless, despite its vast potential, plant biotechnology is met with ***high levels of concern and suspicion from consumers in the EU*** (less so elsewhere). The fears mainly concern the untested environmental side effects such as a reduction of biodiversity through the creation of "super-resistant" plants with the potential to kill other species or the danger for human health, e.g. unintended allergic reactions. Apart from pest and pesticide-resistant GM crops, no other biotechnological application in plants is likely to achieve a breakthrough in the foreseeable future due to a lack of market success.

13 "Essential" in this sense means that the human body is unable to synthesize these amino acids. Instead, they have to be added through the food chain.

2. MARKET – STRUCTURE AND EVOLUTION

The biotechnology market is a cross-section of different industries. Up to now, the most important markets for biotechnology-based products are in pharmaceuticals, agrochemicals and seeds. Smaller applications can be found in environmental remediation (e.g. waste treatment) and in the substitution of conventional large-scale chemical synthesis by biotechnological processes (e.g. vitamins). With a market volume of about USD 17bn in 2000, biopharmaceuticals, that is pharmaceuticals with bio-active versus chemically active ingredients, is by far the largest market segment. It should be noted that this estimate is fairly conservative as it does not take into account the market for biotechnological applications in diagnostics, a fast growing segment whose size, however, is still difficult to assess.

In comparison with that, the market for gene-manipulated (GM) crops and related pesticides is rather small with less than USD 8bn. Biotechnology in the agrochemicals and seed markets mainly concerns GM seeds whereas related pesticides are tailor-made to increase efficiency of crop production in combination with GM seeds. But, the production process of pesticides remains conventional chemistry. Biotechnological applications in environmental remediation, which include mainly water and soil regeneration but also biodegradable plastics, account for less than USD 1bn. Taken together, the market for biotechnology products is estimated at around USD 26bn in 2000.

	Market for biotechnology (USD bn) in 2000	Average growth rate y-o-y (1995-2000), %	Biotechnology products as % of total market	Average growth rate y-o-y of total market (1995-2000), %
Pharmaceuticals	17.0	20	4.8	8
Agrochemicals and seeds	7.5	5	18.0	1
Environmental remediation	< 1.0	n.a.	< 10.0	n.a.
Others	<0.5	n.a.	< 0.1	n.a.
Total	ca. 26.0	ca. 15		

As can be seen from the table, biotechnology-based products have tended to grow much faster than the rest of the market: Growth in biopharmaceuticals has outpaced the market by a factor of 2.5 over recent years. As this is likely to continue, the share of biopharmaceuticals is set to increase further in coming years. Whereas growth of the agrochemicals and seed market has stagnated, GM seeds and related pesticides sales have grown at 5% per year. It can be safely assumed that their share will further rise at the cost of conventional pesticides and seeds in the future. Against this background, the market for biotechnology-based products is set to continue its above-average growth.

The rest of this chapter focuses on the most important market segments: pharmaceuticals and agrochemicals and seeds.

Pharmaceuticals

Market

In 2000, total sales of biotechnology-based pharmaceuticals (“biopharmaceuticals”) reached about USD 17bn – a share of 5% of total worldwide pharmaceutical sales (USD 350 bn). Of the roughly 100 biopharmaceuticals on the market, four reached sales of more than USD 1bn

each[14]. Regional patterns of biopharmaceuticals' sales reflect those for pharmaceuticals in general: North America accounts for roughly half of total sales, Europe for 25% and Japan for 16%.

Pharmaceuticals, in general, are likely to remain a dynamic growth market in coming years. The reasons for this are rising demand from an ageing population in the industrialised countries and often inadequate healthcare in the rest of the world. Facing these needs, biotechnology is seen as the key to providing better and cheaper healthcare. Biopharmaceuticals are considered as one of the main drivers of growth in pharmaceuticals in coming years. Between 1995 and 2000, they recorded growth of more than 20% per year. This compares with growth rates of between 7% and 11% for pharmaceutical sales in general[15]. The massive increase in biotechnological innovation has led to a number of new drugs in the pipeline – although most of them are still in the preclinical stage or Phase I and II of the approval process[16]. According to estimates, 30% of drugs currently in the R&D pipeline are based on biotechnology. This share might increase up to 50%. Thus, in the next decade, we are likely to witness the commercial launch of a large number of new biopharmaceuticals.

Currently, the majority of new biopharmaceuticals target the treatment of illnesses for which traditional drugs are already on the market. Patients should benefit from substituting "old" pharmaceuticals for "new" biopharmaceuticals in terms of more focused treatment, more convenient dosage (e.g. "once a week instead of twice a week", "pills instead of injections") and less side effects. The ensuing "cannibalising" of traditional drugs is likely to increase the pressure on pharmaceutical companies to invest increasing amounts of money in biopharmaceuticals. Future generations of biopharmaceuticals are aimed at diseases for which no (or limited) current treatment exists. Examples are HIV infections, Alzheimer's and Parkinson's disease. Furthermore, biopharmaceutical R&D is concentrating on other disease areas, notably the most common age-related illnesses cardio-vascular diseases, cancer, diabetes, stroke, renal failure and osteoporosis. Growth in these therapeutical areas is forecast to be high. In addition, whereas recently launched biopharmaceuticals consist of recombinant copies of natural human molecules, the next generation of biotechnological drugs will make use of newly designed substances which promise to address illnesses more effectively. A large part of the technology-driven growth of the pharmaceutical market is expected to come from this segment.

Knowledge-intensity

Biotechnology is one of the most R&D-intensive areas. This is particularly true for R&D in biopharmaceuticals. In 2000, global pharmaceutical R&D spending totalled roughly USD 55 bn. Pharmaceutical corporates spent almost 80% of this with the rest coming from focused biotechnology companies. On average, the pharmaceutical industry spends about 16% of sales on R&D. R&D intensity of industry leaders, Eli Lilly, Roche, Pfizer and GlaxoSmithKline ranges between 16% and 19%. 56% of total R&D expenses are incurred in the US.

An increasing part of the R&D budget of large pharmaceutical companies is spent on the clinical evaluation of new drugs ("clinical trials") – and not on drug discovery where knowledge creation is considered to be crucial. The share of R&D expenditure on clinical trials rose from 33% in 1996 to more than 40% in 2000 – and is likely to increase further. At the same time, the share spent on drug discovery has declined from 28% to 24%. Assuming, as mentioned above, that biopharmaceuticals make up 30% of new drugs, corporate R&D spend on biotechnology-based drug discovery can be estimated at roughly USD 4bn annually. This adds to the USD 11bn spent by biotechnology companies themselves.

Biopharmaceuticals can be divided into five categories according to their biological function and chemical structure:

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14 Pharmaceuticals with sales of more than USD 1bn are usually referred to as "blockbusters".

15 Valued at manufacturers' selling prices in constant US-dollars; data from IMS Global Pharma Forecasts.

16 The approval process consists of the pre-clinical and a clinical phase. The latter comprises three stages (Phase I to III). At the end of 2000, almost 280 new biopharmaceuticals of European public biotechnology companies (including Israel) underwent pre-clinical and clinical trial. More than a third was in the pre-clinical stage, whereas roughly 10% were in Phase III of the clinical trials which precedes market launch.

- Proteins
- Antibodies
- Nucleic acids
- Glycotherapeutics
- Cell – or tissue based therapeutics

Proteins have been the most successful biopharmaceuticals so far in terms of sales. They can be subdivided into cytokines, hormones, clotting factors, tissue plasminogen activators and antigenes (vaccines)[17]. Among these, drugs based on cytokines currently dominate the market. Cytokines include growth factors, interferons and colony stimulating factors. 27 of the top 30 biopharmaceuticals use cytokines as active ingredients.

The table on the next page contains a selection of the most important biopharmaceuticals on the market, or in clinical trial, sorted by disease area.

In 2000, the top selling biopharmaceuticals were Procrit (Johnson & Johnson) and Epogen (Amgen) which recorded sales of USD 2.7bn and USD 2bn, respectively. Humulin had sales of more than USD 1bn. Biogen's Avonex accounted for USD 800m. Hepatitis drugs Intron A and Rebetron reached sales of USD 700m, respectively.

While protein-based biopharmaceuticals currently account for the majority of commercial applications in healthcare, drugs using monoclonal antibodies have become the single most dynamic segment. A large and still growing number of monoclonal antibodies (MAb) is in the drug pipeline: The main therapeutic areas targeted are oncology (mainly cancer) and diabetes.

[17] See chapter 2.

DISEASE AREA	ON THE MARKET	PHASE III	PHASE II	PHASE I
Alzheimer's disease			- CX516 (Cortex)	- AN-1792 (Elan/AHP) - CEP-1347 (Cephalon)
Cancer	- Epogen/Procrit (Amgen) - Herceptin (Genentech) - Leukine (Immunex) - Neupogin (Amgen)	- BEC2 (ImClone Systems/Merck) - CeaVac (Titan) - Neovastat (Aeterna Laboratories) - NESP (Amgen) - Onconase (Alfacell) - Panorex (Centocor/Glaxo) - Prinomastat (Agouron)	- Avicine (AVI Biopharm.) - GVAX (Cell Genesys) - SU5416 (Sugen)	
Cardiovascular	- ReoPro (Centocor/Eli Lilly) - Retavase (Roche/Centocor) - Activase (Genentech) - Integrilin (COR Therapeutics/Schering-Plough)	- TNKase (Genentech/Boehringer Ingelheim) - Lanoteplase (BMS)	- 5G1.1-SC (Alexion Pharmaceuticals) - ALT-711 (Alteon) - Angiomax (Biogen/The Medicines Co.) - Cromafiban (COR Therapeutics/Eli Lilly)	
Diabetes	- Prandin (Novo Nordisk) - Humalog (Eli Lilly) - Humulin (Eli Lilly) - Novolin (Novo Nordisk)	- rDNA (Inhaled Therapeutic Systems) - SYMLIN (Amylin Pharmaceuticals)	- rDNA AI-401 (AutoImmune) - SomatoKine (Celtrix Pharmaceuticals)	- Insulinotropin (Scios/Novo Nordisk) - Altered Peptide Ligand (APL) - AC2993 (Amylin Pharmaceuticals)
Growth retardation	- Genotropin (Pharmacia) - Humatrope (Eli Lilly)			
Hepatitis	- IntronA (ICN Pharmaceuticals/Schering-Plough) - Rebetron (ICN Pharmaceuticals/Schering-Plough)			
Inflammatory disease	- Avonex (Biogen) - Enbrel (Immunex)			
Multiple sclerosis	- Avonex (Biogen) - Betaseron (Schering)			
Osteoporosis		- ALX1-11 (NPS Pharmaceuticals)	- PODDS (Emisphere Technologies/Novartis) - SomatoKine (Celltrix/Insmed)	- OPG (Amgen)
Parkinson's disease			- NeuroCell-PD (Diacrin/Genzyme)	- CEP-1347 (Cephalon) - GDNF (Amgen) - GPI-1046 (Guilford/Amgen) - GPI-1216 (Guilford/Amgen) - NIL-A (Guilford/Amgen) - NT-3 (Amgen/Regeneron) - Spheramine (Titan Pharmaceutical/Schering)
Renal failure	- Epogen/Procrit (Amgen) - Renagel (GelTex Pharmaceuticals/Genzyme) - Orthoclone OKT3 (Ortho Biotech) - Simulect (Novartis/Ligand) - Zenapax (Roche)		- NESP (Amgen)	- Osteogenic Protein-1 (Creative BioMolecules)

Market structure

With sales of USD 17 bn and a number of new products about to be approved and launched on the market, the biopharmaceutical industry is slowly reaching a first and preliminary stage of consolidation. This is reflected by an emerging market structure which mainly consists of two different stages: a “traditional”, “downstream” segment where pharmaceuticals are sold to patients and an “upstream” stage for the sale of knowledge from so-called “drug discovery” companies to large pharmaceutical companies.

Biotechnology companies are active in both stages. While the bulk of recently founded, small biotechnology start-ups focus on providing services to established, large pharmaceutical companies, the more mature and grown-up biotechnology companies dispose of own, branded drugs which they market directly to patients. Reflecting this two-stage structure, one can currently find three types of player in the market:

- Established pharmaceutical companies (“big pharma”, e.g. Pfizer, GlaxoSmithKline, Merck, AstraZeneca, Novartis, Aventis)
- “Big” biotechnology companies (e.g. Amgen, Genentech, Millenium, Alza, Gilead, MedImmune, Celltech, Shield, Shire)
- Small biotechnology companies

Depending on their role in the market, each company type follows its own business model:

Business model

As a general rule, big pharma and big biotechnology companies are buying services from smaller biotechnology companies. These services take a number of different forms. First, *“drug discovery”* companies specialise in searching for new molecules which promise to have the desired pharmacological effects. A second group of companies focuses on providing enabling technologies, so-called “tools”, which help other companies to find new molecules or to improve the process of getting them from laboratory to industry scale-up (so-called *“toolbox companies”*). A third type of biotechnology company concentrates on providing techniques and equipment to handle the vast amount of data necessary to systematically screen molecules for their effects (so-called *“bioinformatics”*).

Traditionally, big pharma companies were highly integrated businesses which cover everything from early stage R&D to production and sales & marketing. In the 1990s, driven by breakthroughs in biotechnology and increasing demand across the industrialised world, the pharmaceutical industry started to consolidate. The main reason for this was the need to keep up with the pace of technology and to capture the opportunities of a fast growing, global market. Today, big pharma companies are confronted with high expectations from markets and shareholders to keep up profitable and stable growth. The main challenge is to increase sales through a continuous stream of new blockbuster drugs while, at the same time, filling the rising gap of patent expiries with new products from R&D. Within the industry, large-scale mergers and acquisitions were seen as the only way to acheive critical size in terms of R&D budget and marketing and sales impact in all regions. But even record R&D budgets of up to USD 5bn per year are not enough to guarantee the launch of at least four blockbuster drugs per year, developed in-house, to satisfy growth and profitability targets. Small biotechnology companies which sell their expertise to identify new products or to support enabling technologies are seen as one possible solution.

With small biotechnology companies on the one hand and big pharma companies on the other, big biotechnology companies are stuck in-between. Up to now, there is only a handful of biotechnology companies who have been successful enough to achieve the necessary size to pass the lengthy and costly approval process and launch their own drugs. Amgen and Genentech of the US or Celltech of the UK fall into this category.

Technology development and drug discovery have become a lengthy and highly risky business. Drug development times have increased to more than ten years on average – reducing the time to reap profits before patent expiry to less than seven years. The main reason may be found in stricter and more broad-based clinical trials before approval is granted from regulatory authorities[18]. In addition to that, as the recent example of Bayer's withdrawal of its potential blockbuster, Baycol, shows, the risk of failure after market launch has risen in line with the increase in therapeutical complexity. The growing dilemma for big pharma (and big biotechnology) companies consists in serving two conflicting aims. On the one hand, investors require stable profits, driven by strong top-line growth in high margin products. This can only be achieved by a continuously accelerated market launch of new drugs. On the other hand, risks in providing a continuous stream of new products are rising.

Alliances

As a way out of this dilemma, drug companies are trying to spread the risk of drug development by entering into a large number of "alliances" with small drug development companies. Under this form of division of labour, big pharma companies specialise in marketing and distribution while small biotechnology companies focus on innovative drug discovery. Drug discovery companies normally receive an up-front payment to be able to continue work on the product plus milestone payments when defined targets have been reached. In some cases, remuneration is also linked to future sales of the new drugs. This is usually referred to as "in-licensing". Currently, a significant proportion of R&D expenses of big pharma companies are spent on alliances. The number of vertical alliances has seen a steep rise over recent years[19]. In comparision with mergers and acquisitions, preferred among big pharma companies, this type of co-operation has been described as a "virtual network". The value of the drug discovery and technology alliances is estimated at around USD 15bn.

However, what looks like a healthy symbiosis in a network of complementary assets, often turns out to be a shift in burden sharing. Given the dominance of big pharma companies over their small technology and innovative drug suppliers in terms of market power, the former try to offload the growing inherent risk of drug development. This becomes obvious by the fact that big pharma companies increasingly try to postpone the in-licensing of new drugs to the latest possible moment before global market launch. In some cases, drug discovery companies are required to test-launch the new drug on some national markets at their own risk before global launch. Thereby, the risk of costly failure during clinical trials or early market launch is borne by the small drug discovery company[20].

As a result, knowledge creation will be concentrated more and more among small drug discovery and technology companies, of which biotechnology start-ups will presumably become the most important part. It still remains to be seen whether big pharma companies can keep their market positions by increasingly outsourcing R&D while focusing their core competencies on market launch and life-cycle management. Whatever the outcome, the resource-intensive work of invention, innovation and knowledge creation is likely to be increasingly transferred to the smaller players. Even if a number of future big pharma companies later emerge from this group of smaller players, the market environment for biopharmaceuticals will remain highly volatile and characterised by an unstable market structure.

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18 Only recently, the US regulator, Food and Drug Administration (FDA), again tightened requirements during clinical trials. The stricter practice has already led to a number of delays in market launch for leading big pharma companies.

19 The number of strategic alliances has risen from 179 in 1997 to 403 in 2000. This trend is likely to continue: in the first half of 2001, already 242 new alliances were registered.

20 Recently, however, the drying up of the in-house R&D pipeline has significantly increased, leaving some big pharma companies desperate to find possibilities for in-licensing. The ensuing shift in negotiating power has resulted in some small biotechnology companies receiving larger shares of future drug sales revenue.

Agrochemicals

Agrochemicals and seeds is a USD 43bn global market. It consists of two segments: pesticides and high-value seeds. The pesticide market recorded sales of nearly USD 31bn in 2000 whereas the high-value end of the global seed market accounted for about USD 12bn[21]. As far as pesticides are concerned, North America makes up roughly 40% of the total, Europe accounts for about 30%, Asia and the Pacific region for 15% and Latin America for 13%. In comparision, the high-value seed market is much more skewed towards North and Latin America. Herbicides make up roughly half of total pesticide demand, insecticides account for a quarter, fungicides for one fifth and others (e.g. chemicals for growth control) for 4%. The market for agricultural biotechnology is divided into USD 2.7bn for pesticides and USD 4.8bn for the seed business. This adds up to a total current biotechnology-based market volume of USD 7.5bn, roughly 40% of that in pharmaceuticals.

Technology

Biotechnology in the agrochemicals and seed markets mainly concerns the gene manipulation of seeds. Gene-manipulated (GM) seeds show a desired, slight variation in traits such as resistance to, either, specific pesticides or pests, higher yields or enhanced nutritional value. Pesticide resistance can be considered as the first generation and, currently, the most common form of gene manipulation of crops. Pesticide resistance allows for the use of non-selective pesticides which kill all plants except for those with an in-built resistance to it, such as the crop. The potentially lower dosage of pesticides and more effective weed control should help to generate higher crop yields at lower costs. Products currently on the market such as Monsanto's "Round-up Ready" or Aventis' "StarLink" are advertised with the promise to generate 10% higher yields than conventional crops[22]. The tailor-made pesticides, used in combination with the GM crop seed, are still produced on the basis of conventional chemistry. The crop seed and the pesticide are sold together as one "technological package". The most wide-spread applications are in herbicide and insecticide resistance[23].

A second generation of GM crop seeds, currently under development, promises an increase in plant quality such as higher nutritional value and better taste. Examples are Monsanto's "beta-carotene rich "golden" rice, currently tested in field trials in Asia, or the "FlavrSavr" tomato, originally invented by Zeneca of the UK (today part of Syngenta), which slows down and delays natural decay. Another trait of second-generation GM crops will be resistance, not to pesticides, but to pests – thereby dramatically reducing the need for pesticides. Insect-resistant cotton is likely to be the first product on the market.

In comparison with biopharmaceuticals, where benefits for the consumer in terms of a less expensive and improved effectiveness of treatment are evident, the merits of GM crops for the consumer are less obvious. Benefits from the use of GM crops are shared between the seed producer, the farming and the food industry. It is presumed that as long as no clear advantage for the consumer becomes evident, resistance to GM food will persist in some countries. For example, studies show that in the case of GM corn seeds most, but not all of the benefits from the new technology, are reaped by the seed producer, the rest being left with the farmer. Intriguingly, public concerns about food safety and the environment are most widespread in Europe and Japan whereas in North America, resistance is significantly less pronounced. Currently, commercialisation of GM crops is effectively blocked in Europe.

In developing countries, on the other hand, the use of GM crops is clearly less controversial as the new technology is seen as a key to solving the problem of malnutrition through higher yields and enhanced nutritional value. Most of the countries in the developing world face the

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21 This analysis focuses only on the high-value part of the seed market which is relevant for biotechnological applications and excludes conventional seeds.

22 The contention of a higher yield combined with less pesticide requirements is questioned by some analysts and farmers which cite evidence from across the world which shows that at least equal levels of pesticide dosage are necessary to get the same yield.

23 There are currently no GM crops with resistance against fungicides on the market.

double challenge of a fast rising population and a simultaneous impairment or even a reduction of agricultural land. The so-called “golden” rice, is one example of a GM crop tailored to address the most urgent problem of these countries - in this case the prevention of vitamin A deficiency. The same applies to other sorts of GM rice which require considerably lower amounts of often scarce water.

R&D/knowledge intensity

In comparision with pharmaceuticals, agrochemicals are clearly less dependent on R&D. Market leader Syngenta spends about 11% of sales on R&D. Average figures for the industry are around 8%. Agricultural biotechnology, however, requires significantly higher levels of R&D expenditure. As with pharmaceuticals, an increasing share of R&D spending goes into field tests and (mostly national) approval procedures which have become more lengthy and costly. As a consequence, larger and financially strong companies have advantages in getting market approval and access over their smaller rivals.

Applications/use

Apart from very small applications in vegetables (e.g. tomatoes), GM crop seeds mainly gained market shares in soybeans and corn (maize). In 2000, about 100m acres of agricultural land were planted with GM crops, an increase of 2500% over 1999. About 70% of this concerns soybeans, the rest is planted with corn. In the US, the percentage of GM soybean acreage has reached 65%, in Argentina it is as high as 95%. For corn, the shares are lower with 25% in the US. For the coming years, the percentage of GM crops is expected to increase further, especially in North America.

For the future, it is anticipated that other GM crops such as cotton and rice will see a similar surge, particularly across Asia.

Growth

The global market for agrochemicals is forecast to stagnate up to 2005 with growth of about 1% annually. Market dynamism will be severly constrained by the economic slowdown of the world economy and the fall in agricultural commodity prices. The outlook is particularly clouded in Europe where market regulation and consumer restraint in the wake of a number of food scandals weigh on demand for agricultural products in general and GM food crops in particular. Compared to that, growth in North and Latin America will be somewhat higher. Longer-term forecasts predict a continuation of sluggish growth.

Contrasting with that picture, the prospects for biotechnological applications in agrochemicals and seeds are brighter: GM crops and related pesticides are forecast to grow strongly at more than 5% per year at the cost of conventional agrochemicals and seeds. The decline in demand for conventional agrochemicals is expected to come in two steps. First, increased use of “first generation” GM crop seeds reduces the amount of so-called “stand-alone” pesticides. Stand-alone pesticides are those in use today, which are not specifically tailored to be applied in combination with GM crop seeds. In a second step, pest resistance (not to be confused with pesticide resistance) of second generation GM crops will again lower demand for pesticides. It is estimated that, at the end of the substitution process around 2010, 50% of the global herbicide and 30% of the insecticide market will have been transferred to GM crop seed producers. Fungicides are anticipated to be left almost unaffected.

By 2005, the combined GM crop and related pesticide market will have a size of roughly USD 10 bn, that is about 22% of the total market.

Market structure

Although agricultural biotechnology directly affects only the seed market, its impact on the market for agrochemicals is tremendous. Most likely, both markets will merge in some years from now. This notwithstanding, it is worthwhile to look at each market independently.

Over recent years, agrochemicals have become a highly concentrated market. The largest ten players accounted for 82% of the market in 2000. The largest seven (soon to be six) producers are Syngenta (formerly the agrochemicals business of Novartis and Zeneca), Monsanto, DuPont, Aventis CropScience, BASF, Dow Chemical and Bayer[24]. Together they make up almost three quarters of the market. Interestingly, while synergies from R&D in biotechnology were originally seen as the main reason for the formation of so-called "life science" companies, the current demerger of agrochemicals from pharmaceutical companies marks the end of the life science strategy. The foundation of Syngenta and the sale of Aventis CropScience to Bayer which announced it will manage the business in a separate company signal a parting of the ways for pharmaceutical and agricultural biotechnology.

Compared with agrochemicals, the seed market underwent a similarly dramatic consolidation process recently but is still less concentrated. In 1994, the top 12 producers accounted for 20% of the market, Today, this share is held by the top three players. The top ten companies make up 30% of the market. The main players in the seed market are Cargill, Archer Daniels Midland (ADM), Bunge and Continental. They are pure seed companies with large interests in the trading of agricultural products. To get a foothold in the rapidly expanding GM crop seed market, the leading agrochemical companies have entered the high-value end of the seed business. Today, DuPont, Monsanto, Syngenta, Aventis and Dow sell their own GM crop seeds. The other major players such as Bayer and BASF can be expected to follow soon. The following table summarises the current situation in terms of sales and market shares.

Company	Agrochemical sales (USD m, 2000)	Seeds/biotechnology sales (USD m, 2000)	Total (USD m, 2000)	Market share (%)
Syngenta	5.9	1.0	6.9	16
Monsanto	3.6	1.6	5.2	12
DuPont	2.0	1.8	3.8	9
Aventis CropScience	3.5	0.2	3.7	9
BASF	3.3	0.0	3.3	8
Dow Chemical	2.6	0.2	2.8	7
Bayer	2.3	0.0	2.3	5
Sumitomo	0.8	0.0	0.8	2
MAI	0.7	0.0	0.7	2
FMC	0.7	0.0	0.7	2
Total market	31.0	12.0	43.0	100

Alliances

The foreseeable merger of agrochemicals with the high-value end of the seed business has already led to a number of acquisitions and alliances. Dow Chemical acquired parts of ADM's seed business, Cargill teamed up with Monsanto and Syngenta is in an alliance with ADM. Meanwhile DuPont decided to go it alone on the basis of its strong Pioneer division. Apart

[24] After closing the acquisition of Aventis CropScience, Bayer CropScience will be second behind Syngenta.

from exploiting the potential of biotechnology, these alliances target a wider vision in the long-term, the integration of the whole GM food chain into one company ("from gene to supermarket").

The upcoming merger of agrochemicals with a part of the seed industry throws up a number of problems. The basic problem is that of merging two industries with distinctly different strategies and cultures. The second is that established seed producers often lack a sound base in GM crop technology. Most of the chemical companies in agrochemicals continue to invest heavily in it because agrochemicals add a distinctive non-cyclical and high margin business to their portfolio. As has been stated above, the pressure on chemical companies to enter biotechnology and GM seeds is rising as sales and profits from conventional agrochemicals decline dramatically. GM seeds are the only segment of the market which is expected to grow significantly in the future.

Teaming up with established seed producers aims at getting a foothold in biotechnology and increasing market share as fast as possible. However, as all large agrochemicals producers are rushing to acquire parts of the lucrative segments of the seed business at the same time, prices for the few available assets have risen to comparatively high levels[25]. Combined with a stagnant market, net margins can be expected to fall – wiping off much of the putative benefits of the business. Second, integrating a research- and capital-intensive industry with a small-scale business, whose tradition lies more in trading than in production, consumes a large amount of management capacity.

The potential "cultural clash" between the agrochemical and the seed business and the lack of technology of established seed producers may be the reason why some agrochemical producers simultaneously follow an alternative path: Some of them have already acquired small-scale biotechnology start-ups with a sound technology base in plant genomics. In addition, they have entered into research agreements with public institutions (e.g. universities). Examples of this increasing trend are BASF's acquisition of Swedish GM seed company Svalöf Weibull.

Compared with the situation of biotechnology in pharmaceuticals, the number of start-ups in agricultural biotechnology is considerably smaller. On the one hand, this might reflect the less encouraging market outlook of a comparatively small market, moderate growth and a high concentration among producers which leaves small start-ups with less room for growth. On the other hand, this situation is the result of a consolidation phase in the 1990s when independent biotechnology companies were snapped up by large incumbents. However, while fruitful and valuable in terms of technology transfer to the chemical companies, this type of alliance has the disadvantage in that it does not provide the large agrochemical players with the urgently needed market access to farmers in the seed market.

As a result of the rising number of alliances and fierce battles for technological leadership in the market, another problem arises: the increased degree of concentration in the industry leads to the dominance of a handful of large players over modern crop and agrochemicals technology. In some cases this has already led to discriminative pricing between different national markets. A second development has also given rise to fears of market dominance: GM seeds are often sold in the framework of contracts which generally preclude seed-saving by farmers. Saving seeds for further sowings is a long-established tradition in the crop business[26]. Some companies such as Monsanto have taken action against seed producers who attempt to save seeds, on the basis of "infringement of intellectual property rights". In general, agrochemical companies have developed technologies that render GM crops sterile. If this trend continues, farmers will depend on a few seed suppliers. A possible abuse of pricing power cannot be excluded.

[25] Recent deals have been closed at prices of about seven to eight times future expected EBITDA.

[26] It is estimated that, today, about 25% of soybean and wheat seeds are farm-saved.

3. FINANCIAL RESOURCES AND AVAILABILITY

The funding structure of the global biotechnology industry is heavily skewed towards equity funding. In 2000 alone, biotechnology companies raised almost EUR 40bn worldwide, an increase of 540% over 1999 and more than the aggregate amount of the five years before. Only 15%, or EUR 6.6bn, of that total went to European companies. Although there is a lack of exact statistics, it can be assumed that other forms of finance such as debt or public funding in forms of subsidies or research contracts are dwarfed by the value of new equity. However, this trend was mainly driven by the development of the stockmarket in that particular year.

The following table shows a breakdown of the development of equity financing in biotechnology:

TYPE OF EQUITY (EUR bn)	EUROPE		US		TOTAL	
	2000	1999	2000	1999	2000	1999
IPOs	3.0	0.3	6.7	0.6	9.7	0.9
Capital increase and others	2.4	0.2	23.2	4.3	25.6	4.5
Venture capital	1.2	0.6	3.2	1.4	4.4	2.0
Total	6.6	1.1	33.1	6.3	39.7	7.4

Source: E&Y European Life Sciences Report 2001

It should be noted that the year 2000 was a record year for the stockmarket in general. A similar picture to that of biotechnology can be drawn for other high tech sectors which benefitted from investor optimism. Indications (from half-year figures) are that equity funding to the biotechnology sector in 2001 will be no more than 50% of the 2000 level. This development is reflected by the increase of equity finance for biotechnology raised on the stockmarket compared with venture capital and private equity finance. In 2000, stockmarket-raised equity rose more than six times, compared with 1999, whereas venture capital increased “only” by the factor of two. In general, stockmarkets contributed almost 90% of equity finance for the biotechnology industry. In 1999, that share was about 70%. The overall decline of the stockmarkets in the second half of 2000 and in 2001 has virtually closed the “easy” access of biotechnology companies to this type of finance.

In 2000, European biotechnology companies raised about EUR 2.95bn through IPOs. German IPOs account for 28% of total amounts raised, followed by the UK with 14%, Italy with 10%, the Netherlands with 8%, Switzerland with 7% and Sweden with 5%. Interestingly, three Israelian IPOs succeeded in collecting nearly EUR 170m, or 6% of the total. Most of the European IPOs were placed on Germany’s Neuer Markt (37%), although some of them were listed simultaneously on the NASDAQ. The London Stock Exchange attracted 13% of the total volume, followed by Italy’s Nuovo Mercato.

In comparision with the US, however, the European biotechnology sector is still less dependent on stockmarket finance. The overall volume of equity finance in Europe is still considerably smaller than in the US. The limited access to equity finance becomes even more obvious when compared with the number of companies: Whereas there are about 1,300 biotechnology companies in the US, Europe counts roughly 1,600 firms. On average, US companies have sales of about EUR 19m, compared with less than EUR 6m in Europe. As stockmarkets tend to reward size, larger US companies have disproportionately profited from the boom. The ability of US biotechnology companies to raise larger amounts of equity over the stockmarket is also reflected by the amounts raised in the years after their going public: US companies, on average, raised EUR 414m compared with just EUR 33m for European start-ups.

As a consequence, European biotechnology companies are much more dependent on other forms of equity financing, notably venture capital and private equity, than their counterparts in the US.

Public funding

In the five-year period between 1994 and 1998, public funding of biotechnology in Europe reached about EUR 10bn[27]. 17% of that total came from the European Commission's life science programmes[28], the rest from national and regional programmes. National programmes in Germany, the UK and France together accounted for EUR 7.7bn, or 77% of total spending. This compares with about EUR 6.4bn (USD 6bn) which was spent at the federal level in the US in 1999 alone[29].

COUNTRY	TOTAL PUBLIC FUNDING OF BIOTECHNOLOGY 1994-98 (EUR bn)	SHARE (%)
Germany	3.0	30
UK	2.6	26
France	2.1	21
Belgium	0.6	6
Netherlands	0.3	3
Sweden	0.3	3
Finland	0.2	2
Italy	0.2	2
Norway	0.2	2
Denmark	0.1	1
Portugal	0.1	1
Others	0.3	3
Total	10.0	100

Compared with the size of its economy, Italy's share of just 2% of public funding within Europe is remarkably low.

Public funding is generally aimed at complementing private industrial activity in those sectors where either public interest (e.g. public health) or public infrastructure is concerned. Public funds normally come from state bodies at the European, national or regional level. In most European countries, significant amounts for the support of R&D in public institutions come from industry. This holds especially true for Germany, the UK and France, but also for smaller countries such as the Netherlands, Sweden, Denmark, Switzerland and Iceland.

In addition to state and industry funding, charities play an important role in financing biotechnology in some EU member states. In Sweden and the Netherlands they contribute more than a quarter of total financing. Charities in France and Portugal account for around

27 See European Commission: Inventory of public biotechnology R&D programmes in Europe. The study covers 14 EU member states (except for Luxemburg), Iceland, Norway and Switzerland.

28 Mainly through the "Biotechnology II", the "Biomed" and the "FAIR" programmes.

29 See: European Biotechnology Innovation System, EC Policy Overview, University of Sussex, October 2000. It is estimated that spending on the level of individual states is on the same order of magnitude.

20%, those in the UK and Norway for about 15%. In sum, charities' contributions are estimated at roughly EUR 1.1bn in the period between 1994 and 1998.

The majority of public funding is not specifically directed to biotechnology, but is channeled indirectly through various budgets with an, often, general-purpose character. Only 31% of total funding is spent on R&D through specific biotechnology programmes, another 13% through general programme funding. On the other hand, 56% of total public funding of biotechnology is spent through general financing of the national or regional R&D systems, e.g. block funding of research institutions with a research agenda not specifically dedicated to biotechnology[30].

Regarding the allocation of public funding to different areas of biotechnology, almost half of total funding goes into human and veterinary biotechnology which is largely identical with pharmaceutical biotechnology[31]. Research into the basic principles of biotechnological processes account for about one fifth, plant and animal biotechnology for 9% and 8%, respectively. Industrial biotechnology makes up 6% and environmental biotechnology 3% of total spending. There is some evidence that public funding of different biotechnology areas generally reflects industrial activity. Pharmaceutical and plant biotechnology are given priority with a combined share of almost 60% of total public funding.

Regarding the specialisation of individual countries on different areas of biotechnology there is no clear picture. Almost all countries support R&D in pharmaceutical-related areas. Contrary to that, only a small group of countries such as Italy, Belgium, Spain and Ireland puts emphasis on the more controversial plant biotechnology. Given its competitive advantage on the global market, it is striking that there is a lack of public R&D funding for biotechnology in environmental technology.

As a conclusion, access to private or public funding for European biotechnology companies has improved over recent years. In comparision with the US, the amount of privately financed funds raised – especially those over the stockmarket - has been considerably smaller in Europe. Although serious efforts have been made, public funding of biotechnological R&D still clearly lags behind the US. In addition, European public R&D funding is highly concentrated on a small number of – mainly larger – countries. All in all, the lower amount of funds available to European biotechnology companies weighs on their ability to grow.

30 This is usually referred to as "non-policy directed funding". This way of indirect financing is particularly common in France where more than 90% of total funding for biotechnology is spent through this mechanism.

31 For the definition of the breakdown of biotechnology into different areas, see: European Commission: Inventory of public biotechnology R&D programmes in Europe. As there is considerable overlap between some of the areas, conclusions have to be drawn with some caution, particularly, as they do not fit with boundaries of single industries.

4. ETHICS

Modern biotechnology opens up vast global social and economic opportunities. It is, however, inconceivable that science will be able to deliver the benefits at no risk. In such circumstances, ethical conduct essentially means acting responsibly, i.e. to weigh up carefully the benefits and harm that one's own actions can bring - and to act accordingly. In practical terms, the prospect – for some a moral imperative - of using genetically modified crops to increase food production so as to meet basic nutritional needs in developing countries must be considered[32], for example, against possible social, industrial, or other negative effects.

Another important dimension of ethics is to do with the maintenance of people's rights, e.g. the right of consumers not to be involuntarily subjected to the potential risks of GM foods or the right to choose not to consume such foods; the rights of people in developing countries to have their interests considered in international policy-making and regulatory regimes. A third aspect to bear in mind is that of justice, or fairness, e.g. is it fair that only people in the rich part of the world have access to medicines against e.g. HIV, with 90 percent of all HIV patients living in poor countries whose economies are being devastated by the epidemic.

In practice, ethical concerns assume different weights in relation to different members of the biosphere. Plants – as opposed to humans and some animals – are not perceived as having 'rights' on an individual basis and issues here mainly have to do with the ecological and social aspects of plants, cultivation and processing, and of final plant products. In veterinary and human biotechnology, the rights of animals become important issues as obviously does, in the instance of the latter, respect for individual and social *human rights*. Cutting across these issues are concerns with intellectual property rights and the patentability of genes.

Bearing in mind these ethical concerns about and the inherent complexities of biotechnology, the Bank's services will very carefully consider its engagement in the sector on an individual basis and, in any case, always in line with the relevant EU and National Policies.

[32] Greenpeace, otherwise firmly against GM crops, has acknowledged that vitamin A enhanced rice may be acceptable (Scrip Magazine March 2001).

5. THE REGULATORY FRAMEWORK

Biotechnology is being applied towards a multitude of research and manufacturing processes and is included in an increasing number of final products. However, it is clearly the genetic modification of crop plants – much more so than of animals – that has attracted the most attention from regulators and lawmakers. This applies in particular to the conditions under which such plants are used experimentally and industrially, or released for planting. Concerns have naturally centred on environmental effects, particularly biodiversity, and on human health effects.

Initially, when it was realised that industrial and other uses of modern biotechnology would have a substantial impact on manufacturing processes, agricultural inputs and techniques, consumer goods, and biomedical products, the inclination was, at national as well as Community level, to amend the existing body of legislative and regulatory provisions adopted to safeguard against chemical and biological substances, to protect human beings, to prevent pollution etc. Thus, where such broader provisions have not been superseded or exempted by newer rules, they still apply. This is also the case, for instance, for Good Manufacturing Practice standards, including Good Industrial Large-Scale Practice which, under the coordination of the OECD, have assembled years of relevant experience with the handling of micro-organisms and developed it into practice guidelines for the pharmaceutical as well as the food industry.

Recent food scares such as BSE and the dioxin crisis have reinforced the change in public policy focus and also resulted in a further strengthening of regulations and safety criteria in the food and feed sectors. In its White Paper on Food Safety[33] the Commission identified the need to address the issue of securing the confidence of consumers and trading partners in the European food supply. This was reconfirmed in the proposal on the General Food Law and establishing the European Food Authority[34] which lays down the general objectives of European food law and a number of principles including precaution, traceability, liability and protection of consumers' interests.

At Community level, legislation specifically related to GMOs has been in place since the early 1990s and since then, the regulatory framework has been further extended and refined with a view to protecting citizens' health and the environment and to ensuring that biotechnology is not used as a pretext for raising barriers to trade. Directive 90/219/EEC regulates the contained use of genetically modified microorganisms for research and industrial purposes, while Directive 90/220/EEC regulates deliberate release for R&D and the placing on the market of products intended for subsequent deliberate release. It also imposes environmental evaluation and step-by-step approval for the dissemination of GMOs. Since 1997, it equally prescribes the labelling requirements for plants and seeds. A revision of the Directive (2001/18/EU) intended to increase efficiency and transparency in the decision-making process, clarify certain operational aspects, harmonise risk assessment, and introduce better control and traceability has recently been adopted by the European Parliament.

Authorisation for release can – in accordance with Directive 90/220/EEC - be given on the basis of a favourable opinion by competent authorities of a Member State or – if objected to by another MS – by the Council on the basis of a decision by the Commission. The Directive prescribes procedural documentation requirements, including those relevant to risk assessment. The latter seeks to take into account:

- the source of the genes to be introduced and detailed molecular analysis of the modified plant and organism, including which genes are incorporated and where in the recipient genome;
- risks associated with the gene products in the plant. It is necessary to document that the gene does not encode for a protein that is toxic to humans or does not produce an allergic response or other unexpected effect;

[33] COM (1999) 719 final

[34] COM (2000) 716 final – 2000/0286 (COD)

- investigation of the possibility that the inserted gene may be transferred to other organisms. This has particular relevance to the possible transfer between bacteria of genes encoding for antibiotic resistance.

Supplementing the above general legislation, Regulation (EC) 258/97 on Novel Foods and Novel Food Ingredients specifically sets out rules for authorisation and labelling of GMO derived food products and other novel foods. While procedures vary slightly from those under Directive 90/220/EEC, the basic rule is similar. In general, the authorisation of GMOs is a one-step process if all Member States agree to the initial assessment of a Member State, and a two-step process if one or more Member States object. The Regulation introduced a simplified so-called "substantial equivalence" procedure for foods derived from GMOs but no longer containing GMOs. If such are substantially equivalent to existing foods with respect to composition, nutritional value, metabolism, intended use and the level of undesirable substances the companies only need to notify the Commission when placing a product on the market together with either scientific justification or a Member State's competent authorities' opinion to the same effect. The product can then be marketed in the entire EU.

These legislative developments illustrate the recognition, at Community level, of the need for convergence. However, the actual number of authorisations given in recent years also is indicative of the difficulties encountered with the procedures. As regards commercial release of GMOs, no consent has been given since October 1998. Fourteen approvals are pending; in most of the cases where a temporary ban has been required on grounds of safety concerns, the information submitted by the Member State in question has been deemed by the Regulatory Committee not to justify a ban. Whether the situation will substantially change as a consequence of efforts to improve and simplify the regulatory environment[35] is too early to tell. Since the entry into force of the Novel Foods Regulation ((EC) 258/97) no products consisting of or containing live GMOs have been authorized, though nine applications are pending at different stages in the procedure[36]. Eleven products have been notified to the Commission as being substantially equivalent.

Directive 91/414/EEC[37] concerns the authorization, placing on the market, use and control of plant protection products including those containing or composed of genetically modified organisms. Other pieces of legislation pertain;

- to the medical and veterinary use of genetically modified organisms (Regulation (EEC) 2309/93),
- to the protection of workers from risks of exposure (Directive 90/679/EEC)
- to the transport of dangerous goods (several Council Directives).

Aspects of liability, in terms of health and damage to property, are addressed by Directive 99/34/EC, imposing strict liability on the producer or importer. Environmental damage, not covered by this directive, is the subject of a separate legal initiative currently being discussed by the Commission, as well as a White Paper, requested by the European Parliament. An overview of current, general EU legislation in force and a practical guide to its use, along with directives applicable specifically to genetically modified organisms (GMOs), laboratory practices etc., is available as the 'Handbook on the Implementation of EC Environmental Legislation'[38].

In the international arena, the Cartagena Protocol[39], also known as the Biosafety Protocol, as adopted by more than 130 countries in January 2000, is the framework for a partial codification of the Precautionary Principle[40]. The Protocol aims to create an effective regime

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35 Improving and Simplifying the Regulatory Environment. Interim Report from the Stockholm Summit. Brussels, 7.3.2001COM (2001) 130 final, at: http://europa.eu.int/comm/stockholm_council/pdf/regenv_en.pdf

36 Facts on GMOs in the EU, at: http://europa.eu.int/comm/dgs/health_consumer/library/press/press63_en.pdf

37 can be found at: http://europa.eu.int/eur-lex/en/lif/index.html

38 Can be found at: http://europa.eu.int/comm/environment/enlarg/handbook/gmo.pdf

39 e.g. at: http://usinfo.state.gov/topical/global/biotech/00021601.htm

40 One of the principles on which the concept of sustainable development in the 1992 Rio Declaration on Environment and Development is based states: In order to protect the environment, the *precautionary* approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible

for minimizing the potential risks posed by the trade or accidental release of genetically modified agricultural and food products. Intended to ensure the safe transfer, handling and use of (living) GMOs that may affect biodiversity, its focus is on cross-border movements and risks to human health. It establishes procedures for imports of living GMOs intended for food, feed and for processing, and it provides a basis for decision making on imports, documentation requirements etc. In addition, it contains provisions on information-sharing, capacity-building and financial resources, with a special view on the situation of developing countries. As of May 2001, 107 countries, including all 15 Member States of the EU, had signed the Protocol. However, only two have, as yet, ratified the Protocol; transposition into legal provisions at Community and MS national levels will only come gradually.

The Biosafety Protocol is under the auspices of the UNEP, the UN's environment agency. The OECD, as well, undertakes certain tasks on behalf of its member states (and in collaboration with UNEP and UNIDO, the UN Industrial Development Agency), related to biotechnology, safety and regulatory oversight. This takes place in the framework of three working groups:

- The Ad hoc group on Food Safety;
- Task Force for the Safety of Novel Foods and Feeds; and
- The Working Group for the Harmonisation of Regulatory Oversight in Biotechnology.

Reports of the three working groups can be found on the website of the OECD.

Further, under the auspices of the Codex Alimentarius Commission (CAC) a number of committees and task forces are undertaking work related to food. Several of these have implications for modern biotechnology and food safety in general. One such, for instance, is the Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology, working to establish principles for risk analysis of foods derived from modern biotechnology, and guidelines for safety assessment of foods derived from GMO plants.

CAC was set up in the 1960's as a joint instrument of the United Nations Food and Agriculture Organisation and the World Health Organisation with the purpose of developing food safety standards as references for international food trade. Hence, it has seen its role as a normative body strengthened under the rules of the WTO. The Member States of the EU are all members of the Codex Alimentarius, and the Commission is an observer. The Commission and the MS attempt to present joint comments on issues discussed in Codex Committees, which are within the competence of Community legislation. Coordinating this work, the DG for Consumer and Health Protection also makes the comments available at its website[41].

damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation. An annex to the Convention on Biological Diversity (CBD), the Protocol's full text can be found at: http://www.biodiv.org/doc/legal/cartagena-protocol-en.pdf

[41] at: http://europa.eu.int/comm/food/fs/ifsi/eupositions/eupositions_en.html

6. PATENTS AND THE PROTECTION OF INTELLECTUAL PROPERTY (IP) RIGHTS

Despite general international agreement that "patents shall be available for all inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application[42]" the granting of biotechnological patents has been practiced perceptibly differently in the US from the EU. In part, this relates to divergent perceptions of the extent to which live phenomena or biological principles, e.g. genes or gene products such as proteins already existing in nature, can be patented. However, more general aspects of patenting IP are at issue as well, i.e. aspects that apply to biotechnology as well as to artistic creations, computer software, and internet business models. In brief, national legislation and international arrangements for patent rights for IP are in flux.

Intellectual property (IP) differs from tangible forms of property in being non-rival in consumption. It is argued that this invalidates the economic case for exclusivity, e.g. in the form of patent protection. However, while IP comes in many forms with different characteristics, it is equally clear that biotechnology R&D on the scale necessary to bring its potential to fruition would not be possible if such research would not be likely to deliver tangible results from which revenues would flow and enable investors to recover their outlays.

IP is a way to give the innovator an exclusive legal right to the economic exploitation of his innovation for a period of time. Given the "public good" characteristics of innovation, the innovator needs to be protected to avoid widespread copying of the innovation and hence to diminish both returns to the innovator and the incentive to innovate. The ability to exclude imitation is the most important aspect of IP rights.

The tension between the goals, on the one hand, to encourage investment in R&D and, on the other, that of ensuring efficient access to knowledge, has real policy implications in several contexts – not least at the international level.

The implementation of TRIPs[43] (Trade Related Aspects of Intellectual Property) by very poor countries is argued to make, for example, pharmaceuticals, or bio-engineered, highly productive seed varieties used to boost yields, improve nutrition and achieve food security more expensive where they are most sorely needed. That the discussion of the international implications of IP patents is far from trivial is illustrated by the fact that implementation of TRIPs in the World Trade Organization (WTO) has been calculated to create more than USD 5.8bn per year in additional licensing profits for American manufacturers that own patents abroad, with similar gains emerging from copyrights and trademarks[44]. Thus, while the in-licensing of e.g. technologies by manufacturers 'abroad' will be the basis of economic benefits in the countries in question, it is equally clear that – at least in the short term – the implementation of TRIPs will represent a significantly redistributive 'New Deal' between research-intensive, innovative countries, i.e. first and foremost the US, and those who tend to be 'adopters' of technology.

In 1999, the US Patent and Trademark Office awarded a total of 161,000 patents - close to twice as many as a decade ago – and there is little doubt that the patenting environment in the USA has been an important encouragement to the development of many areas of biotechnology over the last two decades. A comparison of the US and European patent environments reveals that:

- European universities have been relatively slow in encouraging their scientists to patent inventions;

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42 Agreement on Trade- Related Aspects of Intellectual Property Rights, at: http://www.wto.org

43 Idem.

44 Keith E. Maskus. Intellectual Property Rights in the Global Economy. Institute for International Economics, Washington D.C., August 2000, at: http://www.iie.com/Publications/publication.cfm?pub_id=99

- US patent applicants have a grace period, of up to 1 year, which is particularly useful in allowing academics to publish work. Prior disclosure invalidates patents in Europe;
- The US system is based on a first-to-invent filing system rather than the first-to-file process in Europe;
- The USA provides a more secure intellectual property environment than Europe. For example it is standard practice in the US to grant a patent for a gene without requiring a description of its action. Equally, patents awarded by European patent authorities are easier to challenge.

While some fear that the differences in practice may lead to a gene patent trade war[45] others claim that there is a growing sense in the US that patenting practice has gone too far and that a lot of 'bad' patents are being issued. This seems to apply in particular in the Internet sector, but practice is equally said to be changing – i.e. become more restrictive – in the biotechnology field.

Intense discussion of the issues concerning IP and genetics takes place in various fora, most notably the World Intellectual Property Organisation (WIPO) and the World Trade Organisation (WTO). For example, an Intergovernmental Committee on Intellectual Property and Genetic Resources, under the auspices of WIPO, held its first session in April-May 2001, and a series of specific tasks are included in the organisation's work programme[46]. The WTO, in general, and the provisions of TRIPs' Article 27.3 (b) concerning the patentability of plants and animals, in particular, have been the target of much reproach, especially by NGOs. Disagreeing with the criticism for non-compliance with the Convention of Biodiversity (CBD), the EU, in a review of April 2001, states that "the CBD and the TRIPs Agreement do not conflict with each other"; but acknowledges the legitimacy of some of the concerns expressed by developing countries and discusses ways of addressing these[47]. Thus, despite frictions there is general agreement, including by developing country governments, that the international framework for intellectual property rights' protection will be that provided by the WTO, i.e. the TRIPs Agreement and that, by implication, the world's patenting systems are slowly coming together.

Irrespectively, the European Patent Convention, under the European Patent Office (EPO)[48], of which now 20 nations, including all of the EU, are members, went into force in 1978. While the EPO does provide a common examination and granting procedure, a European patent still only results in a "bundle" of national patents, i.e. a real "community patent" has not emerged. Under Article 53(a), the Convention considers the following biotechnological 'inventions' unpatentable:

a. processes for cloning human beings;
b. processes for modifying the germ line genetic identity of human beings;
c. uses of human embryos for industrial or commercial purposes;
d. processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

At the level of the EU, a Directive[49] based on the TRIPs agreement was adopted in 1998. Implemented, this would eliminate many of the advantages of the US patent practices that have allowed firms, universities, federal laboratories and individual scientists to outmanoeuvre Europe in this field. However, the Directive still remains to be transposed into national law in the majority of Member States almost a year after the expiry of the deadline[50], and it has recently been suggested that the wide range of attitudes among these States relegates important ethical aspects of patents and patentability to subsidiarity for the time being,

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45 US and Europe set course for gene patent trade war. Pharmaceutical Business News, January 2001.

46 An overview and WIPO's work programme in IP and biotechnology can be found at: http://www.wipo.org/biotech/documents/index.html

47 At: http://europa.eu.int/comm/trade/pdf/dc_bdtrips.pdf

48 At: http://www.european-patent-office.org/index.htm

49 Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, *Official Journal L 213 , 30/07/1998 p. 0013 – 0021*

50 Prescribed deadline is 30 July 2000

because no uniformity can be achieved. What, if any, action the Commission will take is not known, and whether the Lisbon process – and, in the EIB context, the i2i – and the recommendation by the Parliament in March 2001: to give more prominence to biotechnology; to call for the drawing up of a Bio-Europe Action Plan; to move towards a single EC patent; and to have Member States ratify the Directive as soon as possible, will give impetus to the implementation of the Directive remains to be seen. At this stage, further developments seem dependent on the political and legislative resolve of the Member States.

7. OPERATIONAL ASPECTS

At the European Council in Lisbon in March 2000, the European Union set itself a new strategic goal for the next decade, to become the most competitive and dynamic knowledge-based economy in the world capable of sustainable economic growth with more and better jobs and greater social cohesion. The EIB introduced its "Innovative 2000 Initiative" (i2i) as concrete response to this objective.

In its follow-up report, of February 2001, to the Stockholm European council under the so-called Lisbon strategy, the Commission recalled the economic, social and environmental potential of life sciences and biotechnology and, in consequence, the strategic and long-term importance for Europe of mastering those sciences and technologies and their applications. The Commission also announced its intention to present, by the end of 2001, a strategic vision of life sciences and biotechnology up to 2010 and beyond.

Access to sufficient appropriate finance is critical to the establishment and growth of innovative/science/technology based companies, particularly biotechnology. Such companies play a key role in turning scientific discoveries into product ideas with commercial potential. The financing requirements of such companies, however, change significantly over time. SMEs can find it difficult to obtain finance during the critical early product development phase because of the, often, long time horizons involved, the absence of tangible assets and the lack of immediate prospects for earning revenues. An increased availability of Venture Capital[51] [52] would go some way to addressing this problem.

The "new" biotechnology industry entered its third decade, the late 1990s, with what was perhaps the largest disparity in its short history between the quality of its fundamentals and value recognition for those fundamentals by the financial community. This disparity, especially when viewed in the context of the strong (although this is changing) performance of the information technology sector, caused a portion of the venture community to shy away from a long-standing interest in early stage biotechnology. Why was this?

The answer appears to be insufficient short-term returns combined with illiquidity. The venture-type returns that mainly public market investors sought on the "high-risk" biotechnology companies had not yet, for the most part, been realised. This was in sharp contrast to the software, communications and Internet companies. In addition, there exists a financial mismatch between the institutional investment community and its need to deploy increasingly large amounts of capital in liquid securities, and biotechnology companies, more than 60% of which have market capitalisations below € 100m.

It is possible to demonstrate the strength of the industry's fundamentals at a variety of different levels that include product sales, product pipeline, alliances with pharmaceutical companies and the pace of technological innovation. Therefore, it is perhaps no surprise that equity input into the sector in 2000 jumped to € 40bn worldwide although Europe represented only € 6.6bn. Half-year figures suggest that 2001 will see a fall to about € 20bn. This volatility highlights one of the challenges facing the biotechnology industry.

In spite of the dearth of later stage private and public market interest in biotechnology stocks, it would appear that there is no shortage of funding for very early stage ("seed") biotechnology companies. Significant resources continue to be employed by government agencies to support research that is often the genesis of these companies and by the venture capital community to fund the actual launch of these companies. The German government's DM 150 m (EUR 90 m) BioRegio programme, launched in 1996 has helped create, on average, about 6 companies per month[53].

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[51] EIB Lending to SMEs within the EU, H. Jahn/P. Guinet, PJ/I&S/2001-953/JAH/bbm

[52] Financing Innovative Firms through Venture Capital, C. Christofidis & O. Debande, PJ Sector study, December 2000

[53] Herr Hartmut Thomas, Bio-Gen-Tec-NRW, Brussels, 15/10/01

While the venture capital community as a whole remains supportive of early stage biotechnology, with approximately € 1bn invested in each of the last three years, the mix of participating venture players is in flux. A significant number of the hybrid Information Technology/Health Care Technology venture firms are "heading for the Web" looking for higher returns. The early stage funding gap that their departure leaves is being filled by a hybrid of venture capital funds with long-term solid and sustainable track records in biotechnology and by new healthcare specific funds.

Prior to the well-publicised clinical trial failures of British Biotech, Scotia and others, institutional investors and pharmaceutical companies were willing to put equity into biotechnology companies at a very early stage in the product development cycle. This is no longer the case as they seek more confidence in the product. This leaves a financing gap which provides a well identified opportunity for additional venture capital or alternative type funding.

The biotechnology sector, as other innovative rapidly developing sectors such as Information and Communication Technology (ICT) and Multimedia, will increasingly generate wealth and employment. However, to do this, individual companies require the injection of finance at different stages in their development.

Large companies embarking on biotechnology based R&D programmes have to underwrite the cost of these, often very long, programmes prior to receiving any revenues. The Bank should, and indeed already has in certain cases[54], identify such opportunities and seek to support investment of this nature.

Established medium-sized companies in the sector require funding to enable them to grow. Long-term debt may be appropriate in certain circumstances but the Bank would almost certainly require guarantees[55].

Development of "Hi-Tech" clusters in various locations in Europe (see appendix E) provides opportunities for the Bank to support investment in the creation of enabling fixed assets such as technology parks and incubators[56]. These facilities provide accommodation and supporting skills and knowledge sources to start-up companies. Typically this would include laboratory and office space, legal, insurance, patenting and financial advice, available skilled labour and the opportunity to "network" with likeminded people and organisations. The promoter of the facilities would receive rental income and fees for other services but may also take equity in the start-up company in return for lower rental charges particularly in the early years.

SMEs in the sector are finding it increasingly difficult to obtain equity and this is an opportunity for Venture Capital funds. The EIF should seek to identify such funds and evaluate whether they have the necessary expertise to successfully invest in the likely winners. The participation of the EIF in such funds would bring increased credibility and also increase the size, thereby allowing more SMEs to be funded. In addition, it is important that such SMEs optimise the timing of an IPO or a sell-off. The need for some form of affordable bridge-finance might provide an opportunity for the Bank.

The environment for biotechnology in the foreseeable future is likely to hold:

- continuing although decreasing (albeit slowly?) regulatory uncertainty, particularly in Europe;
- intellectual property protection issues adding to the unpredictability of the industry;
- more alliances between traditional pharmaceutical companies and biotechnology operations, as patents on many drugs expire and the pharmaceutical companies seek to

54 For example; Roche Penzberg Biomedical Research, Boehringer Ingelheim II

55 For example; Hovione Pharma Science

56 For example; Heidelberg Bioscience Infrastructure

replenish their product pipelines, improve their expertise in areas such as diagnostics and genomics and optimise their drug delivery systems;

- increasing focus on the ethical issues implicit in “new” biotechnology.

In order to continue to make the correct decisions about which actions and projects to support the Bank needs to keep itself informed of developments in the sector and to maintain a dialogue with the Commission and other relevant parties.

8. TECHNOLOGY TRANSFER – A 'MISSING LINK'?

Irrespective of how one measures it, Europe has been substantially less successful in exploiting biotechnological developments industrially than the US: 160,000 research jobs in modern biotechnology in the US as against 60,000 in the EU, investments (€ 33142 m versus € 6551 m) and firms' revenues (€ 23750 m versus € 8679 m). However, this gap applies equally in other high technology sectors, and a near-consensus appears to be emerging regarding some of the sources of this transatlantic difference - although their relative significance is not universally agreed to. An important factor is considered to be a difference in US and European risk aversion – as relates to financing (i.e. venture capital availability) as well as to 'job safety'[57] Other important disparities often mentioned include differences in entrepreneurial mentality among scientists, i.e. aptitude to exploit academic breakthroughs, an academia vs. a commercial cultural disparity, attitudes towards failure, and institutional arrangements for technology exchange. A 'skill deficit' resulting partly from far more restrictive European immigration policies is also mentioned as a factor.

The American achievement in high-tech industries is generally viewed as being the consequence of a US advantage on most, if not all, of these counts. Interestingly though, one potential source of the discrepancy seems to be less well researched; while several descriptive and evaluative studies exist of Federal as well as EU research programmes, a study of the comparative advantages of either– from an applied research and industrial application point of view – does not appear to have been done. It is not within the scope of this paper to examine the issue in detail. However, an outline might serve to illustrate a point.

The US Government operates a multitude of Federal laboratories and, not least, important 'procurers' of mission-related applied research, i.e. the Department of Defense and the Department of Energy. In addition, several research programmes exist, e.g. the National Science Foundation (NSF), sponsoring basic research, and the Advanced Technology Program, operating in the middle ground between basic research and product development. Further, the US is endowed with a multitude of large, private foundations that encourage and finance research, if often with an emphasis on basic science. Worth noting is, as well, that US Federal laboratories and programmes are strongly urged, with the possible exception of NSF, to consider a project's applicability explicitly and, indeed where relevant, actively seek to promote the diffusion of technologies. As well, since 1980, legislation specifically encouraging universities to licence to private industry discoveries made with federal funds has contributed to technology transfer; in 1999, this added $38bn to the US economy, creating over 300,000 jobs and hundreds of new companies[58]. Only a fraction of all this - funding and outcomes - is, of course, related to biotechnology research.

The EU essentially – at least at Community level – channels its support for R&D through its Research Framework Programme – with its particular restrictions to applied research, i.e. that any indication of patentability is tantamount to elimination. Admittedly, national contributions towards R&D in the EU provide some of the funding that in the transatlantic context is a Federal responsibility. All the same, not only are European investments in biotechnology R&D much smaller than American; the approach to ensuring the industrial utility of research – a conduit to economic benefits – appears to be far more deliberate in the US than in Europe - this despite universal concurrence to its critical significance. The point is that not only is there a case for increasing investments in R&D in Europe; it is equally vital to establish and sustain effective mechanisms for technology diffusion.

One of the ways in which technology transfer has been sought – other than through the means mentioned above, and including a well-functioning venture capital market – is through technology incubators, also called science parks or innovation centres. These are often publicly supported entities intended to help small, innovative firms overcome the market and

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[57] Hauser H. Nothing ventured, nothing gained. EIB Papers. Vol. 6, No. 1 2001, at: http://www.eib.org/ced/papers.htm

[58] Hall Z. & Scott C. University Industry Partnership. Science Vol. 291. 26 January 2001, p. 553.

systemic failures that limit their ability to survive in the early stages. Their objectives usually are economic development; technology commercialisation; real estate development; and entrepreneurship.

There are several hundred incubator schemes of different sorts operating throughout Europe and at least 550 in the United States – only some of these accommodating biotechnology. Outside the OECD they are also becoming an increasingly popular policy instrument for economic and employment development. Aiming to assist entrepreneurs with enterprise start-ups and development, they typically seek to provide office or laboratory space, often on preferential and flexible terms, for a specific industry or type of firm, as well as workers, management support, IT infrastructure, legal and patenting assistance, networking leads, and access to venture capital. Set up with a variety of aims and partly therefore the subject of relatively scarce systematic evaluation, incubators have nevertheless been experienced to be beneficial as launch pads for research-based spin-offs and to increase the survival rate of such firms – including a large number of biotechnological ventures.

A number of studies suggest that – apart from incubator centres – there is a general lack of institutions promoting technology-transfer between university and industry. Even given the existence of so-called "bridging-institutions" whose aim is to smooth the transfer of knowledge to industrial application, like Fraunhofer institutes in Germany, this institutional set up in Europe is dwarfed by the wealth of alternative channels in the US.

The following elements[59] [60] appear to be critical to the success of high tech incubators:

- A focus on cluster-based technologies, e.g. biotech, software, can help achieve critical mass and enhance synergies. Universities are often pivotal to such networks, although the absence of any substantial technology incubator phenomena at several old, respected academic institutions on both sides of the Atlantic indicates that such institutions do not nurture incubators spontaneously;
- Define objectives and mission from the outset. In several instances a lack of clear objectives has led to conflicts between technology development and, for instance, short-term considerations of incubator income and stakeholder revenue;
- Experienced and entrepreneurial incubator management;
- Selection of new tenants according to 'fit' with existing ones;
- Diversification of income, i.e. not relying on a single source of income;
- Sharing of experience.

Europe's falling behind in applied biotechnology is arguably partly due to a less entrepreneurial 'culture' among its scientists, and a comprehensive remedy may well need to include institutional and legislative elements. However, fostering entrepreneurship also requires conscious and tangible efforts devoted to technology transfer – not necessarily only in the shape of incubators – but nevertheless arrangements frequently involving investments in infrastructure.

[59] OECD. Technology Incubators: Nurturing Small Firms OCDE/GD(97)202, at: http://www.oecd.org//dsti/sti/s_t/inte/prod/e_97-202.htm

[60] Hauser, H.: Op. cit.

APPENDICES

HISTORY, PRESENT AND FUTURE

The history of the development of biotechnology divides into three parts: the early 'magical period' where discoveries made by accident were incorporated into daily life simply by following rules of thumb; a middle period beginning around the seventeenth century, when scientific explanations for these simple processes began to be established and followed; and the modern period when microbes have become the basis of great industries and modern techniques have given us new and far-ranging powers over micro-organisms.

The recent spectacular development of ***genetic engineering*** (gene splicing) is referred to as 'new biotechnology' to distinguish it from what went before. However, genetic research, applied to microbiology, had been in existence for many years, although its practical side had been limited to "careful selection of the best strains". Genetic engineering enables this “careful selection” to be accelerated, amplified and optimised.

It had been known for many years, since the work of Mendel in the nineteenth century, that every life form contained within its cells the 'blueprint' for reproducing itself. Mendel laid out a structure of rules governing the transmission of this information, but the mechanisms involved had to wait for the more sophisticated techniques (and more powerful microscopes) available in the 20th century.

This research began to suggest that the information was somehow encoded in the chromosomes (coloured shapes), tiny bodies visible as rod shapes in the nucleus of each cell. Later studies showed that these chromosomes are themselves made up of even tinier units called genes. It was the patterns contained in these genes that in some way enabled the organism to replicate itself or 'breed true'.

It was found that the genes were composed of a complex chemical known as DNA (deoxyribonucleic acid). It was not, however, until as recently as 1953 that two researchers working at Oxford, Francis Crick and George Watson, finally uncovered the precise shape and function of the DNA molecule. This was the now famous 'double helix', roughly the shape of a spiral staircase.

When the cell reproduces, the rungs of this staircase split down the middle of each tread and the two spirals that remain (with the half treads) act as a template for the formation of new complementary molecules, exact copies of the original parent DNA, except when there is an error (mutation). The treads of the staircase are composed of strings of units known as nucleotides, different kinds of nucleic acid. There are only four different types, but the staircase is extremely long and the sequence of nucleotide bases can easily convey a great deal of information. The arrangement of these nucleic acids, in specific sequences, carries all the detailed information necessary for the construction of a new organism - ***the genetic code***.

Genomics is the name given to the study of the genetic code. The complete sequencing of the human genome has recently been completed. If initial predictions prove correct, this could enable the development of ***pharmacogenomic*** drugs and treatments targeted at specific groups of patients with a common set of therapeutic needs. At its simplest, a pharmacogenomic drug would be discovered and optimised based on detailed genetic knowledge of the specific segment of a disease population in which it was most active. Diagnostics developed using the same technologies would identify the appropriate patient population that might benefit from a drug.

Genetic engineering refers to the recent development of techniques concerned with producing what are effectively controlled mutations. The techniques, often called gene-splicing, are methods of constructively rearranging the genetic code to produce an organism with new, desirable characteristics. The process has two distinct aims. It can either be used to increase the production capability of the microbe concerned (amplification) or an entirely new production ability can be grafted in. Insulin, for controlling diabetes, which was originally

produced synthetically, was the first drug to be engineered this way. It was licensed for human use in 1982 by both Eli Lilly (US) and Novo Nordisk[61].

It seems likely that any substance produced or secreted by an animal or plant can be reproduced in this way, probably more conveniently, more safely, more economically than by “classic synthetic” methods. This gives biotechnology an almost limitless potential in food, energy and medical science. Achieving this potential, however, depends on the establishment of an effective infrastructure for basic research, development, testing and commercial exploitation of the technology.

Genetic engineering also requires the rigorous and rational analysis of the ethical issues that will enable an effective and foolproof regulatory framework to be established.

> *"However complex the computer may eventually become, every part of it will still be produced by human ingenuity and so will be analysable, controllable and repairable by human agency. With biotechnology, one is dealing with the complexity of Nature herself, many orders of magnitude more complicated than anything Man has yet created. The potential to change the world is certainly there, what is questionable is simply our ability to realise it in full - and to control it." Anon.*

The challenge facing the "New Biotechnology" industry is to combine achieving the first of these with satisfying itself and the rest of the world that it can fully achieve the second.

61 The Bank has financed two R&D related projects with Novo Nordisk.

ISSUES IN THE DEVELOPING WORLD

Whilst recognising that the "developing world" is not homogenous, the views and concerns of those countries outside the "developed world" are different in a number of fundamental ways from those inside! Apart from the fact that they focus more on the benefits than the problems, these differences can be summarised as follows;

Health Care – the costs associated with the emerging treatments are often prohibitively expensive. Treatment for HIV/AIDS demonstrates this quite clearly. The developing world is in desparate need for some of these treatments but it cannot afford to pay "western prices". Recent patent litigation over cheap generic copies of branded HIV drugs in South Africa gave a first indication that international drug companies are increasingly aware of this dilemma. Following the final settlement with the South African government a general change in their patent and licensing policy towards developing countries is underway.

Agriculture – GM improved crops can bring significant benefits to the poorer areas of the world through higher yields, better disease resistance and higher quality (e.g. golden rice). Often these benefits are needed urgently thereby minimising concerns about the release of GMOs into the environment. This has to be balanced with the genuine concerns about these GMOs and the lessons from the introduction of DDT should not be forgotten. On the other hand, GM crops have to be fine-tuned to the environment in which they are supposed to grow. As current applications of GMOs in agriculture focus on North America, developing countries risk of being left behind for the simple reason that genetic engineering and field trials ignore their particular environmental needs.

Regulation – developers and producers will tend to migrate to those regions where regulation is most conducive to the proliferation of biotechnology related activities. This factor will need to be considered when assessing project proposals in the developing world.

An additional factor is that of ability to export to the EU. If the developing world introduces GM crops then, under current legislation, it cannot export its produce to the EU.

BIOTECHNOLOGY CLUSTERS IN EUROPE

LIST OF USEFUL CONTACTS AND TOPICS DISCUSSED

EuropaBio – ***http://www.europa-bio.be***
Background information on several aspects

1. Proposal for a Council Decision Concerning the Multiannual Framework Programme 2002-2006, COM (2001) 94 final, at http://europa.eu.int/comm/research/pdf/com-2001-94-en.pdf
2. In addition to the Charter, ten EU Member States are signatories to the Council of Europe Convention on Human Rights and Biomedicine, 4 April 1997, though the convention has only yet been ratified and entered into force in three. The General Conference of UNESCO in 1997 adopted the Universal Declaration on the Human Genome and Human Rights (http://www.unesco.org/opi/29gencon/esyn.htm). The extent to which the latter applies at national level is not clear. Under the auspices of UNESCO operate the World Commission on Ethics of Scientific Knowledge and Technology (COMEST) as well as the International Bioethics Committee (IBC). Nine Member States have national ethics committees.
3. The triage screening system is developed on the basis of the EU, national and international bioethics documents referred to above, and: Citizens Rights and the New Technologies: A European Challenge - a report to the President of the Commission by the European Group on Ethics in Science and New Technologies, dated Brussels, May 23, 2000, available at: http://europa.eu.int/comm/secretariat_general/sgc/ethics/en/prodi_en.pdf
4. Improving and Simplifying the Regulatory Environment. Interim Report from the Stockholm Summit. Brussels, 7.3.2001COM (2001) 130 final, at: http://europa.eu.int/comm/stockholm_council/pdf/regenv_en.pdf
5. Facts on GMOs in the EU, at: http://europa.eu.int/comm/dgs/health_consumer/library/press/press63_en.pdf

6. http://europa.eu.int/eur-lex/en/lif/index.html
7. http://europa.eu.int/comm/environment/enlarg/handbook/gmo.pdf
8. http://usinfo.state.gov/topical/global/biotech/00021601.htm
9. One of the principles on which the concept of sustainable development in the 1992 Rio Declaration on Environment and Development is based states: In order to protect the environment, the *precautionary* approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation. An annex to the Convention on Biological Diversity (CBD), the Protocol's full text can be found at: http://www.biodiv.org/doc/legal/cartagena-protocol-en.pdf
10. http://europa.eu.int/comm/food/fs/ifsi/eupositions/eupositions_en.html
11. Agreement on Trade- Related Aspects of Intellectual Property Rights, at: http://www.wto.org
12. Keith E. Maskus. Intellectual Property Rights in the Global Economy. Institute for International Economics, Washington D.C., August 2000, at: http://www.iie.com/Publications/publication.cfm?pub_id=99
13. An overview and WIPO's work programme in IP and biotechnology can be found at: http://www.wipo.org/biotech/documents/index.html
14. http://europa.eu.int/comm/trade/pdf/dc_bdtrips.pdf
15. http://www.european-patent-office.org/index.htm
16. Hauser H. Nothing ventured, nothing gained. EIB Papers. Vol. 6, No. 1 2001, at: http://www.eib.org/ced/papers.htm
17. OECD. Technology Incubators: Nurturing Small Firms OCDE/GD (97) 202, at: http://www.oecd.org//dsti/sti/s_t/inte/prod/e_97-202.htm

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1. Definition by the 1992 Convention on Biological Diversity (CBD)
2. When Crick and Watson developed the double helix model for the molecular structure of DNA, where genetic information is encoded.
3. "Towards a strategic vision of life sciences and biotechnology", currently in preparation
4. Viruses consist of a section of DNA (or RNA) wrapped in a protein envelope. They have no metabolism of their own and can only multiply using the intracellular apparatus of animal or plant cells, or even bacteria, to replicate their DNA and proteins. In the process, some viruses cause considerable injury to their host. Prions, i.e. the entities involved in causing Bovine Spongiform Encephalitis (BSE) and its human variant Creutzfelt-Jacob, are 'misshaped' proteins – not on its own living matter.
5. Proteus – in Greek mythology a god who knew all things past, present, and future but disliked telling what he knew. From his power of assuming whatever shape he pleased, Proteus came to be regarded as a symbol of the original matter from which all is created.
6. At the time, in 1798 viruses were not known to exist and the knowledge of micro-organisms and their role in pathogenesis was in its earliest infancy. Jenner, a British country medical practitioner, had observed, however, that milk maids would occasionally suffer a minor, short illness accompanied by a skin rash (i.e. cowpox), and that these maids would never be sick from smallpox, an otherwise often deadly disease eradicated from the world only in 1977.
7. These are biologically active chemicals produced by the body; in the case of these disorders for reasons not well understood.
8. SCRIP, March 16th 2001: Therapeutic vaccines on the horizon.
9. Duke University Medical Center: Universal cancer vaccine shows promise in lab. 29 August 2000 at:http://www.dukenews.duke.edu/Med/vaccine1.htm
10. In vitro and in vivo are expressions designating that a process takes place in the test tube or in the living organism, respectively.
11. Other vectors are used as well.
12. Mice, cattle, goats, and pigs have now been cloned.
13. "Essential" in this sense means that the human body is unable to synthesize these amino acids. Instead, they have to be added through the food chain.
14. Pharmaceuticals with sales of more than USD 1bn are usually referred to as "blockbusters".
15. Valued at manufacturers' selling prices in constant US-dollars; data from IMS Global Pharma Forecasts.
16. The approval process consists of the pre-clinical and a clinical phase. The latter comprises three stages (Phase I to III). At the end of 2000, almost 280 new biopharmaceuticals of European public biotechnology companies (including Israel) underwent pre-clinical and clinical trial. More than a third was in the pre-clinical stage, whereas roughly 10% were in Phase III of the clinical trials, which precedes market launch.
17. See chapter 2.
18. Only recently, the US regulator, Food and Drug Administration (FDA), again tightened requirements during clinical trials. The stricter practice has already led to a number of delays in market launch for leading big pharma companies.
19. The number of strategic alliances has risen from 179 in 1997 to 403 in 2000. This trend is likely to continue: in the first half of 2001, already 242 new alliances were registered.
20. Recently, however, the drying up of the in-house R&D pipeline has significantly increased, leaving some big pharma companies desperate to find possibilities for in-licensing. The ensuing shift in negotiating power has resulted in some small biotechnology companies receiving larger shares of future drug sales revenue.
21. This analysis focuses only on the high-value part of the seed market, which is relevant for biotechnological applications and excludes conventional seeds.
22. The contention of a higher yield combined with less pesticide requirements is questioned by some analysts and farmers which cite evidence from across the world which shows that at least equal levels of pesticide dosage are necessary to get the same yield.
23. There are currently no GM crops with resistance against fungicides on the market.
24. After closing the acquisition of Aventis CropScience, Bayer CropScience will be second behind Syngenta.
25. Recent deals have been closed at prices of about seven to eight times future expected EBITDA.
26. It is estimated that, today, about 25% of soybean and wheat seeds are farm-saved.
27. See European Commission: Inventory of public biotechnology R&D programmes in Europe. The study covers 14 EU member states (except for Luxemburg), Iceland, Norway and Switzerland.
28. Mainly through the "Biotechnology II", the "Biomed" and the "FAIR" programmes.
29. See: European Biotechnology Innovation System, EC Policy Overview, University of Sussex, October 2000. It is estimated that spending on the level of individual states is on the same order of magnitude.
30. This is usually referred to as "non-policy directed funding". This way of indirect financing is particularly common in France where more than 90% of total funding for biotechnology is spent through this mechanism.
31. For the definition of the breakdown of biotechnology into different areas, see: European Commission: Inventory of public biotechnology R&D programmes in Europe. As there is considerable overlap between some of the areas, conclusions have to be drawn with some caution, particularly, as they do not fit with boundaries of single industries.
32. Greenpeace, otherwise firmly against GM crops, has acknowledged that vitamin A enhanced rice may be acceptable (Scrip Magazine March 2001).
33. In 1973, a famous immunologist, MacFarlane Burnett, stated that the chance of ever being able to do gene therapy using a virus vehicle to carry a new gene and replace a faulty one "will remain infinitely small to the last syllable of recorded time". It was being done less than 25 years later.
34. Proposal for a Council Decision Concerning the Multiannual Framework Programme 2002-2006, COM (2001) 94 final, at http://europa.eu.int/comm/research/pdf/com-2001-94-en.pdf

35. The Charter on Fundamental Rights of the European Union (Charter 4487/00) 28 September 2000. The EU has equally established an ethics advisory committee, the European Group on Ethics, EGE (see below).
36. In addition to the Charter, ten EU Member States are signatories to the Council of Europe Convention on Human Rights and Biomedicine, 4 April 1997, though the convention has only yet been ratified and entered into force in three. The General Conference of UNESCO in 1997 adopted the Universal Declaration on the Human Genome and Human Rights (http://www.unesco.org/opi/29gencon/esyn.htm). The extent to which the latter applies at national level is not clear. Under the auspices of UNESCO operate the World Commission on Ethics of Scientific Knowledge and Technology (COMEST) as well as the International Bioethics Committee (IBC). Nine Member States have national ethics committees.
37. The triage screening system is developed on the basis of the EU, national and international bioethics documents referred to above, and: Citizens Rights and the New Technologies: A European Challenge - a report to the President of the Commission by the European Group on Ethics in Science and New Technologies, dated Brussels, May 23, 2000, available at: http://europa.eu.int/comm/secretariat_general/sgc/ethics/en/prodi_en.pdf
38. As a minimum the Council of Europe's Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes shall be respected.
39. It is worth noting that the application of science is, in fact, far more heavily regulated than basic research - in the field of pharmaceuticals e.g. the World Medical Association Declaration of Helsinki, Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines, the European Medicines Evaluation Agency (EMEA) and national counterparts, to name a few statutes and actors.
40. Communication from the Commission to the Council, the European Parliament, the Economic and Social Committee and the Committee of the Regions. Towards a European Research Area. Com(2000)6. Brussels, 18 January 2000.
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49. at: http://europa.eu.int/comm/food/fs/ifsi/eupositions/eupositions_en.html
50. Agreement on Trade- Related Aspects of Intellectual Property Rights, at: http://www.wto.org
51. Idem.
52. Keith E. Maskus. Intellectual Property Rights in the Global Economy. Institute for International Economics, Washington D.C., August 2000, at: http://www.iie.com/Publications/publication.cfm?pub_id=99
53. US and Europe set course for gene patent trade war. Pharmaceutical Business News, January 2001.
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55. At: http://europa.eu.int/comm/trade/pdf/dc_bdtrips.pdf
56. At: http://www.european-patent-office.org/index.htm
57. Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, *Official Journal L 213 , 30/07/1998 p. 0013 – 0021*
58. Prescribed deadline is 30 July 2000
59. EIB Lending to SMEs within the EU, H. Jahn/P. Guinet, PJ/I&S/2001-953/JAH/bbm
60. Financing Innovative Firms through Venture Capital, C. Christofidis & O. Debande, PJ Sector study, December 2000
61. Herr Hartmut Thomas, Bio-Gen-Tec-NRW, Brussels, 15/10/01
62. For example; Roche Penzberg Biomedical Research (Agora N° 20000324), Boehringer Ingelheim II (Agora N° 20000380)
63. For example; Hovione Pharma Science (Agora N° 20010104)
64. For example; Heidelberg Bioscience Infrastructure (Agora N° 20000547)
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68. Hauser, H.: Op. cit.
69. The Bank has financed two R&D related projects with Novo Nordisk, see, for example, report
70. PJ/Ind-1/97 958/JvdM/CC/mp.