Regulation of the United Kingdom biotechnology industry and global competitiveness.

HOUSE OF LORDS

SESSION 1992—93
7th REPORT

SELECT COMMITTEE ON SCIENCE AND TECHNOLOGY

REGULATION OF THE UNITED KINGDOM BIOTECHNOLOGY INDUSTRY AND GLOBAL COMPETITIVENESS

Ordered by The House of Lords *to be printed 13 July 1993*

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CONTENTS

References in the text are as follows:

(Q) refers to a question in oral evidence.
(p) refers to a page in HL Paper 80-I.
(P) refers to a page in HL Paper 80-II.

Written evidence received up to 30 April 1993 - HL Paper 80-I

Oral and written evidence - HL Paper 80-II

SEVENTH REPORT

13 July 1993

By the Select Committee appointed to consider Science and Technology.

ORDERED TO REPORT

REGULATION OF THE UNITED KINGDOM BIOTECHNOLOGY INDUSTRY AND GLOBAL COMPETITIVENESS

CHAPTER 1 INTRODUCTION AND EXECUTIVE SUMMARY

1.1 Biotechnology is the use of biological processes, like fermentation or selective breeding for making useful products. Since the early 1970s, advances in molecular biology have enabled scientists, by a variety of techniques, to move genes from one organism to another in a controlled and highly specific way. This is called genetic modification or genetic engineering and it is subject in most advanced countries to regulation by government.

1.2 We undertook this enquiry following allegations by industry that recent changes in the regulations governing biotechnology both in contained use and following deliberate release into the environment were likely to place United Kingdom industry at a competitive disadvantage, particularly in comparison with non- EC competitor countries like the United States and Japan[1].

1.3 We find that the "new" biotechnology of genetic modification is an exciting and continually evolving set of applications of molecular and cell biology. Its processes are already in everyday use and result in well known medicinal products, vaccines, and household goods like washing powder. Extensive agricultural applications are imminent, as is gene therapy for hitherto incurable hereditary conditions. Thus the benefits of biotechnology are already well proven; biotechnology and products of biotechnology are with us to stay; and these products will yield enormous future benefits to mankind. What is more, United Kingdom scientists and industry are good at it. We think that in all areas where biotechnology has applications, people should be able to exploit its economic benefits, subject only to such regulation as may be necessary to meet identifiable disbenefits, especially to preserve safety.

1.4 Early fears of scientists relating to genetically modified organisms (GMOs) in contained use turned out to be unfounded. As a general principle, except where pathogens are involved,

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[1] The membership of the Sub-Committee which conducted the enquiry is set out in Appendix 1. The Committee met 17 times; heard 30 witnesses or sets of witnesses; and received 105 pieces of written evidence. This evidence is printed in companion volumes to this report, as follows: Written Evidence (to 30 April 1993) in Session 1992-93, H.L. Paper 80-I; Oral Evidence and Further Written Evidence (since 30 April 1993) in 1992-93 H.L. Paper 80-II. The Committee appointed Dr Brian Richards as Specialist Adviser and are grateful to him for his valuable assistance. The Committee are also grateful to Dr Simon Shackley who assisted the Committee in preparing their synthesis of overseas regulatory practice. Visits were made to Zeneca Seeds at Jealott's Hill and to the Advanced Centre for Biochemical Engineering at University College London. Members made private visits to Smithkline Beecham and the Bio Industry Conference in Brussels.

separate regulation of GMOs in contained use is unnecessary over and above current good laboratory practice; and deliberate release of GMOs, except where bacterial or virus vectors, live vaccines or modification of the genome of animals are involved, is not inherently dangerous.

1.5 Unfortunately, in our view the United Kingdom regulations, which are in turn based on EC Directives, take an excessively precautionary line based on a view of the technology which, in terms of scientific knowledge, was already obsolescent when the Directives were being prepared in the late 1980s. In framing them the Commission appears to have been impervious to advice tendered to it by scientists, industry, and national experts.

1.6 We find that the current regulatory regime is unscientific in that both sets of regulations fail to discriminate between activities involving real risk and those which do not. Moreover, they scrutinise any act of genetic modification which forms part of the process of making a product rather than the better targetted and more economical method of regulating the product itself. The regulations are therefore bureaucratic; costly; and time consuming. They are an unnecessary burden to academic researchers and industry alike.

1.7 Other factors - principally the level of investment and considerations relating to intellectual property rights - govern the competitiveness of United Kingdom biotechnology as much as, if not more than, regulation. But in our view any regulation which reduces competitiveness must be reviewed critically, especially when it cannot be justified on scientific or public interest grounds.

1.8 Our specific recommendations are that:

— the Government must press for amendment of the EC contained use Directive so as to substitute a risk assessment system in place of the current classification of risk according to size of operation and pathogenicity; meanwhile, as interim measures, we recommend that use of safe organisms should be subject only to notification procedure whatever the scale of operations; and the Health and Safety Executive should aim to give consent for use of unsafe organisms well within the 90 day maximum;

— the Byzantine structure of deliberate release regulation must also be reformed. The Government must press for amendment of the EC deliberate release Directive to enable certain activities, as selected by a group of EC national experts, to be exempt from the present provisions; meanwhile, as interim measures, we recommend that the current number of questions to be addressed in the risk assessment questionnaire be reduced by making them specific to the type of organism involved; that applications should be processed in not more than 30 days; and that universities and research councils should be exempt from paying fees on their applications;

— as a matter of principle, GMO-derived products should be regulated according to the same criteria as any other products. The present process-based system should be retained only for the limited areas where regulation is required - that is to say all work involving pathogenic organisms and for deliberate release of GMOs outside the low to negligible risk category; work on further process-based regulatory EC draft Directives on GMOs should cease forthwith;

— the DTI Deregulation Task Force should review the current regulations with a view to revising both the United Kingdom regulations and where necessary the parent EC Directive;

— promotion of public understanding of biotechnology is important but should not preclude evolution of regulation; education in schools is one of the most important methods of achieving public understanding in the longer term; in the short term, scientists and industry with assistance from government have the chief responsibility for promoting wider public understanding. Because of its implications for

competitiveness, DTI is ultimately responsible for ensuring that public perceptions are based on reason and knowledge.

1.9 The report is set out as follows. We begin by describing what biotechnology is in simple terms (Chapter 2); we then describe the applications of biotechnology as described to us in the evidence we received and its economic value (Chapter 3); the regulations governing biotechnology are then summarised (Chapter 4). Following these introductory chapters, we review such evidence as we received and considered relevant to the central issue of competitiveness (Chapter 5). Finally we give our opinion (Chapter 6) and a summary of conclusions and recommendations (Chapter 7).

CHAPTER 2 WHAT IS BIOTECHNOLOGY?

2.1 Biotechnology is the use of biological processes to make useful products (organisms, substances and devices). It has been used since earliest times to make beer, wine, bread and cheese, and in the selective breeding of plants and animals and the treatment of sewage. Thus naturally occurring organisms like yeasts have been exploited to make new products by fermentation, like wine out of grape juice; the propensity for plants and animals to mutate has been taken advantage of and accelerated to make new varieties which are of greater utility to man, for instance, breeding edible cereals from grasses. More recently, fermentation has been used to produce antibiotics such as penicillin. The knowledge and skill which informed this "classical" use of biotechnology has of course increased enormously over time.

2.2 Since the early 1970s, however, biotechnology has been taken a step further. Major advances in molecular biology have given rise to a variety of techniques which enable scientists to move genes from one organism to another and to get them to work in the recipient organism and hence to give it new properties. This is sometimes called genetic engineering or genetic modification and the result is a genetically modified organism (GMO). Genetic modification is the "new" biotechnology and its regulation is the subject of this report.

Cells, genes and DNA

2.3 Before looking at the various kinds of biotechnology, it would be helpful to consider briefly what genetic modification actually means.

2.4 All forms of life are made up of cells. The cell is the building block of living tissue. Every cell in plants, animals and humans contains within it a nucleus surrounded by cell fluid (cytoplasm) bounded by a cell wall or cell membrane. The nucleus contains the genes. In humans, the genes are arranged linearly on 23 pairs of chromosomes. Each chromosome is made up of a long string of DNA (deoxyribonucleic acid) divided into segments, some of which are individual genes. Each chromosome contains an estimated 50,000 to 100,000 different genes and the entire collection of genes in a cell is called the genome.

2.5 Collectively, genes make up the blueprint of the life form and they govern its biological functioning. Genes do this by issuing instructions to the materials in the cytoplasm, usually via messenger RNA which carries the message out from the nucleus. Cells in complex organisms like humans have highly specialised functions - such as liver cells or muscle cells. In these specialised cells only part of the genetic information is used while the rest stays "switched off". A fuller description of the role of the genes may be found in Box 2.1.

2.6 Genetic modification means making changes to the genes, the way in which they are combined together and transferring genes from one genome to another. It requires manipulation of the DNA sequence which makes up the individual gene. By so doing it is possible to impart new qualities to or remove defects from the "blueprint" and hence the life form. Even though a gene in a cell may be modified the cell nevertheless retains its essential characteristics.

BOX 2.1

1. Every cell in an organism, whether a bacterium, plant, animal or a human contains a complete set of genes, known as the genome. Plants and animal cells consist of a nucleus, enclosed by a membrane, and surrounded by the cytoplasm. The cytoplasm contains various specialised parts of the cell. In animals all the contents of the cell are held within a membrane and in plants they are additionally held within a cell wall. Bacterial cells are different as they have a single chromosome which is not enclosed in a nucleus. The genome of a human cell is made up of 23 pairs of chromosomes which rest within the nucleus of the cell. Each chromosome consists of a very large molecule of deoxyribonucleic acid (DNA) together with associated proteins. The chemical building blocks of DNA are nucleotides, each comprising a nitrogenous base, a deoxy sugar and phosphate group. The bases are of four kinds, adenine (A), cytosine (C), guanosine (G) and thymine (T). Arranged in linear sequence, they constitute the four letter genetic code. DNA is a ladder-like helical double-stranded molecule. The bases join to form the rungs of the ladder pairing specifically, A with T and G with C, giving a complementary base sequence on opposite strands. The complementary structure makes DNA capable of self replication. As the two strands separate a new complementary strand assembles on the old thus providing the basis of genetic continuity. Sometimes errors occur, the wrong base being inserted, giving rise to a mutation. In sexual reproduction the chromosomes from two parents recombine thus providing genetic variation.

2. Genes are segments of the DNA strands so a chromosome consists of a series of genes strung together linearly and separated by non-genic material. Some genes are small and consist of only tens of the bases whereas others may be tens of thousands of bases long. The linear sequence of the bases that make up the gene provide the instructions for the cell to construct proteins. There are thousands of different proteins that perform a wide variety of tasks within a complex organism. Proteins are the biological tools and building materials of the cell. Examples are hormones - the signalling and messenger substances such as human growth hormone; enzymes - the catalysts for reactions within the cell that play vital roles such as the breaking down of food, transport and storage of energy; and antibodies - defensive substances of the immune system.

3. Proteins are made from combinations of 20 different amino acids arranged in linear sequence on instruction from the genes. Each sequence of three bases of the gene provide the instructions for adding a particular amino acid to a chain of amino acids which when complete forms the protein. Proteins consist of between one and several hundred amino acids. The gene thus provides the instructions that determine the length and order of amino acids along a chain that forms a particular protein. (The aim of the Human Genome Organisation (HUGO) is to identify the function of every gene of the human genome.)

4. Every living organism uses the same instruction "language" (the genetic code) from the same set of 20 amino acids. Thus if the gene that provides the instructions for a human cell to produce human insulin is removed from the cell and inserted into the genome of a bacterium, the bacterial cell will follow the instructions and string together the same amino acids in the same sequence and produce a chemically identical insulin.

5. The process of "reading" the instructions of the gene and assembling the amino acids to form proteins is achieved within the cell using ribosomes. The ribosomes are the "factories" of the cell located in the cytoplasm. They receive instructions of what to manufacture in the form of a working copy of the gene made of ribonucleic acid (RNA) which is similar to DNA but single-stranded. The RNA is produced in the nucleus but is able to leave the nucleus and enters the cytoplasm where the ribosomes are able to 'read' the instructions on this 'messenger' RNA, again in the form of sequences of bases; they then assemble the protein chain of amino acids. As the chain is forming it folds into the three-dimensional structure of the protein.

Contd

BOX 2.1 continued

6. Most cells in a large organism have a specialised function such as those in the kidney, liver or muscle. In the specialised role the cell "switches off" parts of the genome; ie those genes that provide instructions for products that the cell does not need to survive or fulfil its role are deactivated. Thus every cell has the potential to provide instructions for the cell "factory" to produce every protein needed for human life but the cell chooses to provide the instructions for only selected proteins. The mechanism by which this is achieved is the subject of much research.

7. Viruses are non-cellular particles consisting of a protein shell and a DNA or RNA genome. A virus may contain from a few to several hundred genes. Viruses cannot reproduce themselves but need access to a host organism's cell machinery. They are able to penetrate the cell walls of most organisms and corrupt the instructions of the cell, causing it to make many copies of the virus. Viruses are useful in biotechnology as they can be used to transport useful genes into a cell and sometimes into the genome.

What are the technologies?

2.7 Biotechnology is not a single discipline; it is a collection of quite different enabling technologies resulting from advances in cell and molecular biology over the last twenty years. The technologies associated with the recent developments in genetic modification, with which this report is concerned, are noted below.

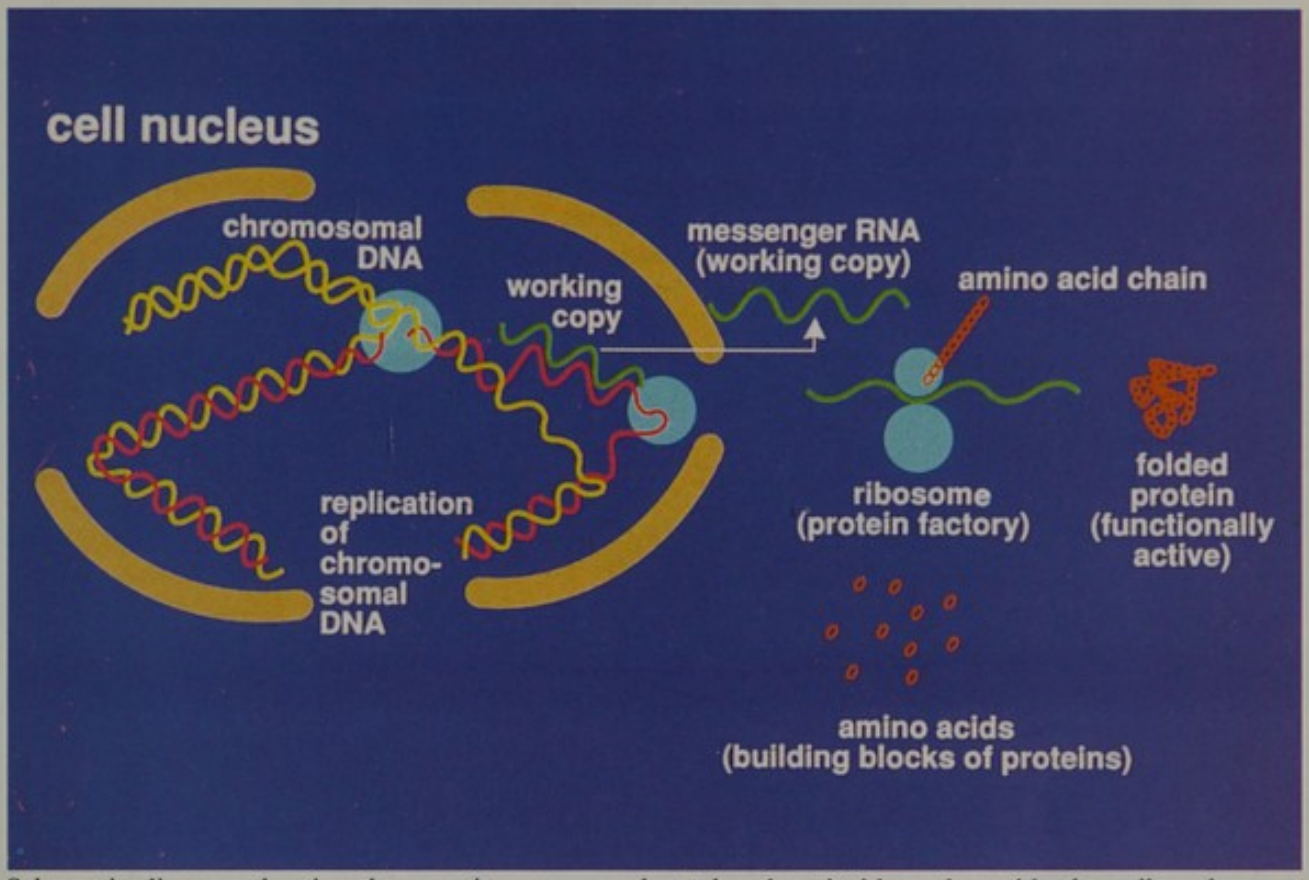
— *Recombinant DNA (rDNA)* is the result of cutting (using "restriction" enzymes) and splicing DNA (using "ligating" enzymes). Restriction enzymes are naturally produced proteins designed to cleave DNA at the site of a specific base sequence. Ligases rejoin the cut ends of DNA in any chosen order in a precise manner. In this way it is possible to remove the DNA fragment carrying a specific gene coding and "recombine" it into the DNA of another organism. The utility of this technology depends on the scientist's ability to identify particular genes and the proteins they help to make.

— *Fused cell technique (or in the case of plants protoplast fusion)* is the ability to fuse two cells by removing their walls to yield a novel cell containing the whole or parts of the genetic code of both parents. An important form of this technology is the manufacture of "*monoclonal antibodies*" already used in medical diagnosis.

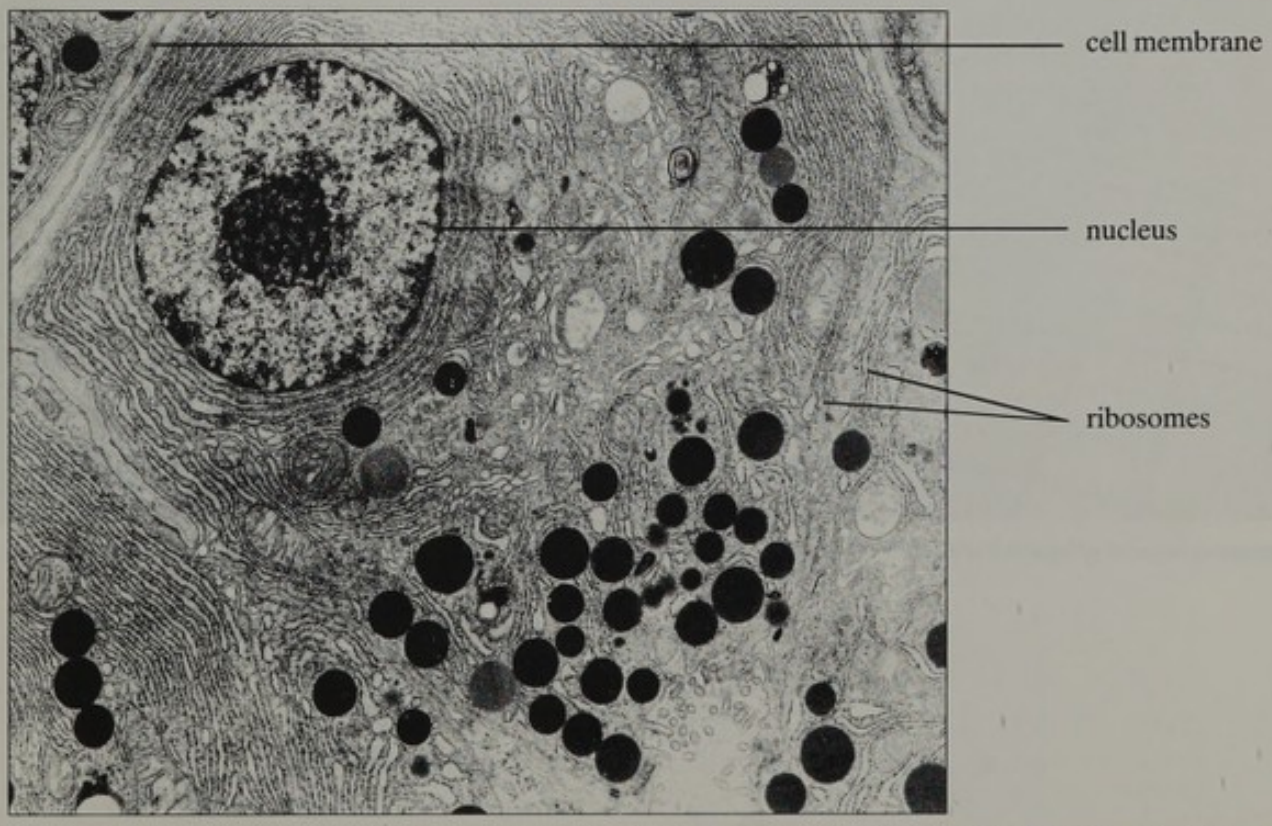
— *Micro-injection* enables DNA to be injected by syringe into a cell or its nucleus. The injected DNA carries 'signals' to locate sites on the host DNA at which it inserts itself to become part of the genome of the host cell.

— "*Biolistics*" involves using a particle gun to shoot DNA-coated tungsten particles through plant cell walls to impart new genetic qualities. Any plant tissue can be used as a target.

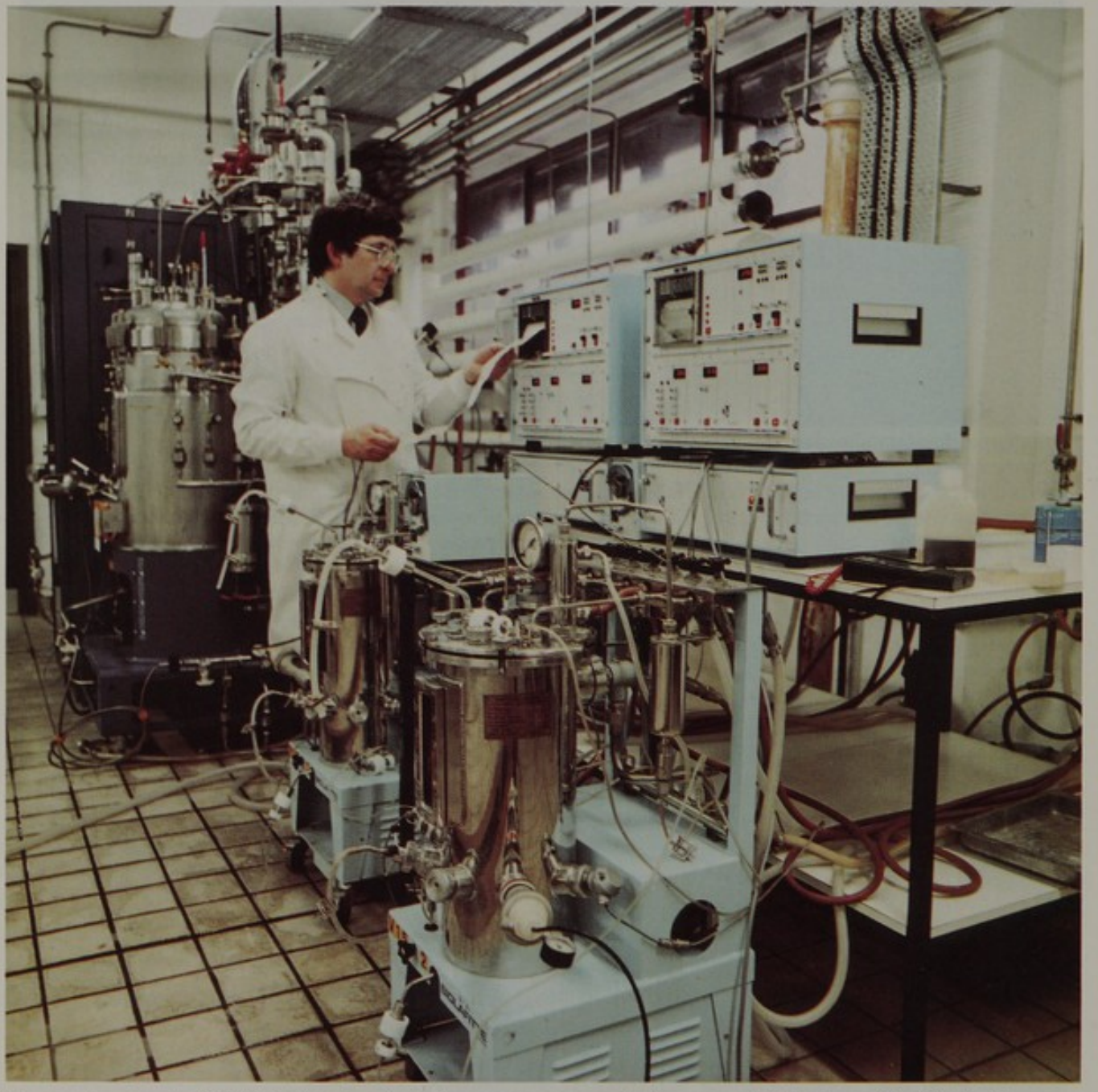
— *Viruses* can be used as "vectors" to carry segments of DNA into a cell. A piece of DNA carrying the required gene is inserted into the virus. A virus is non-cellular and cannot reproduce itself. Instead it penetrates cells and uses the cells' own machinery to make copies of itself. Some viruses integrate their genetic material into that of the host cell.



Schematic diagram showing the genetic processes that take place inside and outside the cell nucleus. Chromosomal DNA is split in the nucleus into its two separate strands (going left and right in the diagram) and is then copied before cell division. Proteins are manufactured by the ribosomes using instructions from the appropriate gene which are carried from the nucleus as messenger RNA (single stranded, shown in green). (Reproduced with permission from *Genetic Engineering What's happening at Roche?* Editiones Roche 1992).



Transmission electron micrograph of a human pancreas cell (mag. × 6000). The cytoplasm surrounds the nucleus and is bounded by the cell wall. There are various bodies within the cytoplasm including the ribosomes which appear here as numerous tiny specks. (Reproduced by kind permission of Dr Susumu Ito, Harvard Medical School).



Fermentation research at SmithKline Beecham. In the foreground are two ten litre fermenters; in the background is a fifty litre fermenter.

— *Fermentation and cell culture* are techniques which enable large amounts of cells to be grown. DNA may be introduced into bacteria either by using viruses or plasmids (small DNA molecules separate from the chromosome often found in bacteria) as vectors or by micro-injection. Supplied with the right nutrients these bacteria reproduce rapidly, passing on their newly acquired genetic characteristics to their daughter cells. DNA may also be introduced by virus or plasmids into yeast cells or tissue culture which can then be grown in great quantity by fermentation or massive cell culture.

The limits of the technology

2.8 DNA can apparently be transferred from any organism to another using appropriate techniques. However there are some limitations at present. Gene transfer into bacteria or yeasts is limited only by the length of DNA to be inserted relative to the size of the vector. Potential for gene transfer into animals seems to be unlimited but some plants remain resistant to current insertion technologies.

2.9 Each inserted gene requires instructions to "express" or make its product. Usually the instructions can be provided by the host genome but sometimes they need to be taken with the gene from the donor genome.

2.10 At present gene transfer is confined to single genes. In future, as the analysis of the human genome proceeds, scientists may wish to insert combinations of genes - for example for gene therapy of complex multi-genic diseases, like coronary heart disease.

CHAPTER 3 APPLICATIONS OF BIOTECHNOLOGY

3.1 The range of technologies collectively known as biotechnology can be used in an increasingly wide range of sectors. As we have seen, "classical" biotechnology has been applied in the food and brewing industries for centuries, and more recently in the production of antibiotics. However, following the advances outlined in the last chapter a range of powerful new techniques is now available which dramatically increase the potential applications of biotechnology in industry, agriculture and health care. In some cases, the techniques have enabled the making of products that would have been unobtainable or vastly too expensive to produce using conventional means: in others, they provide cheaper and more efficient routes to produce substances already in use. In this chapter, we look briefly at the range of applications and prospective applications and their estimated economic value.

Pharmaceuticals

3.2 Biotechnology has already led to major developments in the pharmaceutical industry as it has opened up new manufacturing routes. Examples of the application of biotechnology in this sphere are:

— *Manufacture of human proteins*. Human proteins may be produced by introducing the specific genes required into bacteria or other cells. This avoids accidental contamination of the product, for example, the risk of HIV infection in the treatment of haemophilia has been removed by the use of Factor VIII, a substance which can now be produced by way of recombinant DNA (rDNA) technology rather than by extraction from human blood. Human growth hormone and human insulin are also now manufactured more safely because of biotechnology, (BioIndustry Association (BIA) p 18, Professor Goldspink p 95; Wellcome Foundation p 203). Interferon, the commonly used cancer drug, is a genetically engineered protein (Department of Health p 76). Recombinant DNA technology has resulted in 16 proteins being manufactured and marketed as pharmaceutical products and many more are being developed (BIA p 18, Science and Engineering Research Council (SERC) p 169).

— *Opportunities for drug design*. It has been possible, using the new techniques, to produce large quantities of the protein on a cell wall that acts as the receptor for a particular drug. This enables the receptivity of a drug to be tested cheaply and easily *in vitro* without recourse to animal experimentation (Professor Goldspink p 95; SmithKline Beecham p 180).

— *Manufacture of new vaccines*. The new techniques allow the identification and manufacture of individual proteins or fragments of proteins from pathogens that provide protection for, but are well tolerated by, the recipient. The opportunity can be taken to use only non-infectious fragments of the genetic material of the pathogen and not the infectious pathogen itself. New vaccines of this type providing protection against hepatitis B and whooping cough are already launched. Vaccines against malaria, AIDS, polio, cholera, leprosy and many others for humans and animals are being developed (BIA p 26, Pfizer p 148).

Health and treatment

3.3 New ways of understanding disease and treating it have emerged.

— *Diagnosis*. Tests which can accurately diagnose diseases at early stages of infection allow the correct treatment to begin earlier (Professor Goldspink p 95). Many of these tests are based on the generation of monoclonal antibodies and others on the polymerase chain reaction (PCR). Monoclonal antibodies are very pure forms of single antibodies. They can be used to detect the presence of any specific chemical or antigen which may be present because of a particular disease. They may also be used in tissue staining techniques to identify the presence and location of specific proteins which are

present normally but which are absent or reduced in disease states (eg dystrophin in some forms of muscular dystrophy). Monoclonal antibodies are produced using cell fusion techniques. PCR is a technique for rapidly multiplying copies from a tiny amount of DNA, to make enough for analysis and identification. It has widespread diagnostic and forensic application. This has been one of the areas of very rapid development. The world market for these diagnostic tests which are sold as kits was estimated at $300 million in 1987 (*A Survey of Biotechnology, The Genetic Alternative,* The Economist, 30 April 1988 p 10).

— *Gene therapy*. The cause of hereditary diseases, like cystic fibrosis and Huntington's Chorea, can be traced to defective genes which means that certain cells do not produce certain proteins or produce a defective version. If such a gene can be identified and replaced, a cure of a hitherto disabling or fatal disease would have been found. Gene therapies of this kind are being developed to counter many of the hereditary diseases. Treatment of patients suffering from adenosine deaminase (ADA) deficiency, a deficiency which prevents the development of a completely functioning immune system has already begun in the United Kingdom. In America there have been at least 43 applications for proposed gene therapy experiments (Science, 2 May 1993). More than 20 firms world wide are at present engaged in some form of gene therapy research (BIA p 18; British Bio-technology Ltd (BBL) p 37). Germ line gene therapy (affecting sperm or ova) is not yet permitted.

— *New cancer treatments*. Gene therapy approaches are being used to stimulate the body's immune system so that it can recognise cancer cells and destroy them. This offers the possibility of reducing the use of toxic chemotherapeutic agents and perhaps curing the disease (The Times 2 March 1993, New Scientist 6 March 1993, Medical Research Council (MRC) Press Release 21 June 1993).

— *Research*. The ability to move DNA from humans into animals opens up the possibility of producing animals with near exact versions of human diseases — for example the cancer-prone mouse known as the 'onco-mouse'. These transgenic animals have tremendous potential as research tools (Professor Goldspink p 95; Dr Kinderlerer p 115).

Agriculture

3.4 The application of rDNA technology to agriculture has great potential. In the words of the OECD, 'When one looks back on the 1980s, it is apparent that the scientific developments underpinning agrofood biotechnologies have been extraordinary both in speed and scope' (OECD *Biotechnology, Agriculture and Food, 1992*).

— *Plant breeding*. The production of transgenic plants using rDNA techniques can be seen as an extension of traditional plant breeding techniques which aim to improve particular characteristics of plants. However the use of rDNA provides potentially greater precision than traditional breeding techniques leading to a wider variety of the improvement of species. Targets are the improvement of yield by increasing resistance to drought, temperature, salinity, acidity, alkalinity (Chemical Industry Association (CIA) p 57), pests and diseases (Ministry of Agriculture, Fisheries and Food (MAFF) p 45; Scottish Agricultural Science Agency (SASA) p 171), herbicides (BIA p 18), introducing the ability to fix nitrogen (Pfizer p 148) and improving composition and nutritive quality. Plants with herbicide, insect, disease and virus resistance have been tested (BIA p 29). BIA provided us with a list of 394 field releases of transgenic plants covering 25 different species which have been approved world wide (BIA p 30). Insect-resistant strains of maize and cotton are expected to be marketed within the next few years (US News and World Report, May 3, 1993, US Department of Agriculture, Agricultural Research, December 1991). Traditional plant breeding methods can also be speeded up by using markers for particular desirable genes which can be easily

identified so that plants inheriting the desirable gene can be recognised before the trait is expressed in a fully grown plant.

— *Diagnosis of disease*. Rapid diagnostic tests developed using the new biotechnologies will lead to correct disease identification and should reduce the need for precautionary crop spraying (SASA p 171, MAFF Foodsense Factsheet No.3). Kits are already being marketed to detect the presence of potyviruses (named after potato virus Y) that affect many important crops such as maize, soyabeans and wheat (US Department of Agriculture, Agricultural Research Service, *Solving Agricultural Problems with Biotechnology*, Program Aid 1445, January 1990).

— *Non food uses for crops*. The genetic make up of plants may be changed so that they provide raw materials for the polymer, fuel and chemical industries. Oils, starches and sugars may be turned into industrial products (Agricultural and Food Research Council, (AFRC), P 7)). Potatoes have been modified so that they produce the thermoplastic polyester poly-B-hydroxybutyrate (Institution of Professionals, Managers and Specialists, (IPMS) p 108).

— *Animal health*. Developments in human healthcare are paralleled by those for animals and fish. New safer vaccines are being developed (MAFF PP 44-45; Hoechst Q 360). Vaccines against rabies, feline leukaemia and foot and mouth disease have already been developed (BIA p 26). New diagnostic agents are available to identify accurately viral, bacterial and parasitic diseases, an example of the last being trichinosis (the presence of the parasitic trichina worm) in pigs (US Department of Agriculture, Agricultural Research Service, *Solving Problems with Biotechnology*, Program Aid 1445, January 1990). Diagnostic reagents, often in kit form, are available for the detection, regulation and synchronisation of breeding cycles, thereby improving the efficiency and welfare of livestock production.

— *Transgenic animals*. As in plant breeding, the ability to transfer desirable traits accurately from species to species may improve the productivity and usefulness of animals and fish. The ability to identify and breed out undesirable genes or insert desirable ones could lead to improved disease resistance (Professor Goldspink p 95) and more efficient utilisation of forages, including the use of industrial waste as animal feed.

Food

3.5 Many of the improvements in crops and animals will have direct effects on food quality but rDNA technology will also have an impact on food processing technologies and food safety.

— *Food quality*. Improvements in food crops such as being able to reduce the amounts of naturally occurring toxins in crop plants, to increase the more desirable components in edible oils and to increase the starch to sugar ratio in potatoes will lead directly to improved food quality (MAFF p 11). Other properties such as storage properties and shelf life (Calgene's Flavr-Savr tomato) can also be improved.

— *Food processing*. Enzymes are widely used in food processing; for example, chymosin and renin are used in cheese making, glucose isomerase (a sweetener) is used in producing corn syrup; and papain is used for tenderising meat and dehazing beer. In the case of chymosin, the 'natural' product is extracted from the stomachs of calves but it can now be produced using a genetically modified bacterium. A genetically modified yeast has been approved for use in the baking industry. We were told by a Unilever representative on our visit to Zeneca Seeds that the sales of food products produced using enzymes is now £700 million per annum. Enzymes produced using rDNA technology are often purer than those produced using more conventional technologies (MAFF P 45).

Insect resistance in tomato plants.

Above: The plant on the right has been genetically modified using genes from bacillus thuringiensis (Bt) so that the plant produces insecticidal proteins.

Below: Fruit from modified and unmodified tomato plants (as above) after exposure to the insect heliothis armigera.

(photographs courtesy of Plant Genetic Systems NV, Belgium)

Test plots of genetically modified oilseed rape *(photograph courtesy of John Innes Institute, AFRC).*

— *Food safety*. Diagnostic kits which are rapid and accurate are being developed using the new biotechnologies. These offer the possibility of improving food safety by testing for the presence of chemical and microbial contamination both in food and equipment used in food preparation (Financial Times 7th May 1993). Some of these kits are now commercially available.

Chemical industry

3.6 The chemical industry is already using new manufacturing processes based on biotechnology and is looking for other uses.

— *New feedstocks*. Genetically modified plants and bacteria may become new sources of raw materials. Plants, for instance, may be used to generate plastics (IPMS p 108). There is the potential to change the type of oils produced by, for example, oilseed rape so that it resembles an oil that is more desirable commercially. Better and more readily obtainable starches may be procured from potatoes, cereals and rice for industrial uses such as paper making, textiles, adhesives, and drilling fluids for the oil industry (*Biotechnology, Agriculture and Food*, OECD 1992 p 106).

— *New manufacturing methods*. Chemicals such as enzymes, colourings, flavourings and pesticides manufactured using biotechnology offer the possibilities of being cheaper, of higher purity, and producing less noxious waste (CIA p 57; MAFF P 45). Subtilisin, an industrial enzyme, is commonly used in "biological action" washing powders and industrial cleaning applications. It is produced naturally by certain bacteria and fungi. To improve the yields, the gene encoding the enzyme can be transferred into other organisms which will produce the enzyme more efficiently and can be grown more easily in fermenters. Three quarters of all "enzyme" detergents now use enzymes derived from modified micro-organisms. The ACOST report *Developments in Biotechnology 1990* stated that the "current world market [for industrial enzymes] is estimated at $750 million a year ... It is likely that half the industrial enzyme market will be supplied by engineered enzymes within a decade". Traditional production routes usually produce mixtures of steric isomers. These are chemical compounds which have identical formulae and composition but that are, geometrically, mirror images of each other and may have very different properties. Often only one steric form has the desirable properties. The others may be merely inactive but can be harmful. The new biotechnologies offer the possibility of producing a single steric form (Professor Burke p 47).

— *Biosensors*. These are sensors based on the response of, for example enzymes to the presence of particular chemicals. In an industrial setting they could be used to monitor and control waste for the presence of heavy metals or organic chemicals. The "Microtox" system for monitoring toxic chemical in effluent is already commercially available (National Rivers Authority (NRA) p 137).

Environmental applications

3.7 Biotechnology (using naturally occurring bacteria) is already used to remove nitrogen and phosphates from sewage and for cleaning industrial effluent (NRA p 136). It is hoped that the new biotechnologies will in future provide efficient means of monitoring heavy metal and organic pollutants and that new means of pollution treatment will be developed. Enzymes produced from modified micro-organisms are increasingly used for the removal of hair from animal hides and to treat shavings containing toxic chromium salts in tannery waste streams allowing re-use of the chromium containing chemicals (Senior Advisory Group Biotechnology (SAGB) *Benefits and Priorities for the Environment*).

Mining

3.8 It has been proposed that microbes could be used to leach and concentrate valuable metals such as silver, gold and platinum and recover residual quantities of oil. However the ready availability of easily mined deposits and recent advances in conventional drilling technology means that there is little economic advantage in using a technology that would require considerable investment to develop (BIA p 27, *Recombinant DNA safety considerations*, OECD, p 22, 1986).

Engineering industry

3.9 New manufacturing and processing methods and the research and development facilities require new types of machinery such as fermenters, containment and sterilizing equipment, new monitoring and control systems, and specialised apparatus (for chromatography, electrophoresis and ultra-filtration) for product recovery and analysis, thus presenting further opportunities for industry. The safety requirements of biotechnology demand high standards in the quality of this equipment. This provides a spin-off for industry

Economic assessment

3.10 We received a number of estimates of the current and projected economic value of biotechnology, both for the United Kingdom and for the global economy. In such a rapidly developing field, figures are bound to be unreliable but they were often quoted in evidence[1]. While we set out the information we were given as an indicator of potential growth we do not specifically rely on it.

3.11 We have been told by SAGB (a body created by the European Chemical Industry Federation (CEFIC) in 1989) that a poll of its 30 member companies revealed that they are currently investing $1.3 billion in Europe and $1 billion in the United States. SAGB companies employ about 6500 people in Europe associated with biotechnology and about 5000 in the United States and it provides a forum for debating policy issues affecting biotechnology in the European Community. The CBI, in written evidence, quoted an article in Bio-Technology June 1992 which estimated that in 1991 biotechnology sales in the United Kingdom stood at $650 million and at $4000 million in the United States (CBI p 63). SmithKline Beecham suggested that in 1990-1991 sales of biopharmaceuticals world wide were over $4 billion (SmithKline Beecham p 181). Professor Lilly stated that in 1990 six therapeutic proteins made by recombinant DNA technology each had annual sales of more than $100 million (Professor Lilly p 119).

3.12 The BioIndustry Association provided us with a list of 54 new biotechnology businesses which have been started up in the United Kingdom since 1980 and a list of a further 48 United States biotechnology subsidiaries set up in the United Kingdom. The 54 new businesses currently employ about 5000 people (BIA p 25). In oral evidence the BIA suggested that the current market for biotechnology derived products is $8 billion in the United States and about $500 million in the United Kingdom and growth rates are 20-30 per cent per annum (BIA Q 548). The United Kingdom Biotechnology Handbook (1993) lists 678 organisations. Among these are 363 companies which use biotechnology directly, 149 service companies provide support for the industry, 25 institutions provide investment support and 113 academic institutions doing research in this area. British Biotechnology Ltd stated in written evidence that the United States biotechnology industry now generates revenues of $8.1 billion, an increase of 28 per cent over the previous year (BBL p 36).

3.13 Predictions about the size of the world biotechnology market in the future are very wide ranging. The ACOST report *Developments in Biotechnology* (1990) quotes OECD and UN reports which forecast the size of the world market to be between $9 billion and $100 billion in the year 2000. The Royal Academy of Engineering in their written evidence predicted a market size of

[1] The ACOST report *Developments in Biotechnology, 1990 (p.8)* states that the "wide range in the prediction of the size of the market in the year 2000 reflects the difficulty in estimating the scale of exploitation possible at this relatively early stage in the development of the new biotechnology". It is important to note that all the more recent predictions of potential market size are very much at the upper end of this range.

between $30 and $50 billion in the year 2000 for biotechnology derived products excluding fermented food and drinks (RAE p 157). From BIA projections we might expect a world market size of $90 billion world wide by the year 2000. SAGB in their brochure *Economic Benefits and European Competitiveness* project the total value of biotechnology products and processes by the year 2000 at $100 billion.

3.14 In sum, evidence tells us that the estimated size of the current market for biotechnology derived products in the United Kingdom lies between $4 and 8 billion a year: the estimated size of those markets in the year 2000 are, respectively, $2 - 4 billion for the United Kingdom and up to $100 billion for the USA.

3.15 Not all industrial sectors are expected to find applications for biotechnology at the same rate. In the preceding paragraphs we saw that applications were uneven and this is expected to continue. Thus SAGB, in its brochure *Economic Benefits and European Competitiveness*, states that most advanced current commercial applications of biotechnology are in the chemical, pharmaceutical and instrumentation (including diagnostics and specialised equipment) sectors because the technical hurdles have been more rapidly overcome. It suggests that commercial applications in food and agriculture will develop more slowly until the mid 1990s because of significant technical hurdles.

Biotechnology and the United Kingdom economy

3.16 A recent study by the Centre for Exploitation of Science and Technology (CEST), entitled *Biotechnology as a Competitive Advantage* (Draft Version 3, 22 April 1993), has considered the changes likely to be brought to United Kingdom industry by biotechnology (CEST PP 217-221). The conclusion drawn by the author is that the agriculture and food, chemical, and healthcare industries which do or could use biotechnology account for 12 per cent of United Kingdom GDP. However some 10 per cent of this is food and agriculture based. Thus the likely impact of biotechnology at the macro-economic level may well be only marginal. Indeed the author concludes that "a 10 per cent increase in the value added due to biotechnology will only add 0.15 per cent to the United Kingdom annual growth [of GDP]" (CEST *Biotechnology as a Competitive Advantage* p 17). At current rates of growth some might say that 0.15 per cent was by no means insignificant. But some witnesses considered the CEST assessment was unduly pessimistic and based on data which was now out of date. They preferred to use recent projections from other sources as a measure of likely impact on GDP (Association of the British Pharmaceutical Industry (ABPI) Q 844).

3.17 Nonetheless at the level of the individual firm the CEST study concludes that 'In microeconomics at the firm and industry levels biotechnology is crucial and a core technology. Firms that do not use it effectively will be at a competitive disadvantage'. (CEST P 221). 'If biotechnologies are chosen well and used to add variety together with good logistics and distribution, they are a force for the development of a real innovative economy' (CEST P 220).

CHAPTER 4 THE REGULATIONS

Background to the regulations

4.1 The issue of regulation of biotechnology first arose in the early 1970s when scientists themselves questioned the safety of what was then the new techniques of genetic modification. In 1974, a National Academy of Science study group in the U.S.A called for a moratorium on certain GMO experiments. In response to this call the UK Advisory Board for the Research Councils set up a working party under Lord Ashby. In 1975, the working party recommended that genetic modification techniques should be used but with rigorous safeguards. The Genetic Manipulations Advisory Group (GMAG) was set up to examine proposals for genetic manipulation and under the Health and Safety (Genetic Manipulation) Regulations 1978 it was required that any activity involving genetic manipulation should be notified to the Health and Safety Executive (HSE) and GMAG. In 1984 GMAG became the Advisory Committee on Genetic Modification (ACGM), which continues to this day (Kornberg Q 769; HSE PP 2-3).

4.2 In 1989, the regulations were altered slightly to extend notification requirements to both the use of GMOs and the release of GMOs to the environment but the duties of the HSE were limited only to considering the protection of human health. The ACGM provided extensive guidance notes concerning risk assessment. Under the 1989 regulations any proposal to release a GMO into the environment had to be notified to the HSE at last 90 days in advance. The risks associated with the release had to be considered by the institutions' genetic modification local safety committee and the results sent to the HSE where they would be reviewed by the Intentional Introduction Sub-Committee of the ACGM.

4.3 In response to the 13th Report of the Royal Commission on Environmental Pollution *(The Release of Genetically Engineered Organisms into the Environment),* Part VI of the Environmental Protection Act (1990) provided specific regulation to prevent or minimise the damage to the environment from GMOs. This Act required a safety assessment to be made and submitted to the Department of the Environment (DOE). In certain cases a consent had to be obtained and the Advisory Committee on Releases to the Environment (ACRE) was created from the Intentional Introductions Sub-Committee of ACGM to advise the Secretary of State on these matters. Thus the United Kingdom, unlike most of the countries with which it competes, had by 1990 evolved its own regulatory system.

4.4 Moreover, it was a system which - at least so far as health and safety was concerned - few saw reason to change (MRC QQ 809-12). Thus HSE told us that "the fact that the new contained use regulations bring in a concern about environmental effects is an additional responsibility that the regulatory system, as it were, has to take account of. However, to put it more bluntly, my Lord Chairman, we should have been reasonably content as the Health and Safety Executive, and so far as the protection of human health is concerned, to have continued along with the 1989 basis, but frankly there was a very great deal of quite emotional argument, quite a lot of attempts by some other countries, to go even further towards rigorous regulation in the discussion of the Directives and we came out with a conclusion that was the best that could be secured meeting what most Member States were prepared to accept" (HSE Q 44).

4.5 At an international level during this period the OECD Committee for Scientific and Technological Policy set up a Group of National Experts for Safety in Biotechnology to establish scientific criteria for the safe use of GMOs in industry, agriculture and the environment. In 1986 the Group reported its conclusions in the book *Recombinant DNA Safety Considerations.* The principal conclusions of the Group were that there was "no scientific basis for specific legislation for the implementation of rDNA techniques and applications", and that "any risks raised by rDNA organisms are expected to be of the same nature as those associated with conventional organisms. Such risks may, furthermore, be assessed in generally the same way as non-recombinant DNA organisms", and that "although rDNA techniques may result in organisms with a combination of traits not observed in nature, they will often have inherently greater predictability compared to conventional methods of modifying organisms". The Group considered that "the vast majority of

industrial rDNA large-scale applications will use organisms of intrinsically low risk which warrant only minimal containment consistent with "good industrial large-scale practice (GILSP)" and they detailed the criteria that needed to be met for an organism to qualify as low risk. GILSP is thus the set of standards currently used in large scale industrial production involving low risk organisms that have not been genetically modified. It includes established principles of good occupational and environmental safety. Containment "approaches" for those GMOs that do not qualify as low risk are also detailed in an appendix of the OECD book.

4.6 OECD did recommend, however, that countries should ensure that rDNA organisms are evaluated for potential risk prior to applications in agriculture and the environment by means of an independent review of potential risks on a case-by-case basis using assessment criteria relevant to the particular proposal. The report contains appendices with extensive lists of factors that should be considered when assessing the possible risks, the potential human health considerations and the potential environmental and agricultural implications associated with the use of rDNA organisms. However, the report readily states that not all questions will be applicable to every case and that it is expected that individual proposals will only address those that are appropriate. Similarly the level of detail required will also vary according to the application.

4.7 A further report form the OECD Group of Experts *Safety Considerations for Biotechnology 1992* has now been published. This report is written in the light of experience from field tests performed with conventional organisms and the 500 or more experiments carried out with organisms with new traits since 1986. The BIA told us that 1500 releases have now taken place. The experts develop general principles that should be followed in the safety assessment of low or negligible risk small scale field research known as Good Developmental Principles (GDP). The key factors to be considered are the characteristics of the organisms, the characteristics of the research site, and the use of appropriate experimental conditions.

4.8 We were also told about continuing discussions at OECD on a series of guidelines which might harmonise regulatory procedures in the Developed World. Moves towards world wide harmonisation were broached by the United Kingdom and the Netherlands with a view to laying out some principles in Agenda 21 for the UN Conference on Environment and Development held in Rio de Janeiro in June 1992, but with limited success (DOE (Fisk) Q 77).

The EC Directives

4.9 At the European Community level regulations concerning the contained use and release of GMOs were formulated and issued as the Directives 90/219/EC (Contained Use) and 90/220/EC (Deliberate Release) in May 1990. These Directives should have been implemented by all Member States before 23 October 1992. To date the Directives have been implemented by Great Britain, Germany, Denmark, France, and the Netherlands (DOE P 21). The Contained Use Directive covers only genetically modified micro-organisms whilst the Deliberate Release Directive covers both micro and large organisms.

4.10 The Contained Use Directive was based on the 1986 OECD publication. A member of the committee which wrote the OECD book told us that the committee had consisted mainly of government officials save for five industrialists all of whom came from the pharmaceutical industry. He states in evidence that the containment measures were detailed for organisms that did not fall within the category of safe GLISP organisms and were meant "purely as examples". He also states that these examples which have now been incorporated into legislation have "... in the eyes of many, been assumed to have some form of connection with the requirements of GLISP. This is in practice reasonable only in the case of the pharmaceuticals industry but not for other industries". The Deliberate Release Directive seems also to have been based on the lists of questions contained in the appendices of the OECD book (Thorley P 261; HSE P 2).

4.11 Witnesses expressed surprise to us that, following the recommendation of OECD's Group of National Experts in 1986 that there was no scientific basis for genetic regulation, the EC decided nevertheless to act at all in this matter. There was also evidence that insufficient consultations were

undertaken by the Commission during preparation of the draft Directives (SAGB QQ 514-5). Moreover it was suggested to us that such advice as was tendered at this pre-legislative stage was not accepted. Thus "during the very early phases when we were being consulted or various people in Europe were being consulted informally there was a lot of advice against the approach being taken, and I would say that that was not followed in much of the Directives which you now see" (SAGB Q 521). We were told by ABPI that originally DGXI (Environment) of the Commission was responsible for preparing a Directive on release and DGIII (Industry) on contained use. Eventually, however, DGXI took over both. Representations made by the pharmaceutical industry through their European Federation before the Directives were published were, they maintain, totally ignored (ABPI Q 846).

4.12 Although more discussion took place after publication, the opportunity for amendment thereafter was slight. Save for amendment by the European Parliament, it was alleged that "Academic and industrial interests at European and national level were systematically excluded from this debate" (BIA p 19). The Commission, by contrast, felt that these allegations were ill-founded; that the Commission had decided to regulate in the 1970s; and that plenty of opportunity had been given for comment during preparation of the Directives in the late 1980s (EC Commission QQ 893-8).

4.13 Because biotechnology affects many sectors, regulation involved DGIII (Industry), DGXI (Environment) and DGXII (Science). Oversight is attempted by the Biotechnology Coordinating Committee.

The present position

4.14 "New" biotechnology in Great Britain[1] - that is to say the use, manufacture, release or marketing of genetically modified organisms (GMOs) - is now governed by two principal regulations: the Genetically Modified Organisms (Contained Use) Regulations 1992 and the Genetically Modified Organisms (Deliberate Release) Regulations 1992 (hereafter referred to as the contained use and deliberate release regulations respectively). The contained use regulations apply to GMOs used under controlled conditions designed to minimise the possibility of escape, for example in the laboratory or factory. (They also cover deliberate release into the environment of genetically modified micro-organisms). The deliberate release regulations apply to GMOs released into the environment - for example, for field testing - or placed for sale on the market. Both regulations apply only to viable organisms, that is to say organisms which can replicate themselves.

4.15 These regulations implement the two European Community Directives - 90/219/EEC on the contained use of genetically modified micro-organisms and 90/220 EEC on the deliberate release into the environment of genetically modified organisms.

4.16 The regulations are backed up by further clarificatory documentation. The Health and Safety Executive has published "A Guide to the Genetically Modified Organisms (Contained Use) Regulations 1992" and the Department of the Environment is in the process of publishing "Guidance to the Regulatory Control of the Deliberate Release of Genetically Modified Organisms".

4.17 In addition to the regulations and supporting documentation each Department has an advisory committee to adjudicate upon applications made under the regulations and on other issues - the Advisory Committee on Genetic Modification (ACGM) advises HSE and the Advisory Committee on Releases to the Environment (ACRE) advises DOE. ACGM (and its predecessor body) has also published a series of eleven Guidance Notes on good practice in various aspects of contained use work. The "Brenner" system for risk assessment began life as Paper Number 7 in this

[1] Northern Ireland regulations are in preparation, under the aegis of the Department of the Environment (NI), the Department of Economic Development, the Department of Agriculture (NI) and the Health and Safety Agency for Northern Ireland. The regulations will be closely based on the Great Britain GMO Regulations 1992 for contained use and deliberate release.

series. These guidance notes frequently refer to two widely accepted sets of standards on occupational and environmental safety - Good Large Scale Practice (GLSP, equivalent to OECD's GILSP) is set out in ACGM guidance note 6 and requires no containment measures and includes the techniques and training that should be used and given to operators; the general facilities that should be available; general design features of the laboratory and administrative procedures that should be in place in every microbiological laboratory. These collectively are GMP. We return to the concepts of these sets of standards later in the report.

4.18 The two sets of regulations are mutually exclusive and, although they enjoy certain common features, their salient features must be considered separately.

Contained use regulations

4.19 The purpose of the contained use regulations is to protect people against risks to health from activities involving GMOs under controlled conditions such as those in laboratories or in industrial processes. Any operation involving genetically modified organisms in contained use is prohibited unless it is undertaken in accordance with these regulations. Containment is achieved by physical means (eg cabinets or fermenter vessels) and biological means (eg reduced viability) supplemented by chemical means (eg disinfection). Levels of containment are specified for systems falling into various different categories.

4.20 The regulations provide that no one may carry out genetic modification work unless the risk it presents to human health and the environment has been assessed according to a method approved by HSE. Each institution that notifies the HSE of its intention to conduct work using GMOs must appoint its own genetic modification safety committee to make this assessment.

4.21 Levels of risks are estimated from the characteristics and properties of the donor and recipient organisms (ie pathogenic or non-pathogenic) and of the vector used to transfer the DNA from donor to recipient organism (ie the likelihood of the vector carrying the inserted DNA anywhere else or transferring any additional properties by nature of itself rather than the inserted DNA).

4.22 Regardless of the levels of perceived risk, applications to HSE undergo different procedures according to the scale and pathogenicity of the organism under scrutiny.

Operations are classified as:

Type A: small scale, usually bench top, for teaching or research in academic or industrial laboratories. The original EC Directive suggests 10 litres as an appropriate maximum volume;

Type B: all other operations, especially with large volumes as in commercial production.

Organisms are classified as:

Group I: inherently safe recipient or parental organisms (ie non-pathogenic) and the vector used and inserted DNA are well characterised, poorly mobilisable, and free from harmful sequences;

Group II: which are those which for any reason (eg pathogenicity) do not fall in Group I.

4.23 A person must notify HSE of the intention to use *premises* for genetic modification for the first time. In the case of Group I micro-organisms the activity may begin 90 days after notification. In the case of Group II (pathogenic) organisms specific consent of the HSE is required

in writing. The HSE have stated that they will inform notifiers of the outcome of consideration of consent applications within 90 days of the receipt of the application.

4.24 A person must also notify HSE of individual *activities* involving genetic modification. Here again, the provisions vary according to the nature of the organism and the scale of operations:

A: small scale activities using safe organisms require only annual retrospective notification; (Group I, Type A);

B: large scale activities using safe organisms and subsequent small scale activities using unsafe organisms may be undertaken 60 days after notification; (Group I, Type B and Group II Type A);

C: first time small scale activities using unsafe organisms and subsequent large scale use of unsafe organisms require specific consent of HSE within 90 days. (Group II, Type B).

4.25 Enforcement is effected by assessment of risk, notification of work to, and consents and inspections by the HSE. Inspection and enforcement is carried out by a team of HSE inspectors which forms part of the HSE's Technology and Health Sciences Division. It has six members, all qualified to at least degree level in relevant disciplines. They also undergo a further year of specialist training and continue a structured programme of training whilst in post.

4.26 It is proposed that fees be charged by HSE as follows: £100 for notification of activities using GMOs for the first time; £130 for notification of activities requiring consent for the first time; £180 on each notification of individual activities involving GMOs or £270 if consent is required.

4.27 It is important to remember that the contained use regulations do not affect other legislation that may also have a bearing on work with genetically modified organisms, for example, the Medicines Acts 1968 and 1971 (human and veterinary medicines), Food and Environment Protection Act 1985 (pesticides), Plant Health (Great Britain) order 1987 (plant pathogens, genetically modified material and plants), Animals (Scientific Procedures) Act 1986 (transgenic animals), Wildlife and Countryside Act 1981 (introduction of novel species). In addition all work activities including those concerned with genetic modification are covered by the Health and Safety at Work Act 1974 including the Control of Substances Hazardous to Health Regulations 1988.

Deliberate release regulations

4.28 The purpose of the deliberate release regulations is to protect both human health and safety and the environment from risks associated with the deliberate release of GMOs into the environment or the marketing of GMOs.

4.29 Release of GMOs is permitted only after their capacity to cause harm either to any other organism or by means of toxic wastes has been assessed by the Secretary of State for the Environment, and written consent has been given by the Secretary of State.

4.30 The information to be contained in the application to the Secretary of State is prescribed. A detailed assessment of risks to the environment covering the potential impacts on the ecosystem (such as genetic stability and mobility, pathological, ecological and physiological traits, antibiotic resistance, ecological aggressiveness etc) and of risks to human and animal health is required. Measures to monitor and control the spread of the GMOs, means to clean up wastes and emergency plans to abort the release are also required. The Regulations give a list of 89 questions that should be answered.

4.31 The application must also give notice of the location, date, purpose and nature of the release to:

A the owners of the site for release;

B the local authority for the area of the proposed release;

C English Nature, Scottish Natural Heritage or the Countryside Council for Wales (as appropriate);

D the Forestry Commission and, if the release is to be in England, the Countryside Commission;

E the local water supplier and the National Rivers Authority (or regional equivalent);

F the local press;

G each member of the applicant's own genetic modification safety committee; and

H register all relevant information in a public register.

4.32 The Secretary of State has responsibility to evaluate risks associated with the application, inspect sites and make control tests (with the help of the HSE) and liaise with the HSE on issues relating to human health. The Secretary of State has the duty to communicate a decision to the applicant within 90 days. A "stopped clock" procedure operates if additional information is required from the applicant. Applications for consent to market a product consisting of or including GMOs must first be cleared with other Member States via the Commission of the EC. Products cleared under the Regulations may then be marketed throughout the Community, subject to the (non-GMO) requirements of any relevant product legislation.

4.33 The Advisory Committee on Releases to the Environment (ACRE) was appointed under the Environmental Protection Act to advise the Secretary of State on these matters.

4.34 Proposed fees to be charged for an application for consent to release are £1,800 and for consent to market are £2,900. Streamlined proposals, where it is deemed that there has been a sufficient body of data acquired already by ACRE about the particular type of product involved in the release so that the consent can be given rapidly, will cost £450 for release and £1,700 for market.

Commercially confidential information

4.35 The DOE told us in evidence that "both EC Directives specify that with certain exceptions, competent authorities may not divulge commercially confidential information. Information relating to the exceptions (eg description of the GMO) cannot be kept confidential. However, such information may be framed, where appropriate, in such a way which protects intellectual property rights since the Directives imply an overriding obligation on competent authorities to protect such rights" (DOE P 24).

Administrative arrangements for the regulations

4.36 The HSE and DOE are joint competent authorities for the purposes of the EC Directives on contained use and deliberate release of GMOs. HSE leads on contained use and DOE lead on deliberate release. DOE, (jointly with the Scottish Office, Welsh Office and MAFF) retains lead responsibility for policy, setting standards and guidance in relation to all environmental issues in relation to both contained use and deliberate release of GMOs. HSE retains lead responsibility for all human health and safety issues affecting both contained use and deliberate release.

4.37 For applications under the contained use regulations all notifications are made to the HSE which has a duty to pass on copies to the other parties (DOE, Scottish Office and Welsh Office) where appropriate. The agreement of the Secretary of State must be obtained before HSE can issue a consent, insofar as it relates to environmental protection. For applications for release of marketing the DOE is the "post-box" for all applications and has the duty to pass on copies to HSE, MAFF, the Scottish Office and Welsh Office as appropriate. The DOE has the duty to co-ordinate responses.

4.38 The HSE, DOE, MAFF, the Scottish Office and the Welsh Office are party to a memorandum of understanding which states that "all the parties are committed to close cooperation in order both to protect the environment and human health and to ensure that users of GMOs are not faced with conflicting demands which may unnecessarily inhibit research or industry" (Memorandum of Understanding on the Control and Regulation of Contained Use and Deliberate Release of Genetically Modified Organisms (GMOs) April 1993).

Horizontal and vertical regulation

4.39 An essential characteristic of the regulatory regime now in place in the United Kingdom is that it governs any act of genetic modification and not what the final product is or how it will be used. For this reason, it is technically described as a "horizontal" as opposed to a "vertical" system of regulation. (We think that the terms "process" based and "product" based describe the systems better and propose to use these terms throughout the report.) The EC Directives nevertheless provide for the possibility that product based regulation might supplant process based regulation bit by bit.

4.40 Witnesses took considerable pains to describe the relative merits of product and process based regulations for particular uses of biotechnology and, as we shall see, it is a central issue of our enquiry.

The philosophy of regulation

4.41 It is significant that the regulatory regime in the United Kingdom follows different principles from the respective regimes operated by our chief competitors - the United States and Japan. Thus the United Kingdom, in line with EC policy, has instituted a process based statutory system of notification and consents for contained use and deliberate release of GMOs. The underlying assumption is that genetic modification is, in itself, a reason for a separate regulatory regime over and above other health and safety and environmental regulations.

4.42 The United States, by contrast, favours a mix of voluntary and statutory product based regulation for contained use and deliberate release. It is based on the principle that the product not the process should be regulated and that genetic modification does not, in itself, require specific regulatory provision. The President's Council on Competitiveness report on national biotechnology policy (1991) stated that "regulatory oversight should focus on the characteristics and risks of the biotechnology product not the process by which it was created". For high risk work in contained use, the United States, through the National Institutes of Health, operates a process based system of notification however. Japan has instituted a voluntary product based system of sectoral guidelines. The Japanese approach, though voluntary, is otherwise similar in underlying philosophy to that of the United States.

4.43 Some countries like China appear to have no regulatory policy or provision at all.

The way ahead

4.44 The regulatory regime is by no means static. Changes may be made in a number of ways. The EC Commission explained that changes to the scope of the Directives could only be made by amending Directives with the approval of the Council of Ministers. But both Directives provided for technical amendments to be made by the Commission itself to the details contained in the annexes - for example on the kind of information required for consent. In addition, under the Deliberate Release Directive, procedures could also be simplified by administrative action on

request from national authorities. Any amendments under these procedures are likely only when all Member States have implemented however (EC Commission Q 911; HSE Q 7).

4.45 Thus recently Belgium, France, the United Kingdom and Germany have called for streamlining and simplified procedures (Cripps p 68; Brauer Q 360) and at the recent Bio Europe 93 Conference EC Vice-President Bangemann welcomed such submissions for revision as would keep the regulatory framework up to date and in line with scientific and technical progress.

4.46 We have already noted how product based regulations could, in theory, supplant process based regulation on a piecemeal basis (paragraph 4.39).

The Fourth Hurdle

4.47 Although it is not specific to biotechnology, witnesses drew our attention to a further consideration which could, unless checked, affect the future regulation of biotechnology. This was the introduction of the concept of socio-economic need in addition to the current three criteria for product regulation, namely efficacy, quality and safety. DTI opposed this so-called "Fourth Hurdle" (DTI QQ 97-102) though MAFF did use the concept of utility for novel foods.

4.48 At the Bio Europe 93 Conference in June Dr Bangemann stated that the Commission did not propose to add socio-economic need to the three traditional criteria (*source*: Text of Dr Bangemann's speech (unpublished)).

CHAPTER 5 REVIEW OF THE EVIDENCE

5.1 In this chapter we set out the evidence which we consider relevant to our terms of reference. Broadly speaking, witnesses felt that the regulatory provisions on contained use, though in many ways inappropriate, were bearable and administered sympathetically by HSE, while the provisions on deliberate release had very few friends. We review the evidence first by considering what is the real need to regulate and what are current perceptions of risk; then we review the detailed difficulties, first with the contained use directive and secondly with the deliberate release directive; and we consider the evidence on product as opposed to process based regulation. We then turn to the practice overseas; evidence of the impact of regulatory provision on competitiveness; the other factors drawn to our notice which govern competitiveness; and finally the views of witnesses on public understanding of biotechnology.

The need to regulate and the perception of risk: general comments

5.2 A minority of witnesses took the view that genetic modification was inherently risky, whether in contained use or released to the environment. Thus the Genetics Forum thought that genetic enquiry in the laboratory, deliberate release, genetically engineered food, gene therapy and "some biopharmaceuticals" all raised safety issues. Because, they considered that experience with GMOs, particularly those released to the environment, was so limited, they were "against any relaxation of a case by case and step by step approach to regulation. We are opposed to the exempting of particular classes of genetic enquiry or particular crops from regulation, or the granting of blanket or long term licenses for release" (Genetics Forum P 234).

5.3 Greenpeace was totally opposed to the release of genetically engineered organisms to the environment "because of the dangers that the technology poses", principally the possibility of the transfer of genes between crops and weedy relatives, the creation of new pests and the disturbance of ecosystems and natural processes. For Greenpeace, "Genetic pollution may not be detected for decades" (Greenpeace P 237; QQ 916-919). The Green Alliance, by contrast, was more pragmatic and acknowledged that the risks were hypothetical "since no adverse effects have yet been observed from the comparatively small numbers of releases carried out in the United Kingdom and elsewhere". Moreover, Green Alliance were represented on ACRE and were in favour of streamlined regulatory procedures for consent where appropriate (Q 488).

5.4 It is noteworthy that Genetics Forum, Greenpeace and Green Alliance all considered the benefits of biotechnology to be largely unproven. They also relied upon, so far as deliberate release was concerned, the cautious findings of the Royal Commission on Environmental Pollution 13th Report on Release of Genetically Engineered Organisms to the Environment (Cm 720) which was published in 1989. The Royal Commission had discussed the possibility of genetically modified organisms showing unexpected competitive traits, and becoming established, and even becoming pests, in natural and semi-natural environments (4.2 and 4.14-4.29); the possibility of the genetic modification of viruses resulting in altered virulence or widening of host range (4.3); the possible danger of consumption of plants modified to express toxins by non-target organisms or humans (4.5); the spread of resistances to toxins engineered into plants (4.6); possible alteration of nutrient and water cycles through genetic modification of bacteria that play a key role in them (4.8 and 4.9); and the spread of herbicide resistance for modified crops to weeds, making their control more difficult (4.10). Nevertheless, the Royal Commission concluded that there was "no environmental justification for preventing releases that are considered safe from proceeding".

5.5 The views of the United Kingdom regulatory organisations - the Health and Safety Executive and the Department of the Environment - were somewhat ambivalent. HSE, who regulate contained use of GMOs, thought that the caution shown in the 1970s had been excessive and they quoted the 1982 report of GMAG (predecessor to ACGM) which stated "... it has become apparent that the hazards specifically attributable to genetic manipulation of micro-organisms are, if they exist at all, far less than was conjectured when the Group was set up ...". The reason for this relaxation in attitude was, in part, that since 1978 20,000 individual activities involving GMOs had been carried out in the United Kingdom "without the creation of any novel hazard". More

compelling, however, was "that studies designed to test the hypothesis that a host organism can acquire unexpected properties have failed to demonstrate them. To take one of the early fears referred to earlier - that a pathogenic micro-organism might acquire drug-resistant properties and cause untreatable disease - it is now apparent that the combination of events that would have to take place for that to happen is extremely improbable. Combined with this is a growing confidence that the organisms used for GMO experiments can be selected so that they are unable to survive except in the special environment of the experiment or process in which they are used. It is still possible to envisage an act of evil genius, but there is nothing unique to biotechnology in that, and it is probably easier to wreak havoc by more conventional means." (HSE P 5).

5.6 Thus HSE itself concluded that this argument suggested that the regime now in place was stricter than was necessary for the protection of human health and they defended it solely on the grounds of "conjectural" environmental hazards. (HSE P 5)

5.7 The Department of the Environment, regulators of the deliberate release of GMOs into the environment, spoke with much greater caution. They maintained that "The introduction of a new or novel species to a familiar environment, or the introduction of a familiar organism to a new or novel environment, presents hazards which need careful consideration. In line with the Government's policy of taking a precautionary approach to environmental protection, the solution is to carry out risk assessments on a case-by-case basis and to move forward as experience accumulates. This is in accordance with the approach recommended by the Royal Commission in their thirteenth report. GMOs released into the environment raise environmental and human health and safety questions because they are generated by rapid and novel techniques which produce heritable genetic changes. Genes from across species barriers and beyond can now be inserted into a wide variety of organisms for a number of specific purposes, some of which (eg biopesticides) may be intentionally harmful to target organisms. In some cases, the inserted genes or their products may persist in the environment or spread to other organisms, including humans, in ways which have potential effects which may not be obvious (for example, extending the host range of biopesticides to other, beneficial organisms)." (DOE P 19) This was reinforced by Dr Fisk in oral evidence, "... if there is a hazardous effect associated with the release of a genetically modified organism, its risk is that it is potentially self replicating" (Q 66).

5.8 By contrast the evidence we received from practitioners of the technology - whether in industry or in the universities or research council institutes - took the view that the hazards presented by GMOs (with certain theoretical exceptions following deliberate release) were minimal or non-existent. Their arguments were that the caution shown by the scientific community in the 1970s had been excessive and could now be relaxed; that the perception of risk posed by genetic modification had been founded on false premises; that fears about deliberate release had been misplaced; that the act of genetic modification was in scientific terms far more precise and predictable in its effect than the largely serendipitous acts of nature and selective breeding; and that no known accident had ever occurred either from contained use or deliberate release of a GMO. Indeed Dr McDowell of Hoechst UK Ltd told us that, in the case of vaccines a genetically modified strain may be less hazardous than a natural one (Hoechst Q 360).

5.9 Thus leading scientists who had long been involved in genetic modification - principally in containment - were at pains to explain that few risks now attached to the work. Professor Sydney Brenner of the University of Cambridge wrote that the process initiated in 1974 to regulate genetic manipulation in research, with which he had been associated, was founded on the "mistaken concept that organisms, which had been altered by *in vitro* manipulation presented intrinsic risks that could be scaled by the nature of the DNA inserted into the vector host systems required to clone the genes. After some years of debate, this totally illogical and unrealistic way of dealing with conjectural risks was altered, and the total genetically modified system was treated as the entity. The conjectural risks and any measures taken to deal with them were assessed on a scale that took real risks as the basis. On the original system, cloning lion DNA was thought to be a greater risk than cloning pussycat DNA because lions are clearly more dangerous than pussycats. We now do not think that way, because clearly both kinds of DNA when cloned are harmless because there is

no way that the original pathogens could be assembled from an ensemble of clones. We should be reminded that the most dramatic consequence of this change in thinking was that work on determining the structure of the AIDS virus and all subsequent research proceeded very rapidly, because it was realized that cloning the virus into a bacterial host actually *attenuated* pathogenicity over that of infected blood, for example, and while the modified bacterium still has to be compared to an unmodified one, this can be dealt with by simple measures" (Brenner p 33).

5.10 Sir Walter Bodmer, who had also been involved in early regulation of genetic modification (both he and Professor Brenner had been members of the Ashby working party in 1974), said that "right from the start I felt there was no real issue of risk. The risks were raised, I think, by concerned individuals, scientists, who perhaps on the one hand did not fully appreciate working with microbes and understand the issues of micro-biology and the fact that pathogens, dangerous organisms, are dangerous to work with whether you manipulate them using recombinant DNA techniques or not and if you manipulate them they become safer. Nor did they fully understand basic evolutionary principles. My background as a population geneticist and evolutionist would tell you that on the whole, if you change organisms in defined ways they are very unlikely to have an intrinsic evolutionary advantage. So I feel that even the regulations we have now, which we live with, which produce a lot of paper and require us to have more people to deal with providing the information than we would otherwise need, are to a fair extent unnecessary" (Q 417). Furthermore "handling materials from human individuals who may have infections is a far more serious problem in practice for us than working with microbes which have no pathological consequences in circumstances which are really quite safe" (Q 417).

5.11 Sir Hans Kornberg, currently chairman of ACGM, said that "Experience has shown over the last, I suppose nearly 20 years now, that the hazards which were estimated to be associated with this technique, or with the organisms that resulted from it, were conjectural. There is no evidence that the technique itself is hazardous and indeed a Committee under the aegis of the OECD and a Committee under the aegis of the United States National Academy of Sciences, said that the hazards of genetic manipulation by this means, or genetic manipulation by the traditional means of plant or animal breeding, were really no different and if there were hazards, the hazards would be associated with the product that was formed" (Q 769).

5.12 The supposed hazards were chiefly:

— that GMOs, if eaten, would colonise the human gut and if they produced, say, insulin, overwhelming hypoglycaemia would ensue;

— that GMOs from safe parents would acquire new dangerous properties, for example pathogenicity;

— that GMOs would become drug resistant and cause overwhelming sepsis;

— that the dangers of cloning DNA were in some way determined by its origins, ie that lion DNA was inherently more dangerous than pussycat DNA.

5.13 Other witnesses levelled similar criticisms at the thinking behind the regulation of deliberate release of GMOs. We have already partly noted the views of Sir Hans Kornberg. Sir Hans went on to question the recommendations of the Royal Commission on Environmental Pollution which, in favouring horizontal regulation, "did not entirely accept the scientific view, at least not the biological scientists' view" (Q 777). Were the Royal Commission to reconsider the issue he felt that it might not demand the control of every instance of genetic modification.

5.14 Sir Walter Bodmer thought that "... there clearly could be situations where risk is going to be greater if you release something which is biologically modified, but I am not sure that in general that risk is greater than the risk of ... introducing species from Latin America to Kew or of having new approaches to hybridisation between, say, cultivated crops and their wild progenitors trying to introduce new variations" (Q 425). And an acknowledged expert in this field, Professor

Mark Williamson (Population biologist, University of York) assured us that "The vast majority of the biotechnological developments that are known about at the moment will have no safety implications for the environment" (Williamson p 206).

The need to regulate and the perception of risk: contained use

5.15 A number of witnesses stressed the precision of modern methods of genetic modification as compared with classical methods of animal and plant breeding. Professor Gardner told us that many people perceived genetic modification "as rather evil tinkering with nature but that sort of tinkering with nature done in a slightly cruder way has been with us for millennia in terms of pigeon fanciers, mouse fanciers, dog breeders, all of whom have, for no good reason whatsoever, produced, by capitalising on genetic variation and selection, the most utterly bizarre creatures, for no reason at all. What the genetic procedures allow you to do is to make modifications to some purpose and in a very incisive way" (Q 668). The same point was made by other witnesses. Sir Hans Kornberg used the graphic imagery of delivering coal into the coal shed. "You either use a shovel which means you can very efficiently transfer the coal, but you also transfer pebbles and bus tickets and cigarette ends and anything else that happens to be there, or you use a pair of tongs, which means you pick up each piece of coal individually and although it is slow and tedious and probably more expensive, at least you know what you are transferring. So the procedure of genetic modification is one where we use tongs ..." (Q 769).

5.16 The Natural Environment Research Council (NERC) wrote that "Laboratory studies involving micro-organisms generally involve a high degree of precision and predictability, both because of their limited genomes and because the technologies to introduce genetic change are highly refined. For viruses and bacteria (including plasmids), it is possible to modify their genomes in a prescribed manner (eg by introducing a specific alteration to a specific place) so that no natural function is affected - unless that is what is intended. The alterations can be verified and, if necessary, monitored through a large number of generations, and analysed to document the stability of the changes and the consequences on the host (competitiveness, genetic stability, etc). This precision of laboratory research involving genetically manipulated viruses and bacteria, contributes to the predictability (hence safety) of such research. For transgenic plants and animals, the same precision of introducing genetic changes (sites, copies, effect on resident genes, their flanking sequences and other genes) cannot be realised with presently available technologies (ballistics, virus or bacterial vectors, physical introduction of DNA, etc)" (NERC p 138; see also Bodmer Q 426). However Sir Hans Kornberg gave us an illustration of how traditional plant breeding had been used in the late 1970s to produce a disease resistant potato. "What had not been realised by the plant breeders was that the basis of defending the potato against attack, was that the content of an alkaloid called solanine was raised inside the potato, so that the pest would find it extremely distasteful. What they had not realised was that the schoolboy would also find it distasteful and in fact it was quite harmful" (Kornberg Q 785).

The need to regulate and the perception of risk: deliberate release

5.17 **Plants:** Witnesses were also at pains to allay concerns specific to botanical genetic modification - genetic stability, aggressiveness or "weediness" and cross breeding with indigenous species. Genetic stability in crop plants is an absolute requirement for commercial reasons. Thus there was nothing "funny about recombinant DNA that creates some instability in the wild ... plant breeders are in the business of supplying stable genetics to the customer and they go through seven years of testing to make sure they are genetically stable. This has nothing to do with the regulations, that is to do with the fact that they are selling seeds to the customer and if that seed is not stable they will lose the business" (Zeneca (Dart) Q 186). Moreover "... under the present review of new plants we go through what is known as National List Trials. This is a standard procedure where you verify that your new variety of oil seed rape or new variety of wheat has a certain advantage (if it succeeds). It is declared so-called DUS (distinct uniform stable) ..." (Agriculture Genetics Company Q 337).

5.18 The chances of creating a weed species was remote and avoidable: "A character like weediness is very, very complicated genetically and to actually create weediness by introducing one or two genes is almost impossible. If I were a plant breeder, and in fact I am responsible for a lot of them, I would be quite offended by any implication that I could inadvertently create a weed. Most of the things I am creating are incapable of competing with the wild species in the environment and are only capable of delivering the effects the farmer wants" (Zeneca (Dart) Q 186). Crops bred by man do not have the capacity of competing with wild populations "and the addition of one or two genes" was not going to change that. Wheat fields left fallow reverted to woodland in 15 years (Dart Q 119).

5.19 Cross-pollination between transgenic plants released into the environment and indigenous species might allow unintended "gene drift" and a carrying of unwanted characteristics into a related indigenous species - one of DOE's chief concerns. But AFRC told us that results of their PROSAMO project on pollination and "out-crossing" to other plants of the same species and related species (focusing on oil seed rape and potatoes) had provided "comfort and understanding" (Flavell Q 729). "It perhaps should be noted by one and all, that many of the cross species that we use in the United Kingdom did not evolve here and do not have close relatives and that is a very helpful issue in relation to risk assessment, but of course is not often recognised by people who look at it in a casual way" (Flavell Q 730).

5.20 **Micro-organisms and animals**: Witnesses referred to the perceived risks associated with a number of different forms of release of micro-organisms and animals, specifically of animals deliberately bred to secrete biopharmaceuticals in their milk; breeding of transgenic animals as models for human disease; use of GMOs as live vaccines; and novel foods containing GMOs.

5.21 So far as the breeding of animals is concerned, the concerns were mainly ethical questions concerned with animal welfare. Thus, "The use of biotechnology to impact genetic resistance to infectious and metabolic diseases in farm animals is a positive move. However, the manipulation of animals to produce more meat and milk has the potential to create problems. These include the manipulation of body size or reproductive capacity by breeding, nutrition, hormone therapy or gene insertion in such a way as to reduce mobility, increase the risk of injury, metabolic disease, skeletal or obstetric problems, perinatal mortality or psychological distress. Another area which has additional ethical implications is the insertion of human genes into farm animals so that they can serve as sources of (i) pharmaceuticals, (ii) cells, tissues and organs. By genetic manipulation, peculiar and unnatural animals may result which have characteristics which are undesirable and whose welfare may be compromised. Presently, research on animals is controlled by the Animals (Scientific Procedures) Act 1986 which requires researchers to demonstrate to the Home Office the integrity of the work and that there will be benefits from it. Transgenic animals and animals treated with biotechnical products should have their welfare assessed using proper scientific measures. It may be necessary to monitor over at least two generations before being allowed into general commercial use" (Farm Animal Welfare Council p 87). FAWC felt that the 1986 Act should be extended to cover the development stage. Some balanced form of regulation was necessary because this was "an emotive topic and the public need the facts. Public acceptance is enormously important and unless the procedures are acceptable, it will be very difficult for them to succeed" (FAWC p 88). AFRC told us, however, that while they had held discussions with DOE on "the impact of introducing genetic material into farm animals and into livestock, the way in which that might have an influence on those who are involved in the research itself, (that is the research operators), the possibility that there may be an influence on the animals that would be detrimental in terms of welfare and whether there was any possibility that there was an influence in terms of environmental considerations" (Q 700). Nevertheless they still considered the method of regulation onerous (Q 701).

5.22 The utility of developing transgenic animals has been referred to elsewhere (paragraph 3.4). Witnesses were at pains to point out that this was not inimical to welfare. Professor Polge of Animal Biotechnology Ltd thought that genetic manipulation did "in fact enhance animal welfare rather than detract from it" (Q 333). The hazards here were principally ethical. An

unfortunate case was drawn to our attention where "... an American group supported by the USDA (United States Department of Agriculture) have produced heavily-muscled "Arnold Schwarznegger" pigs by introducing a ski proto-oncogene" (Goldspink p 95). Indeed Goldspink thought that "The production of transgenic animals in Europe will probably not be focused on improving food and fibre value of agricultural animals for some years because of the animals rights and environmental pressure groups. The exception to this is possibly the introduction of gene to improve disease resistance" (p 95).

5.23 We were told that the use of live vaccines in gene therapy, using viruses and bacteria as vectors to carry normal copies of genes into cells and tissues, could carry indirect risks. The concerns expressed were that viruses which had been rendered harmless and non-replicating for use as vectors might recombine with other wild type co-infecting viruses and replicate with devastating effect (Harris p 100; Poste Q 391). Dr Poste speculated that "If you have a pan-tropic[1] vector which can affect all kinds of cell including spermatozoa and ova, then you have inadvertently created a vertical genetic modification" (Q 391). The Clothier Committee on the Ethics of Gene Therapy reported in January 1992 (Cm 1788). It concluded that "... there is insufficient knowledge to evaluate the risks [of gene modification of sperm or ova or cells that produce them] to future generations. We recommend, therefore, that gene modification of the germ line should not yet be attempted".

5.24 **Novel foods:** So far as novel foods were concerned, some witnesses took the view that food substances produced by methods which employed GMOs at some stage in their production present no particular risk to the consumer. "Genetic modification *per se* presents no special food safety risk; modified genes, like the rest of DNA present in food, are digested and cannot be incorporated into our own genetic make up. So, provided the characteristics for which the inserted genes code, if they are present in the food, are themselves safe, the modified organism will be as safe as the unmodified" (Food and Drink Federation p 88). The Department of Health told us that "The use of biotechnology to modify materials consumed as food may lead to the over-production of chemicals that may be toxic, particularly in plants but possibly in animals" (Department of Health p 78). Dupont told us that the United States FDA had also recognised this possibility (Dupont de Nemours (France) S.A. p 87). However, as we have already noted (paragraph 5.16) hazardous levels of toxins, new substances or allergenicity can also occur as a result of traditional plant breeding programmes. It is important to note that many of the safety issues raised are not unique to genetic engineering (Dupont p 81). OECD stated "... the evaluation (of safety) of food and food components obtained from organisms developed by the application of the newer techniques does not necessitate a fundamental change in established principles, nor does it require a different standard of safety" (*Concepts and Principles Underpinning Safety Evaluation of Food Derived by Modern Biotechnology, 1992*) It should be noted that under the present regulatory system all food products, genetically modified or otherwise, must pass the tests of safety and quality.

Contained use: classification of activities

5.25 We turn now to the views of witnesses on the mechanics of the contained use regulations. As we showed in Chapter 4, the procedures governing contained use of GMOs depend on whether they are pathogenic (Group II organisms) or not (Group I organisms) or whether the operations are small scale eg under "about" 10 litres (Type A operations) or bigger (Type B operations). It was pointed out that these classifications "may have changed the atmosphere for the use of modified organisms markedly" (Kinderlerer p 117). They departed from the United Kingdom 1989 regulations and followed EC definitions originally devised by OECD for large scale work. They were unsuitable for laboratory work. Their chief effect is that advance notification rather than retrospective notification is required for low risk activities on a scale of more than 10 litres. On the whole, witnesses found certain aspects of these classifications of scale and pathogenicity risible.

[1] Pan-tropic - able to affect many or all tissues.

5.26 Turning first to *pathogenicity*, witnesses pointed out that the classification into Group I and Group II was a measure of hazard[1] rather than risk[2]. A dangerous organism could be considered low risk if adequately contained. The scheme now imposed under the regulation brings the risk assessment system into disrepute. "A binary scheme which defines most organisms as dangerous and lumps organisms within the same group which are perceived by scientists as being very different in risk potential is again in danger of being "mocked" by scientists who fail to appreciate the difference between hazard and risk. I believe that this new framework may result in less safe working practices and may inhibit research. In theory it is the risk assessment which defines the risk, and which is done first. It has been suggested to me that organism classification is a device used for limited purposes that emerges during the risk assessment but is not the first step or foundation of it. As the classification system determines the requirements for notification and consent it will be that which is first considered by those performing a risk assessment" (Kinderlerer p 118).

5.27 Criticism of the *criteria* used for classifying the scale of activities was equally robust from both the universities and industry. As we saw in Chapter 4, Type A operations are small-scale, ie commonly considered to be less than 10 litres in volume, usually bench-top in glass vessels or fermenters, carried out for the purposes of teaching or research. Type B operations are all others, commonly considered to be greater than 10 litres in volume, usually in fermenters, carried out for the purposes of research, development or industrial production. Witnesses' complaints were that the criteria for deciding between Type A and Type B operations were uncertain, and that the 10 litre distinction was irrelevant to risk.

5.28 It was pointed out that the present definition "is being interpreted such that a Type A activity must be for education, research or development, or be non-commercial, or be non-industrial. If it meets any of these criteria, then a question as to the scale of the operation must also be considered. The inverse, which defines a Type B operation, therefore, is that none of the above criteria may be met. If the process is for research or development and it meets the scale-up criterion, it is a Type A operation. If it is commercial but non-industrial, it is again Type A. A commercial but non-industrial operation will have to be clearly defined in guidance, but it seems that a chemical company which is solely involved in distribution, and not in manufacturing, would be engaging in Type A work, where the storage of modified organisms rather than their marketing is being considered ... Commercial and industrial use of modified organisms may not be large scale or conducted in places where non-specialists have access but will still be Type B. A small-scale research activity is Type A, however commercial it is. So is a small-scale non-industrial activity. Many users (I presume), and all the members of the advisory committees, had not realised ... that the definition of Type B may be interpreted in this way so that it clearly refers to the use of modified organism in a factory environment. Guidance on this issue is crucial, as the delay introduced by inclusion within Type B is very significant" (Kinderlerer p 118).

5.29 Industrial witnesses were chiefly concerned with the problems of scale-up and the arbitrary 10 litre cut off. In the words of one witness, "10 litres is irrelevant to risk. What matters in risk assessment is containment. You can have as much risk with 10 litres on the bench with a sloppy worker and leaky valves as with 3,000 litres in a well-contained and well set up arrangement. People say, "Don't worry, the HSE will take a lenient view of that 10 litres which was meant anyway to be an approximation". I do not think that is appropriate in legislation. Is 100 litres "about 10 litres"? Is 3,000? This is a very important point, sir, because if we put a constraint upon the scale of working within these limits we are going to be highly uncompetitive in research. I am not talking about manufacture. I am talking about research initiatives also" (Dewdney (SmithKline Beecham) Q 388).

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1 Hazard is defined as the situation that in particular circumstances could lead to harm (*Risk: Analysis, Perception and Management,* The Royal Society 1992).

2 Risk is defined as the probability that a particular adverse event occurs within a stated period of time or results from a particular challenge (*ibid.*).

5.30 This illogicality was taken further by Dr Weir of Glaxo who wrote "... an organism which poses a negligible risk to health (Group I) is categorised in the United Kingdom for the purposes of scale-up at the same level as pathogens (Group II) such as Legionella spp. and herpes simplex virus" (Glaxo p 92).

5.31 The effect of these apparently arbitrary classifications was to impose unnecessary extra costs on industry. Dr Poste of SmithKline Beecham, complaining of the effects of scale up beyond 10 litre activity, stressed "You will have a lot of hidden necessary costs - merely because of the false classification as hazardous" (SmithKline Beecham Q.390). Zeneca estimates that the new regulations will increase the cost of genetic modification safety measures by 50 per cent and entail additional capital expenditure of 5-10 per cent on small scale activities and 25-30 per cent on large scale. (Zeneca P 58). The Biochemical Society endorsed this view. "Actual attempts to prevent release have made the equipment and facilities for manufacture at Large Scale Contained Category 2 very expensive" (Biochemical Society P 204.)

5.32 There was a strong view that risk relating to size "... should be based firmly on operational standards relative to the risks as determined by risk assessment and that is not the situation at the present time" (Savidge (SmithKline Beecham) Q 389). Professor Lilly of the Biochemical Engineering Centre at University College London claimed "It is essential that good biochemical engineering studies be carried out to provide the numerical data on which standards can be properly based" (Lilly p 120). The Biochemical Society thought that the present regulations should be regarded as "useful working documents until new research allows proper engineering objectives to be written" (Biochemical Society P 204). Indeed visits by some of our number to the Advanced Centre for Biochemical Engineering at University College and to SmithKline Beecham illustrated some of these points to us forcibly.

Contained use: administrative issues and delay

5.33 Under the contained use regulations, as we saw in Chapter 4, activities on a small scale using safe organisms require only annual retrospective notification; but large-scale activities using safe organisms and subsequent small-scale activities using unsafe organisms may only be undertaken 60 days after notification; and first time small scale activities using unsafe organisms and subsequent large scale use of unsafe organisms require specific HSE consent within 90 days. Contained use projects in research laboratories are probably less sensitive to time delays than projects using plants in the field which rely on growing seasons (paragraph 5.46). Nevertheless witnesses complained about the effects of regulatory delays for a variety of reasons.

5.34 One reason was cost and bureaucratic inconvenience. Pfizer spoke of "lost opportunities" that could arise from a delay of up to 3 months (Pfizer p 150). And Celltech wrote that "The delay in waiting 60 days before some micro-organisms can be imported or stored will be a significant disadvantage for United Kingdom and European contract manufacturers" (Celltech p 56). A similar argument was heard from academic sources. Dr Kinderlerer informed us that ACGMs advice to government had been that the new regulations should be similar in impact as before for contained use with the addition of an environmental assessment. "If, as may be the case, the regulatory burden is significantly increased (and a wait of up to 3 months before work may be commenced is imposed), the United Kingdom and EC research and industry will be harmed. Many United Kingdom companies are likely to find research and development in laboratories where the work can be conducted quickly and with the minimum of regulation". Guidance by ACGM would be crucial to HSE interpretation and "provide the framework for producing risk assessments which may assist scientists in their understanding of the requirements".

5.35 Delay would also slow up research, unless government departments were able to process notifications and consents for biotechnology projects in an expeditious manner (Hoffman La Roche p 105). Wellcome spoke of need to "monitor the effect of regulation in the United Kingdom; particular attention should be focused on the interval elapsing between notification and consent" (Wellcome p 205).

5.36 Delays in research had a particularly worrying implication for patent applications. In the United States priority is given to the first to invent whereas in the United Kingdom priority goes to the first to file the patent application. Any delay in proceeding with experimental work was potentially disastrous. "The regulations are also likely to lead to delays in the initiation of experimental research. This is an important issue, since the patenting of discoveries is central to the biotechnology industry and the USA has significant advantages in terms of claiming priority dates" (Celltech p 56).

Contained use: fees and associated costs

5.37 In addition to the costs incurred by any delay in notification, witnesses were concerned at the direct costs arising from fees for consent and the indirect costs of preparing submissions.

5.38 For industrial production, repeat runs of the same process will not attract repeat charges. Several witnesses agreed that the costs for meeting GMO regulation are not great relative to those required to meet other regulatory requirements. Nevertheless for smaller companies the added cost may be burdensome. "The administrative time and cost in preparing documents, which require many details of micro-organisms, is considerable, even when risk assessment leads to the conclusion that the organism is low risk" (Celltech p 56).

5.39 For academic research, by contrast, fees were proportionately a much higher element in the total cost of a research programme, particularly in the early stage of inventive research where new experiments are regularly taking place. It is acknowledged however that the fees for consent to deliberate release are far higher than for contained use (AFRC (Blundell) Q 713) and so the issue of cost will be more important to those groups of researchers who have to obtain consents under the deliberate release regulations, for example for agricultural applications (AFRC p 9; Grierson p 99). However the regulations allow some mitigation in that a group of activities making up a programme of work may be collected into a single notification. Once a set of activities have been notified the regulations allow for information and developments in it to be submitted without being counted as a new notification liable to a fee (HSE P 4). SERC did not think that the contained use regulations would be unduly burdensome in terms of consents and fees for the universities and research council institutes (SERC p 170). But there was still scope for simplifying paperwork. Professor Trevor Jones of the Wellcome Foundation thought that "Consideration should be given to the design of simple forms to cover multiple activities. Thus, for example, the same risk assessment document should serve for several different government departments for the purposes of registering establishments, applying for consents for projects, for manufacturing licenses and product licenses" (Wellcome p 205).

Contained use: disclosure of information

5.40 The regulations provide that information contained in applications for consent should not be divulged by the regulatory authorities if it is commercially confidential. Certain information, like description of the GMO, cannot be kept confidential, though it may be framed in such a way as protects intellectual property rights.

5.41 Witnesses spoke of the need to balance the need for public information - and hence the promotion of public acceptability - on the one hand and for protection of commercial interest on the other. The general complaint was well summarised by Celltech who wrote, "The disclosure of commercial information is a major concern. The perception that information could be disseminated among Member States will be a competitive disadvantage to Celltech's contract manufacturing business. The administrative load of dealing with confidentiality issues will again be excessive for those micro-organisms which are assessed as being low risk" (Celltech p 56). Companies were most vulnerable at the R&D stage when United Kingdom and EEC companies would have to make disclosures which would not necessarily be required - at least for micro-organisms - in the United States (Kinderlerer p 119).

5.42 Besides this general issue of commercial intelligence, witnesses called attention to the more specific issue of the ability to patent discoveries. Much of their trouble appeared to stem from

the test of novelty that obtains in United Kingdom and other European countries. "If information about an invention is, broadly speaking, in the public domain before an application is made for a patent it will fail the novelty test. In return for the patent rights the inventor discloses to the public information about the invention ... the contained use regulations [in Great Britain] permit information to be excluded from the register if 'it is necessary to withhold, for the time being, certain of the information ... to protect ... intellectual property rights'. Since the [EC] Contained Use Directive states that "in no case may the ... information ... be kept confidential" the crucial regulatory words in terms of reconciliation of the meaning of these provisions are 'for the time being' (Cripps p 69). Pfizer feared "Breaching of confidentiality by the requirement to provide information relating to the genetic manipulation work, with the consequent possibility of invalidating patent claims" (Pfizer p 150). The issue of disclosure also arises in the context of deliberate release.

Deliberate release: bureaucracy and risk assessment

5.43 Witnesses complained that the risk assessment questionnaire for consents for deliberate release is too long; that, since it refers primarily to micro-organisms, it is inappropriate for plants and animals; and more fundamentally, that more bureaucracy does not predicate more safety.

5.44 The length and inappropriate nature of the questionnaire come in for a good deal of criticism. The British Science Society of Plant Breeders wrote that "One of the basic difficulties with the present EC Directive on "Contained Use" and "Deliberate Release" of Genetically Modified Organisms is that these crucial biological differences are not adequately recognised because of the attempt to force everything into a single system originally designed to deal with micro-organisms. At the very least the crucial differences need to be recognised" (p 44; see also Agricultural Genetics Co p 11). Professor Poole of Zeneca said "89 questions have to be filled in ... a lot of which are not relevant to the release but we still have to fill them in and explain why they are not relevant" (Q 220). He suggested that the procedure could be streamlined if it asked generic questions relevant to all releases and then specific questions relevant to the type of GMO, bacterium, virus, plant or animal. Others agreed with that view (Boseley Q 335).

5.45 Moreover, more questions did not mean more safety. As Professor Poole adds "Already it costs a lot more to do the experiment in the United Kingdom then in the United States - I would add that I do not see any evidence that the United States system is any riskier or any more dangerous. I think this is one of the problems we face, the belief that additional regulations, additional bureaucracy, actually increases safety. It does not; it is the appropriate level of safety regulation that guarantees it" (Poole Q 215). Indeed, commercial organisations whose regulations relied on a clean safety record were likely to impose their own stringent criteria where needed (Q 219). These might be more stringent than the national regulations required (QQ 209-210).

Deliberate release: delays and costs

5.46 The effects of delays in obtaining consents were even more critical for experiments involving plants than animals and other organisms. All crop plants undergo an annual growth cycle that is fixed by the geographical location, the environment and the seasons. It follows that in order to develop plants suitable for a particular locale, several cycles of growth are required, the later ones being for stability testing. Delays clearly cost both money and time and so competitiveness is severely affected. We heard of "... an application for a fairly straight forward genetic release pending for two years ..." having been reviewed by HSE, DOE and delayed by (presumably) MAFF (Gardner Q 654). Uncertainties in regulations had strategic consequences, especially for smaller companies, namely, that "... it takes so long to develop a new plant product ... that you are making a strategic decision ... when you do not know what the regulatory climate will be ... (affecting) ... strategic decisions which will dictate the company's future direction" (Gilmour Q 323).

5.47 Unlike the pharmaceutical applications, agricultural applications of biotechnology cannot expect very high levels of profitability. Thus Dr Dart of Zeneca explained that "... in the health care

area the regulations and development of a drug are massively expensive and if that happened in my sector it would just render that sector uneconomic and also it would not be balanced with the perceived risk, in my view" (Q 203). The cost effect of delay was therefore all the more serious.

5.48 The research councils were also anxious about the effects of delays and costs on research. Thus Professor Flavell said that "... if the whole business of gaining permission for release remains as onerous and expensive as it is, then there will be real limitations on the width, strength and depth of the innovative science base in the United Kingdom" (AFRC Q 716). He took this view because of the higher fees charged for consents relative to the costs of experimentation as a whole. The recurrent expenditure for a project involving genetic modification was currently about £8,000 a year for one person. Thus "the cost of [consent under the deliberate release regulations of] each release at £1800 begins to look a very large proportion of the funds available. That spreads up from a very limited flexibility in an individual project, through to a slightly greater flexibility in an institute, but still within those strong restrictions ... It is very significant in the areas of the science base" (QQ 714-15). Large numbers of those applications would have to be run simultaneously. NERC hoped that "all Departments can operate their systems in a timely fashion" (NERC p 139). Professor Grierson wrote that "European regulations appear to be muddled, restrictive, and difficult to operate across the EEC ... . Research is more difficult, expensive, and time consuming because of the existing regulations which are ... expensive in time and money ... some potentially priority work is just not done" in transgenic plants (Grierson p 99).

Deliberate release: disclosure of information

5.49 The same considerations of confidentiality which we have considered in connection with contained use apply to notifications of deliberate release also (paragraphs 5.40-42).

5.50 However, additional notifications have to be made to the public and other bodies (paragraph 4.31) about any proposed deliberate release. Many witnesses recognised that the regulations concerning disclosure of information about the site of releases aimed to make biotechnology more acceptable to the public by incorporating this degree of openness. However this places research very much at the mercy of activist opponents of genetic modification. Security of farm land is very difficult if not impossible since land boundaries cannot be protected from air attack. A militant style campaign of violence, of the kind mounted by the animal activist movement on far more secure sites, would ruin years of work and, very probably, drive the experimenters to a more friendly country. Dr Brauer told us in evidence that "... we currently have certain people who are putting down weeds on those spots where we have certain authorisation to conduct field-testing this year ... to hinder the planting of these recombinant plants or seeds" (Hoechst AG Q 370).

Deliberate release: novel foods and labelling

5.51 The deliberate release regulations govern the sale in the market of viable GMOs. In theory this could include foodstuffs, as and when they appear.

5.52 Although it lies on the margins of our orders of reference we received evidence on novel foods, produced through use of biotechnology, and on the issue of labelling of such foods. We were told that MAFF's Food Advisory Committee had initiated a new consultation exercise in labelling of foodstuffs which were in some degree the product of biotechnology (MAFF QQ 167-170). The ethical questions of genetic modification of foodstuffs (principally the dietary concerns of vegetarians and religious groups) are currently being considered by the Ethical Group on Genetically Modified Food chaired by the Reverend Dr John Polkinghorne, President of Queen's College Cambridge (MAFF p 47). These ethical questions are outside our remit.

5.53 The principal dilemma with food labelling appeared to be how to balance the need to be honest with the public while avoiding such an indiscriminate labelling system which would be unduly burdensome on industry and actually mislead the public. This was well epitomised in evidence from AFRC. Professor Blundell thought it necessary as a general principle to be "quite straightforward with the public" in the area of biotechnology (Q 695). His colleague Professor

Georgala, who was also Deputy Chairman of the Food Advisory Committee, thought that while "we need to be very sympathetic to the possible need for labelling in certain areas", there was need for caution because "our research evidence is that labelling can frighten. It is a very difficult balance. Our own research in the Institute shows that any labelling phrase that we use at the present has a negative connotation" (QQ 696-7).

5.54 The question was complicated and certain elements were fundamental. Should all products produced out of or processed using a GMO be labelled (eg a refined sugar, or a food produced using genetically modified yeast or oils); or only food which were themselves GMOs; or only viable GMOs? (Georgala Q 696; Murphy QQ 168-69). The form of wording was "absolutely vital and virtually impossible to arrive at" (Righelato Q 611). Unsurprisingly the Food and Drink Federation did not accept that labelling was inevitable stating "We firmly believe that labelling should not be used as a substitute for education" and furthermore that "There is a real danger that any kind of special labelling in respect of GMO use will only serve to reinforce popular misconceptions about food technologies rather than provide factual information to help the consumer better to understand the processes used to produce a food or drink" (p 90). Other witnesses thought some middle way might be found in this debate. Thus Dr Steven Hughes (Unilever Plant Breeding Institute) speaking on behalf of the British Society of Plant Breeders Ltd said "... we need to inform customers about things that are significant to their decision making process. What we do not want to do is unnecessarily alarm or confuse in terms of adding blanket labels about technological processes". Labelling "... will need a great deal more debate and probably its own decision tree to develop a workable and pragmatic system" (Q 558; see also Cubitt (Nickersons BIOCEM Ltd) Q 590; and Jarvis Q 613).

Process regulation and product regulation

5.55 In Chapter 4 we saw that an essential characteristic of the regulatory regime for biotechnology in the United Kingdom was that it was based on scrutiny of any act of genetic modification which might form part of the process of making a product rather than on scrutiny of the product itself. It consists of process (horizontal) as opposed to product (vertical) regulation. Discussion of the relative merits of these two approaches was a persistent theme in the evidence we received, both written and oral, and it focused on the practical usefulness of the distinction between the two systems; the extent to which process regulation was desirable; and the advisability of moving away from process to product regulation.

5.56 The view of the United Kingdom enforcing agencies - HSE and DOE - was essentially pragmatic, reflecting their role as implementers of the present regulations. They tended to play down the difference between the systems. Thus HSE thought "... from the strictly scientific and technical point of view there is no difference at all ... Either regime, provided that you are sure that the regulatory body received the right information and can take the appropriate action, will serve the purpose ... there is ... a very practical advantage to horizontal regulation in the workplace". In response to Lord Gregson's comment that horizontal regulation cannot be applied to a product as a product, Dr Smith claimed that "You could set up a regulatory regime under which products as a whole were scrutinised for risks that might be associated with them because of their biotechnological origins ... (but) ... where products are to be vertically regulated ... it makes entire sense - there is no argument about this in any quarter ..." (HSE (Smith) QQ 36-7). Dr Fisk, Chief Scientist at DOE, took "the very strong view that differentiation between horizontal and vertical is academic if the regulations are risk based, ... In our view the role of horizontal vertical is more to do with the efficiency of the regulatory process and its ability to deliver safe regulation" (Q 73). But DOE also wrote, "From the technical point of view, the information requirements currently set out by the GMO "horizontal" regulations could easily be satisfied by "vertical" regulations though this is not yet in place". They considered that a move from one to the other was likely to have little effect on the regulatory "burden" on industry, though it was conceded that "The most likely effect of a more to "vertical" regulation is that industry might find a product approach more convenient to operate under, even though different requirements within the same "vertical regulation" would continue to apply to GMOs and non-GMOs" (DOE p 20).

5.57 It is interesting to note that the Department of Trade and Industry took a much less agnostic view. They wrote that "Where biotechnology raises issues which are not industry-specific, then horizontal regulation may be appropriate. However, where it forms the essence of an industry-specific process or product, then industry-specific regulation may be better" (DTI p 32). They also informed us of the Prime Minister's initiative on deregulation and the need to avoid "unnecessary duplication of testing and authorisation procedures, which incur additional costs without any additional benefit for the consumer ... it is important that procedures are streamlined so that one assessment and notification procedure covers all that is required for product authorisation" (DTI pp 32-33). The Department of Health, which has great experience of regulation of pharmaceutical products, took the same line, and "... strongly supports the Government line of avoiding dual regulation ("one-stop shopping"), moving wherever appropriate away from horizontal process based regulation towards vertical product based regulation which would cover *all* aspects of assessment risk. The so-called "Future systems" approach for licensing human and veterinary medicines in the EC, which reached common position in December 1992, illustrates this commitment" (DH p 75).

5.58 Industry, and academic researchers in the universities and the research councils had a very clear view of what they wanted. The general message was that process based (horizontal) regulation was appropriate for research and development activities but that "having established the consistency and characteristics of the product, regulation should be vertical, in those cases where the product (or services or activities) require regulation" (BIA p 19) The Agricultural Genetics Company wrote, "Horizontal regulation is useful only for the regulation of process technology but not for the regulation of specific products. Horizontal regulation is most applicable to the regulation of biotechnology at the laboratory research level. Once the technology has been used to derive the product then vertical regulation should be adopted under the appropriate sectoral regulation ..." (p 11). Subject to strict product characterisation (Boulter p 32; British Bio-technology Ltd p 39) many other witnesses from industry followed this line (SAGB p 174; Hoechst (UK) Ltd p 102; CIA p 58; Biocatalysts Limited pp 15-16; Cantab Pharmaceuticals p 51; Pfizer p 149; Wellcome Foundation p 203; Glaxo p 69; SmithKline Beecham p 182; Zeneca p 56 and Q 222); as did the research councils (with the exception of ESRC) (AFRC p 8; MRC p 123; NERC p 139) and the Royal Academy of Engineering (p 158); and many in the agricultural sector (Processors and Growers Research Organisation p 154; Farm Animal Welfare Council p 87; British Society of Plant Breeders p 44; Potato Marketing Board p 152); and university based researchers (Slabas p 179; Bodmer Q 445; Boulter p 32; Lilly p 120; Williamson p 206; Fairtlough p 85; Burke p 48; Peters p 147; Grierson p 99; Parsons p 146) and technicians (IPMS p 108). Indeed, the evidence appeared overwhelmingly in favour of product-based regulation after research had been completed.

5.59 The reasons for this preference were that a product derived using genetic modification in the process was essentially no different from any other; that in administrative terms it was to be preferred by industry; that in many sectors using biotechnology the products were already closely regulated - for example pesticides, medicines, and plants - and a further regulatory tier was unnecessary and discriminatory; and that product regulation was actually safer. Thus the MRC pointed out that regulation of process would not distinguish between constructive and harmful applications whereas product regulation could (MRC p 123; see also Grierson p 99).

5.60 Some witnesses took a more cautious or even contrary view. The Director of the Green Alliance said "I would not want to see an abandonment of a horizontal system which seeks to look at applications of this technology" (Q 481), though she later conceded that "As the system evolves, I think it is very likely that certain categories of application or development will be deemed to be able to be put outside the system" (Q 488). Professor Joyce Tait, on behalf of ESRC, considered that "the horizontal regulation can be equated to a proactive, precautionary approach to risk regulation, while so-called vertical regulation is equivalent to a reactive, preventative approach. Industry's desire for vertical, product-based regulation is therefore a facet of its rejection of the precautionary approach to risk regulation which, I believe, has serious implications for the eventual acceptance of such approaches in other areas of risk regulation such as pollution control". She

considered that for the present uncertainties "may provide justification for retaining a horizontal approach into the foreseeable future" (Tait p 158).

5.61 Ultimately, we were told, product regulation by the EC will supersede the current process-based regime. The current EC Directives provide for this (HSE P 7; DOE Q 74) and will then apply only where appropriate product regulation has not yet been put in place. Thus proposals on novel foods, medicinal and veterinary products, animal feedingstuffs, pesticides (plant protection products) and seeds will eventually remove these products from the scope of the present regulations (EC Commission P 231; DOE p 21; Department of Health p 78). It was United Kingdom Government policy to ensure that, when this occurred, there was no duplication of regulatory procedures (Department of Health p 87). DOE told us that "we are up to at least political agreement on the first product Directive that will contain the necessary risk assessment ..." (Q 74). However reality may be different. Denton Hall, Burgin and Warrens told us "The GMO Directive expressly provides that it is *not* intended to apply to a specific area which has its own environmental assessment procedures. The Novel Foods Regulation, which of course does introduce its own procedures, runs counter to this and adds back in much of the GMO Directive compliance procedures: the application for authorisation under the centralised procedure outlined above, must *in addition*, be accompanied by a copy of the written Consent and full technical dossier required under the GMO Directive. This means in effect that two layers of regulation need to be traversed" (Denton Hall, Burgin and Warrens p 74).

Overseas comparisons: is there a "level playing field"?

5.62 We have already observed how the regulatory regime in the United Kingdom, consistent with the EC Directives, follows different principles from those operated by our principal competitors - the United States and Japan (paragraphs 4.41-2). In our call for evidence we sought information on the practice overseas, both from the knowledge of United Kingdom contributors and from foreign governments direct. The responses we received are synthesized in Appendix 4. It is, of course, difficult to infer from rather bald written descriptions what actually happens in practice, following detailed negotiations over how general requirements are to be interpreted in specific cases. The evidence indicates, however, that the difference in approach between the EC and its competitors does give rise to certain practical consequences and that, even within the EC, implementation of what should be a common regime already appears to be very uneven.

5.63 Japan, although it took a cautious approach in early years, (BIA p 20) relies on voluntary guidelines not legislation and these have "been relaxed by a series of revisions ... since 1979" (HSE p 8) (the regime is described fully in Appendix 4 p 78). Japan's philosophy is exemplified in their Government's evidence to us that "The safety of products is ensured by laws corresponding to the respective characteristics (medicine, foods, chemicals, etc) of the products whether the biotechnology is used or not. As to the industrial use of recombinant technology, Japanese government agencies made their guidelines, as stated below, based mainly on the recommendation of the OECD Council in 1986, which stated that there is no scientific basis for specific legislation of the use of recombinant DNA organism" (Japanese Embassy P 239).

5.64 This pragmatism was admired by the research community and by industry. As one witness put it, "The Japanese system is much more flexible than that in either the United Kingdom or the United States. This raises issues about our ability to compete with Japan ..." (Cripps p 68). The Japanese and United States systems were admired not because they were less stringent but because they were "transparent, a natural extension of existing legislation, a recognition that the sector interests are different, and above all comprehensible" (SmithKline Beecham p 183). They were "enlightened" (Hoechst UK Ltd p 102). Moreover an attempt in Japan in 1991 to move over to a regulatory system was opposed by government agencies and industry and shelved (ABPI P 201).

5.65 The United States system was particularly highly regarded by witnesses, many of whom had direct experience of United States operations as researchers or as industrialists operating on both sides of the Atlantic. (The regime is described fully in Appendix 4 p 81). Regulation is

conducted by a variety of federal departments and agencies, under pre-existing health and safety and environmental provisions. United Kingdom government witnesses thought this confusing. We were told that "the regulatory picture is complex and in a state of flux" (DOE P 21) and involves "several different agencies and pieces of existing product based review schemes ..." and "a variety of notification and consent procedures is operated by these agencies" (HSE p 8). In supplementary evidence from the DTI (p 43) we were told that "a multiplicity of Federal agencies ... has led to a degree of overlap and conflicting regulation". According to the DTI the EC Commission's interim report '*Regulatory Framework and Research Policy Effort on Biotechnology in the EC and US, 1992* shows that "... at the pre-marketing stage there is more flexibility in the United States, but that risk assessments seem to be broadly comparable in terms of information requirement and administrative burden" (p 33).

5.66 But the involvement of a number of different agencies did not feature prominently in the testimony of witnesses - possibly because most applications fall under the FDA, EPA or NIH, and possibly because product-based regulation made things easier (Cripps p 68; Dupont de Nemours p 82). On the contrary, practitioners saw many advantages in the United States system:

— because it is based on existing legislation - for example on crop plants and food - there is no disruption of existing product legislation and the degree of oversight can be "easily modulated in the light of experience" (Zeneca P 57; Agricultural Genetics Co Ltd p 11). The Food and Drug Agency procedures illustrate this. "The jurisdiction of the FDA extends to human and animal drugs, foods, food additives, human biological products, cosmetics and medical devices. The FDA review rDNA products on a case by case basis with emphasis on the product rather than the process. The FDA uses documents entitled "points to consider"; these contain guidelines for interpreting and analysing the way FDA regulations apply to biotechnology products. This procedure has proven to be flexible when dealing with product developments, from a fast changing technology base. The FDA has had a significant influence on the commercialisation of technology" (CIA p 58). SAGB found EC regulation "a maze" by comparison (SAGB p 175);

— it was easier and cheaper to perform experiments and obtain consents for release. For microbial pesticides, for example, the data requirements of FDA were "relatively simple, compared to the requirements for an agrochemical". Registration can be granted without generation of further data thus making it quicker and cheaper in the United States than the EC (Agricultural Genetics Co Ltd p 12). Moreover for modified crops, "Less information is also required by the APHIS (Animal and Plant Health Inspection Service) Form 2000. It contains approximately 13 questions as opposed to the release application form in the United Kingdom, which, in following the requirements set out in the Schedule of the Community release Directive, contains 89 questions" (Cripps p 68);

— the recent announcement that for certain key crops (maize, cotton, potato, soyabean, tobacco and tomato) prior notice of release would be reduced from 30 days to 24 hours with only two pages of information on the trial was also commended by witnesses (Zeneca Q 216; Agricultural Genetics Co Q 735; Dupont de Nemours p 82). For other crops consent is given with a maximum of 120 days;

— most GMO work is conducted without any system of consents under NIH guidelines, except that, where pathogens are used or a toxic gene is the product, the Recombinant DNA Advisory Committee of the NIH reviews any federally funded work;

— neither USDA nor EPA charge fees.

5.67 Within the EC itself, although implementation of the Directives in Member States is by no means complete, it is already patchy and interpretation and enactment are inconsistent. So far

as implementation is concerned, as of 1st January 1993 national legislation to implement the Directives 90/219/EEC and 90/220/EEC had been adopted in Denmark, Germany, the Netherlands, the United Kingdom and France. Ireland and Italy had adopted the enabling framework laws, while Belgium, Portugal, Greece, Spain and Luxembourg are at various stages of the decision-making process (Interim report of the EC Biotechnology Coordination Committee (BCC), *Regulatory Framework and Research Policy Efforts on Biotechnology in the EC and US).*

5.68 Even in those countries which have implemented the Directives, the way in which they have been incorporated into national legislation has differed significantly. Some countries such as Germany and Denmark have implemented a much stricter regime than that required by the Directives. In Germany (as we see from Appendix 4 p 75) the provisions of their Gene Law, passed in 1990, contains more restrictive provisions on contained use than does the EC Directive both as to notifications and public enquiry. Involvement of the Länder as regulatory authorities also adds to difficulty. Deliberate release is subject to consent of the Federal Health Office following a public enquiry. In practice such licences are hardly ever issued. Witnesses from Germany companies complained bitterly of the prevailing conditions (Hoechst QQ 354, 360, 361; Bayer pp 14-15). The HSE told us that ... Danish legislation is still more burdensome for "Good Industrial Large Scale Practice (GLISP)" users than the contained use Directive demands, and goes beyond the Directive in a number of other areas (HSE P 7). Other countries have implemented the regulations with little or no modifications such as the United Kingdom. A further group of EC countries have attempted to integrate the Directives into existing regulations with a result that the regulations are somewhat less exacting than the original Directives, for example France and Belgium (AFRC p 8; French Ministry of Agriculture and Fisheries p 91). We were told by SAGB that "Belgium ... has attempted to implement these Directives vertically, that is to say, within the sectors concerned" (SAGB Q 527; see also Monsanto PP 242-3). Thus, of those countries which have taken steps to implement the Directives, "The United Kingdom ... is probably treading the middle path, having more restrictions than proposed in some EC countries, and less than in others" (Pfizer p 150).

5.69 A final factor to be taken into account is the degree to which Member States will enforce the legislation. "Even when all Member States have implemented the Directives we suggest that there will still be differences across Europe because of the varying efficiencies of the inspection systems in place" (ABPI P 201). HSE considered that compliance was not simply a question of inspection. Although the United Kingdom had appointed 6 specialist inspectors for GMO work, elsewhere in the Community inspection fell to non-specialist labour inspectorates. This could "lead to a legalistic approach to compliance with the letter of the law because of a lack of understanding of the technology". Thus after implementation the HSE hoped to seek uniformity of compliance through meetings of competent authorities of Member States (HSE Q 9).

5.70 While it may well have been "a very important part of the European negotiations to produce a level playing field" (DOE (Fisk) Q 77), there is clearly some way to go before this will be achieved. Indeed the pressures are, if anything, to the contrary (paragraphs 4.4-6). (Nevertheless, in safeguarding access for products produced in the United Kingdom to other European countries, free of regulatory barriers, the Directives may well be valuable.)

The regulations and competitiveness

5.71 In our request for evidence we asked witnesses what were the likely consequences of the current regulatory regime on competitiveness of United Kingdom industry and on the exploitation by British industry of the research conducted in the United Kingdom science base. The evidence we received in response expressed fears that research and the location of facilities might be adversely affected insofar as some companies might move abroad. Indeed, there was already some evidence that adverse decisions on location were already being taken.

5.72 Many witnesses were concerned lest research be discouraged. The fears were well articulated by AFRC whose "immediate concern is with the effect of regulation on the science base which underpins industrial development. The present regulations are extensive, time consuming and could be costly if they are not interpreted sympathetically where risks are small and as experience

is built up; the current cost in the United Kingdom for obtaining consent to carry out a release is higher than in some other European countries. The Council is concerned at the adverse effect this could have on research and postgraduate training, with the loss of scientists and ideas. There must be a vigorous United Kingdom research base to enable the opportunities of biotechnology to be realised" (AFRC p 9). But as the Agricultural Genetics Company Ltd recognised, "Presently it is not clear whether the United Kingdom will be disadvantaged compared to other EC Member States by way of investment in biotechnological research" (Agricultural Genetics Co. Ltd p 12). Most other witnesses seemed to take the same line. There was a real danger that research could be affected *sometime in the future* (British Bio-technology Ltd p 41; Burke p 52; Slabas pp 179-80; Celltech p 56).

5.73 In making these warnings, witnesses had before them the experience of biotechnology research in Germany. Bayer complained bitterly of the effect of over regulation of German research effort in both universities and industry. "If the reasons for this burden are analysed, it has to be concluded that the administrative execution of the law certainly contains some "home-made" elements - due to the federal organisation of Germany - but the main reasons are caused by regulations of the "contained use" Directive (90/219/EEC)" (Bayer p 14). We heard of a brain drain of German scientists into the United Kingdom and elsewhere (BioIndustry Association pp 20-21).

5.74 Location of facilities - whether for research, product development or manufacturing - was also remarked upon. Biotechnology companies are highly mobile and have a strong incentive to locate near the source of appropriate research (Slabas p 179). Dr Brauer of Hoechst said that "For the big companies I think it is clear that they can somehow choose where to invest and where to develop a certain product or to produce it. We are talking about bio-technology products and we are not talking about thousands of tons of chemicals per year but of high value products that can be shifted easily. In this respect one always has to consider the time it takes until you have a certain facility installed, in place, and how smoothly you can run it" (Q 359). And SmithKline Beecham, though ostensibly a British company, considered themselves "a transnational pharmaceutical company with R&D operations in the United Kingdom, USA and Continental Europe. Any regulation or economic regime which makes the United Kingdom less competitive than these other countries will encourage us to invest outside the United Kingdom" (SmithKline Beecham p 183; see also Glaxo P 70; CBI pp 64-65). This ability to re-locate was not unfettered in the case of some agricultural businesses, however, because of the need to conduct local development work. Thus, the British Society of Plant Breeders Ltd told us "The most that could happen is that we would be squeezed to using old technology. One of the things about plant varieties is you have to develop them locally because they are adapted to the local climate. So you cannot take a wheat variety from the United States of America and grow it in Europe without doing some development work in Europe. You need local development work even if sophisticated technology was done elsewhere" (Q 603).

5.75 There was some evidence that investment decisions were already going against the United Kingdom and that regulatory considerations were amongst the deciding factors, though not the major factor. Both Zeneca and SmithKline Beecham implied that biopharmaceutical plant might not be located in the United Kingdom. "Where Zeneca will manufacture in the future has not been decided. It is, however, clear that the evolving regulatory climate and attitudes in European Community will make a significant contribution to this decision" (Zeneca P 58). SmithKline Beecham were more forthright. "Major European companies are choosing not to invest in manufacturing plant (involving GMOs) in Europe and the United Kingdom is undoubtedly losing out in equal measure. SmithKline Beecham is currently exploring options for a manufacturing plant for biopharmaceuticals. In spite of a strong research base in the United Kingdom, it is unlikely that Europe will be chosen for the plant; regulatory attitudes and a general unease over biotechnology, are not necessarily the critical decisive factors, but do play a part in the decision process" (SmithKline Beecham p 184).

5.76 The United Kingdom was also missing out on inward investment. "Of the United States companies choosing to locate offices or manufacturing facilities in the EC, many have chosen The

Netherlands for regulatory and tax inducement reasons eg Synergen, EuroCetus (Chiron), Centocor. About 20 United States biotechnology companies have located their marketing and distribution offices in the United Kingdom, but not necessarily their manufacturing and R&D facilities ... Two American companies, Creative Biomolecules and Panlabs actually suggested that a hostile regulatory climate prevented them from locating in the United Kingdom" (BioIndustry Association p 21; see also Zeneca P 58; British Bio-technology Ltd p 41).

5.77 The German experience again featured strongly in evidence as a cautionary tale. We were told that a combination of harsh regulation and adverse public opinion had stifled the German biotechnology industry. Hoechst told us, somewhat resignedly, how they had been obliged to place work overseas. "Pilot plants/experimental upscaling facilities can only be approved as production facilities (interpretation of the Hesse authorities of the "small volume" definition of the EC-Directive 90/219; this is handled differently in other federal states). Any modification or new product development would require additional approval procedures with additional costs and would furthermore allow "professional" public opponents to gene technology to object and delay developments by going to court. Consequently, several potential recombinant products we now develop in facilities in the United States, Japan, Australia and France with investments being directed into the respective facilities (eg more than 50 mio DM to Japan). Since these facilities are modern and therefore competitive, it is very likely, that future projects will be run also at these places" (Hoechst AG p 104). Other oft quoted moves were listed by another witness. "BASF has built its corporate R&D facility in Worcester, Massachusetts. Ciba Geigy has chosen to locate its new £100 million manufacturing plant in France which appears to have a more sensible regulatory framework than Switzerland, where the company has its headquarters. Boehringer Mannheim has just announced it will build a new therapeutic protein plant in Ireland, probably due to a more reasonable regulatory environment and attractive tax benefits and subsidies from the Government" (BioIndustry Association p 21; public hostility and the work of "fundamentalists" was responsible for Ciba's decision, see Ciba p 62). Bayer wrote that they had "decided to produce cell biology-based recombinant medicinal products (eg recombinant Factor VIII) in Berkeley, California. The scientific and technical conditions of the potential production sites Wuppertal, Germany and Berkeley, California proved to be equal according to an extensive strategic investigation. The legal and general conditions and the chances to achieve an approval of a production facility in a foreseeable time-frame was significantly better in the United States than in Germany. This was the determining factor for the decision to invest in the United States. During the past 10 years no foreign biotechnology company has invested in Germany" (Bayer p 15). Many United Kingdom witnesses clearly feared there was at least a possibility that a similar fate might befall United Kingdom industry. (AFRC p 9; Agricultural Genetics Co Ltd p 12; Zeneca P 58; SAGB p 175; British Bio-technology Ltd p 41).

5.78 It was clear, however, that factors other than regulation influenced business decisions in biotechnology and we consider these next.

Non-regulatory factors and competitiveness

5.79 Important though regulatory factors are in determining United Kingdom competitiveness, witnesses thought other factors were more or at least as important (SmithKline Beecham p 184; see also CIA p 58; Harris p 101; MRC p 124; HSE P 8; Fairtlough p 87). The chief factors identified were inadequate financing; unequal patent protection; erosion of the science base; and a miscellany of educational and macro-economic factors which were not unique to biotechnology.

5.80 **Finance:** Witnesses had two complaints. First, that there was a shortage of venture capital available to biotechnology companies in the United Kingdom in the early stages and secondly that the Stock Exchange rules prevented many companies from obtaining listings and hence access to wider sources of money later on. On both counts, circumstances in the USA were more favourable. Cantab Pharmaceuticals put the problem clearly and succinctly. They considered "The availability of finance to fund United Kingdom biotechnology is a key factor for success of the already established United Kingdom biotechnology companies and as a catalyst for expansion of the business sector. Drug discovery and the subsequent development of a product through to

marketing is a process that can take eight to ten years. For a start-up biotechnology company with, as yet, no revenue stream through product sales this represents a substantial length of time to finance the development of products. The investment required for each biopharmaceutical product may range from £50 million to £100 million". Venture capital finance from specialist biotechnology investment funds had "proved to be a reasonable source of finance for start-up biotechnology companies in the United Kingdom", attracted from United Kingdom, United States, European and Japanese fund managers. But venture capital from solely United Kingdom sources had been a "limited source of finance".

5.81 So called "mezzanine" financing, in the intermediate years after the start-up years, at a higher price per share was difficult to attract. United States companies by contrast were better able to conduct private placements of shares or undergo public flotation on the United States Securities and Exchange Commission and the Nasdaq Stock Market, in support of research and development up to product launch. United States companies are able to go public much earlier in their development than in the United Kingdom. This gave companies a wider range of investors and investors suitable "exit routes" if they wished to sell up. In the United Kingdom, by contrast, public finance - whether "mezzanine" or otherwise - was rendered difficult by the listing requirements of the London Stock Exchange, such as that for a company to show a record of three years' profits. The Exchange, recognising the problem, relaxed their rules to facilitate the flotation of British Bio-technology Group plc in 1992 and thus have opened the way for others to follow. Significant hurdles remain, however, such as those relating to at least two products in clinical development (Cantab Pharmaceuticals pp 53-4; for some or all of these arguments see also Celltech pp 56-7; British Bio-technology Ltd p 42; BioIndustry Association p 23; CIA p 60; Harris p 101; MRC p 124; Public Health Laboratory Service p 156; Glaxo P 70; ABPI P 203). DTI recognised the problem too. "Capital and R&D investment requirements in much of biotechnology are high - typically 10 to 20 times more than for manufacturing in general. Second-round funds will typically last only 2 to 3 years in a 5 to 10 year development plan. Most biotechnology companies will therefore need a heavy third round of financing before reaching the commercial stage of product development. Raising such funds has proved difficult for some biotechnology companies" (DTI p 34).

5.82 The practical effects of these financial constraints were very much feared by the research community. "The economic support for biotechnological innovation in the USA is much more likely in the transfer of research and researchers than any regulatory regime. As research and researchers concentrate in the United States, this drift will accelerate. This provides a serious problem for Europe which will have to be addressed. The comparative strength of British and European countries in the sciences could be at risk from the greater overall expenditure on research and development observed in the USA" (Kinderlerer p 119). Professor Weatherall of Oxford University painted a graphic, if disturbing picture. He thought there was "... a major problem in the United Kingdom with technology transfer and its control. Venture capital money is limited and there is considerable difficulty in transferring the bright idea from the basic research laboratory to industry. The bright young men in my Institute are inundated with people from the USA who want to help them develop their inventions; this is not happening in the case of British industry and there is a major gap between the basic research laboratory and the biotechnology industry as a whole. I believe this is a much greater potential problem than the development of a system of regulation which makes us less competitive in the world market; but the problems in Germany should be a constant reminder of how hard we will have to work to maintain public awareness and acceptability" (Weatherall p 202; see also Glaxo P 70).

5.83 **Patent protection:** Witnesses considered themselves disadvantaged by certain aspects of the United Kingdom and European patent law. The most common complaint concerned the British and European practice of according protection to the first to file rather than, as in the USA, the first to invent. There was one reference also to the United States practice of allowing a one year grace period for filing after publication. A more common complaint was the lack of uniformity of patent law within the EC itself and of the breadth of claims being granted patents by the European Patent Office.

5.84 In the United States the priority date of a patent is based on the date of invention (if necessary, as revealed in notebooks of results) as opposed to the date when the application was filed in the patent office. This difference, as we have already observed, renders any delay in obtaining consent to conduct experiments all the more critical (paragraph 5.36). Witnesses called for early harmonisation of the two systems (British Bio-technology Ltd p 42; Cantab Pharmaceuticals p 53; Zeneca P 59). Only MRC draw attention to another inconsistency between United States and European practice, whereby the United States allowed a grace period in which to file of up to twelve months after publication. This they considered, gave United States-based inventors an advantage (MRC p 124).

5.85 Witnesses were also unhappy with the lack of clarity, as they saw it, in interpreting biotechnology patents within the existing framework of patent law. This had led to uncertainty as to the strength and value of biotechnology patent rights (Wellcome p 205) and unevenness in the scope of granted claims for many inventions, particularly by the European Patent Office (British Bio-technology Ltd p 42; Zeneca P 59). Zeneca wrote, "This means that the rest of industry is held up by those claims unless licenses are granted. Improved training of examiners at the EPO in this fairly new area of technology could help to avoid this problem: though, more fundamentally there is a question of whether the EPO's approach gives the proper balance between the rights of the patentee and those of the public". DTI drew our attention to the fact that it is at present not possible to patent plant varieties in the EC and to the conflict between plant breeders' rights and patentees. A problem also arose over access by third parties to material deposited by applicants for patents in culture collections (DTI p 34).

5.86 Witnesses looked to the EC draft Directive on the Legal Protection of Biotechnological Inventions to redress some of these domestic European weaknesses (AFRC pp 9-10; Wellcome p 205; Zeneca P 59). However its efficacy had been so undermined by amendments on farmers' privilege and compulsory licensing inserted at the behest of special interest groups, that some now felt that the original objective of the Directive had been lost and even that it should not now be enacted (Wellcome p 206; see also BioIndustry Association p 23; ABPI P 203).

5.87 **Science base:** Witnesses also pointed to what they perceived to be a weakening of the United Kingdom science base. For AFRC "the main requirement [in maintaining competitiveness] is the maintenance and strengthening of the United Kingdom science base in the relevant disciplines underpinning biotechnology. The United Kingdom is strong in these areas, but in some cases the United Kingdom lead is being gradually eroded as other European countries and Japan catch up. More remains to be done, for example on multigene transfer and gene stability as well as on the wider ecological implications. Greater public funding, and incentives for industrial funding of research, would secure the United Kingdom position" (AFRC p 9; see also Kinderlerer p 119; Zeneca P 59; Wellcome p 206; SERC p 170; SmithKline Beecham p 185; Society for General Microbiology p 185; see also IPMS p 111). "Find good people and fund them well" wrote one (Onions p 145). The Royal Academy of Engineering referred also to the importance of the science base. They were particularly concerned with biochemical engineering. "It is not sufficient to expect industry to fund this research. Most of the techniques which now form the cornerstones of industrial biotechnology were originally developed in academic departments with no thought for future commercial uses. Biochemical engineering is concerned with the development and operation of biological production methods, central to translating, in the shortest time possible, the discoveries of biotechnology into commercial products through processes which are safe, reliable, economic and environmentally acceptable" (Royal Academy of Engineering p 160).

5.88 Collaboration with industry and the establishment of SMEs to exploit academic discoveries were important. Thus Celltech wrote that "A key factor will be the overall level of investment in biology research in universities and research institutes, since this is the foundation of our industry. This investment should have the objectives of fostering creative discovery research and not copying current applied industrial research, of encouraging scientific entrepreneurs to leave universities and found their own businesses and to provide a rewarding career structure that encourages young scientists to take up research" (Celltech p 57; see also Onions p 145; SERC

p 170; Royal Academy of Engineering p 160). The LINK scheme was already "well utilised" in this area (SERC p 170). The difficulties of obtaining finance for small biotechnology companies is also relevant here (paragraphs 5.80-82).

5.89 Better use could also be made of the science base to train people in the relevant technologies. Thus SERC considered that it would be "essential to maintain and continue to develop the science base in biotechnology and to promote and support advanced research and training in the relevant technologies. This will require significant investment in facilities particularly in the area of biochemical process engineering" (SERC p 170). SmithKline Beecham referred to the "erosion of the United Kingdom science base and failure to address industry needs for appropriate scientists (for example, fermentation scientists, protein engineers)" (p 185).

5.90 **Cultural and macroeconomic factors:** Witnesses also, variously, referred to several other factors governing competitiveness of the United Kingdom in general but which they felt had a particular bearing on biotechnology. These included

— the need for government assistance for biotechnology companies (Hoechst p 103);

— More fiscal incentives and write-offs for start up biotechnology companies (Onions p 145; Glaxo P 70; British Bio-technology Ltd p 42; Wellcome p 205; BioIndustry Association p 24);

— Capital grants for establishing manufacturing plants (Wellcome p 205; British Bio-technology Ltd p 42). United States State funding for a Biotechnology Centre in North Carolina to test products for technical and commercial feasibility was admired (BioIndustry Association p 24);

— An economic climate which discourages, or fails to encourage venture capital investment (SmithKline Beecham p 185);

— Shortcomings in science teaching in schools, "the education and training which a country provides for its people", and the need to raise school leavers' skills (Fairtlough p 87; Wellcome p 205; Onions p 145).

Regulation and public understanding

5.91 A number of witnesses spoke of the connection between regulation and public perception, and of the need to improve public understanding of biotechnology. Indeed, public understanding, if adverse, can in some ways be considered as another factor governing competitiveness. Witnesses were at pains to point out that public opinion of biotechnology in the United Kingdom was more benign than, say, in the United States, Germany or Switzerland. "The United Kingdom has not so far had to suffer from the extreme antagonism and vandalism seen in Germany or the Netherlands or from people such as Jerry Rifkind in the United States, but acceptance cannot be taken for granted and there is a ground swell of anti-biotechnology feeling which could well be mobilised" (Society for General Microbiology p 185). Were this sentiment to be mobilised, however, it would not be easy to combat, however. A recent survey by ESRC for DTI on public perceptions of biotechnology showed, among other things, the perceived trustworthiness of sources of advice, information and opinion. Thus "the most preferred sources were Friends of the Earth, Greenpeace, New Scientist magazine, conservation groups and scientists who work in universities, in that order. Working up from the bottom of the list were: tabloid newspapers, multinational companies, Department of Trade and Industry, small companies and the Government. Given that public attitudes are still largely unformed, it is worrying for the industry that its credibility and that of the Government is so low, and that groups likely to adopt anti-biotechnology attitudes have such a high level of credibility" (ESRC (Tait) p 190). Indeed some witnesses saw public perception as another hurdle in the way of industrial competitiveness. A number of ways of improving public confidence and understanding emerged in evidence.

5.92 The regulatory authorities and other government departments saw regulation as a means of establishing public confidence. "Transparent regulation is one way to underwrite public confidence in the safe management of biotechnology ... The scrutiny by ACRE and a strong, well-respected regulatory regime will each help to underwrite public confidence in products of this technology", wrote DOE (DOE p 23). HSE took a similar line. The problems of public education were not to be underestimated on the grounds that "all but the most meticulously open-minded fit new information into an existing belief system and use it to reinforce those beliefs" (HSE p 8). Until the public become more familiar with the technology - especially its medical benefits - "a system of regulation and control which is conspicuously thorough enough to reassure, and a clear willingness by industry to abide by it, will be important" (HSE p 8). DTI thought that "The regulatory framework plays a part in ensuring that products are safe, efficacious and of satisfactory quality, and contributes to public confidence. Regulations should be soundly based on science and sensitive to public concern" (DTI P 34).

5.93 Many other witnesses considered that an open, communicative and well understood regulatory system was a *sine qua non* (AFRC p 9; Wellcome p 205; Greenpeace P 237-8; Green Alliance p 98; IPMS p 111; Onions p 145). but, as some witnesses were at pains to point out, this regulation should be such as to "meet legitimate public concern but also allow the safe development of products with clear benefits to the public and the consumer ..." (AFRC p 9); it should be "reasoned and reasonable" (Kinderlerer p 119); it should be stringent at first "followed by relaxation as a record of safety and sound practice is established" (Fairtlough p 86); and "In considering regulation we should carefully distinguish between what we need to do for objective scientific reasons and what we feel we should do for social and political reasons such as satisfying the public perception of a technology or even public attitudes to science and technology in general" (Brenner p 33). HSE stood prepared to distinguish arguments about health and safety from those "on ethical and other grounds" (HSE p 8).

5.94 To achieve this "reasonableness", in other words to avoid a situation in which excessive regulation was required to generate public confidence, a number of measures were required. These included

— *Education in schools*: this was widely seen as a powerful way of raising the scientific literacy of the population, and a more effective way than simply purveying "information". This would require inclusion in the National Curriculum, teacher training and the provision of teaching and experimental resource materials (BioIndustry Association p 22). "A key element in building acceptance is education. There are too few teachers in our schools who actually understand biotechnology themselves. The industry seeks to heighten public understanding of the science and increased awareness of its benefits, and needs the support of the United Kingdom's education base in this" (Pfizer p 151; see also British Bio-technology Ltd p 42; Wellcome p 205; FAWC p 88; Grierson p 102; SERC p 170). We were told of the University of Reading's schools biotechnology programme (Q 615) and of the Food and Drink Federation's own schools' education programme on food safety which, they felt, could be expanded into food biotechnology. We received a first hand demonstration from Dr Barry Miller of the Royal Botanic Gardens, Edinburgh, of his DNA kit which enables practical DNA technology to be demonstrated cheaply in schools (Miller P 240).

— *Presentation of the science:* Witnesses, including scientists, felt that more understanding of public concerns might be shown in the presentation of research results (AFRC p 9; Boulter p 31; Zeneca P 70; SERC p 170). More pains should be taken to promote the products of biotechnology which brought obvious benefits to mankind - like gene therapy and pharmaceuticals (Agricultural Genetics Company p 13; Wellcome p 205; CIA p 60; MRC p 124; Slabas p 180; Brewers Society p 35). Indeed one witness thought that the medical charities were best placed to undertake publicity on these lines (Celltech p 56).

— *Public information:* Many witnesses put forward a case for improving public information (British Society of Plant Breeders p 45; British Sugar Beet Seed Producers' Association p 45; PHLS pp 155-6). But some witnesses expressed caution. ESRC's survey showed that "the commonly held view that providing people with more information about biotechnology will make them more favourably disposed towards was *not* supported. The two groups most knowledgeable about the technology were the most favourably and the least favourably disposed towards it, to a highly significant extent" (ESRC (Tait) p 190). Thus the Food and Drink Federation spoke of "educating, not trying to reassure" (Q 615).

— *Media involvement:* We received evidence which was deeply critical of the negative media coverage given to biotechnology, not only by the tabloid press but by some radio and television programmes which were more concerned with controversy than information. AFRC referred to "considerable media distortion in favour of the risks of biotechnology which must be corrected". "Consensus conferences" were advocated (AFRC p 9; see also BioIndustry Association p 22; CBI p 65; Zeneca p 70). Zeneca told us that they already communicated with the media but with less than satisfactory results (Zeneca Supplementary Evidence (*not published*)).

5.95 There was some evidence too on who should take charge of such an initiative. Clearly, individual scientists and firms had a role but so did publicly funded bodies and Government. The message from Government was confusing however. HSE told us that it would aim "to provide as clear a picture as possible of the means by which public health and safety are to be secured, and to contribute to an informed public debate on that subject" (HSE p 9).

5.96 DTI felt it was "largely a matter for the companies concerned" (DTI P 34). However we learned that the Biotechnology Joint Advisory Board (BJAB) which advises the DTI and the Research Councils on technology issues (regulatory advice is the province of the Biotechnology Industry Government Regulatory Advisory Group (BIGRAG)) had recently considered issues of public perception (Q 91). BJAB reported in 1991 that "... there is a strong case for publicly-funded initiatives to improve public perception; they should be distanced from company activity, and should concentrate on the provision of objective, independent and authoritative information" (CBI p 65). Moreover in October 1992 BJAB had held a workshop on public perception which recommended the appointment of a sub-group with special relationships for communications between the biotechnology community and other groups including the general public; education, particularly at the schools level; and research to develop greater understanding of the mechanisms of public perception in biotechnology (SERC p 170).

5.97 But of all the Government Departments, only MAFF seemed to have taken a proactive role by compiling its Foodsense Factsheets which included several on biotechnology. These were available only on request however (Q 153). Thus Government activity was patchy and probably inadequate. CBI wrote that despite the 1991 recommendation of BJAB, which CBI supported, "The approach from government departments has been relatively unsystematic and unco-ordinated, and though there are several Departments active in regulating biotechnology, led by the Department of the Environment, there is no equivalent "champion" with a clear remit to promote biotechnology" (CBI p 65). Professor Weatherall was particularly gloomy about the government record in this field. He bemoaned the amount of support for the British Association for the Advancement of Science and similar bodies. "I don't think that the British biotechnology industry is sufficiently aware of the importance of taking the public along with them. Nor do I think government is aware of the importance of the public appreciation of biotechnology and its implications" (Weatherall p 201).

5.98 Finally, several witnesses thought that the Royal Society's Committee on the Public Understanding of Science (COPUS) had a role to play (Dale p 71). Indeed, it already supported "many initiatives in this area" (Bodmer p 106).

CHAPTER 6 OPINION OF THE COMMITTEE

The value of biotechnology

6.1 It is clear to us from the evidence (set out in Chapter 2) that the "new" biotechnology is an exciting and continually evolving set of applications of the molecular biology of genetic modification. The uses and products of biotechnology (set out in Chapter 3) demonstrate just how great is the potential for applying biotechnology in areas of fundamental importance to the quality of life.

6.2 Because the science underpinning the new biotechnology is itself only some twenty years old it is hardly surprising that its full potential has yet to be realised. Relatively few processes have yet been applied or products brought to market and they are chiefly to be found in pharmaceuticals, health, veterinary medicine and food preparation. In agriculture and animal husbandry much is promised soon. In heavy industry and mining, applications are more remote.

6.3 Nevertheless biotechnology is already part of our daily lives. There are well known medicinal products like Factor VIII, insulin, Interferon, vaccines for hepatitis B and whooping cough, antibiotics manufactured using fermentation techniques, kits for diagnosing disease in humans and animals, synthetic enzymes used in food manufacture, and biological action washing powder, for example. But science moves apace. Gene therapy is beginning to be applied; 25 varieties of genetically modified agricultural crops are being tested in the field; Calgene's "Flavr Savr" tomato is already licensed for the market in the USA and new strains of maize and cotton are expected soon.

6.4 We do not, therefore, share the view of some witnesses that the benefits of biotechnology are unproven. On the contrary, **we conclude that the benefits of biotechnology are already well proven; that biotechnology and products of biotechnology are with us to stay; and that these products are likely to yield enormous benefits to mankind.**

6.5 We note that predictions of potential economic value, in terms of the size of the market for biotechnology products, vary widely. Most recent estimates place the world market at between $50 and 100 billion by the year 2000. We consider it unnecessary to pass judgment on the merits of these estimates or any others (paragraph 3.13). It is sufficient for our purposes to know that **biotechnology is a growth area, and that United Kingdom scientists and industry are good at it. We consider, therefore, that in all areas where biotechnology has applications, people should be able to exploit its economic benefits subject only to such regulation as may be necessary to meet identifiable disbenefits, especially to preserve safety.**

Perceptions of risk

6.6 The present regulatory regime, based as it is on EC Directives, seems to rely on the premise that genetically modified organisms - the immediate products of the new biotechnology - are inherently dangerous. But we received evidence to the contrary from some of our most respected biological scientists. All of them emphatically declared the premise to be false. Indeed, many held that genetic modification, if it had any effect at all on pathogenic organisms, reduced their viability (paragraphs 5.8-10).

6.7 So far as contained use of GMOs is concerned, it appears that the very early caution shown by scientists themselves towards genetic modification - commendably responsible at the time - turned out to be largely unnecessary. In the early 1970s, a self-imposed moratorium gave scientists time to reflect, but within a very short time experimentation had shown their fears had been unfounded (paragraphs 5.5-12; 5.15-16).

6.8 Now after 20 years of experience and many hundreds of thousands of experiments, no incident or accident has been reported. Short of an act of evil genius, genetic modification under contained use is not, of itself, an activity to be singled out from other experimental work. Evidence has shown that for laboratory work such practices as "Good Microbiological Practice (GMP) and

for larger scale work GILSP developed by the OECD (paragraph 4.17) are sufficient to deal with any hazard from a non-pathogenic GMO or other organism.

6.9 We draw attention to the uniform view of all those who gave evidence that the HSE, in the exercise of its statutory responsibilities for the contained use of GMOs, provided exemplary service to users. No-one questioned the need for regulations to protect human health, especially where pathogens were being used. But we take particular note of the observation of the Health and Safety Executive that the current regime for contained use is stricter than is necessary for protection of human health and is defensible solely on grounds of conjectural environmental hazard (paragraph 5.6). We agree with that assessment. Furthermore, except in the case of pathogens, we conclude from the evidence that even if there were an accidental release of GMOs from contained use in a laboratory there would be no significant environmental hazard. **We therefore conclude that early fears about GMOs in contained use turned out to be largely unnecessary. As a general principle, except where pathogens are involved, existing laboratory (GMP) and industrial (GILSP) practice provide sufficient safeguards under the purview of institutional biosafety committees. Except where pathogens are involved, separate regulation of GMOs in contained use is unnecessary.**

6.10 It is noticeable from the evidence we received that there is rather more acrimonious debate over the deliberate release of GMOs. But here again some of our most eminent scientists assured us that fears were largely misplaced. The hazards identified by environmentalists, by the DOE as regulatory authority, and by the Royal Commission on Environmental Pollution are conjectural. Many of their fears are grounded solely on experience of ecological or other accidents resulting either from the unforeseen consequences of the introduction of foreign species occurring in nature or from classical breeding methods. In our view reliance on these false analogies must weaken these arguments considerably, especially as they appear to neglect the greater precision of the techniques of genetic manipulation (paragraphs 5.7; 5.13-14).

6.11 Scientific witnesses, by contrast, spelled out how specific fears were misplaced. Thus:

— it is alleged that modified organisms would have a competitive advantage, and could become weeds or pests: but the evidence shows that, since we have no understanding of the genetic basis of weediness, or pathogenicity, we cannot deliberately create weeds or pests and that chance probabilities of creating these characteristics are low. Indeed most attempts to modify organisms result in a weakened rather than a strengthened strain thus making it, in relative terms, less aggressive. Furthermore tests could be conducted to detect such properties before any release took place (paragraphs 5.18);

— it is alleged that gene 'pollution' would spread to indigenous populations, for example making weeds herbicide-resistant; but the evidence so far is that genetically modified plants are no different from their traditionally bred counterparts in this regard. There is one example of cross-pollination between an indigenous weedy species and a cultivated species (Greenpeace P 237), but the cultivated species in question was not a GMO. In any case if this involved a herbicide-resistant GMO other herbicides could be used (paragraph 5.19);

— it is alleged that GMO plants (or animals) might be genetically unstable and unexpectedly develop dangerous properties. But witnesses pointed out that genetic stability is a prerequisite in any breeding programme (paragraph 5.17).

6.12 Although many specific fears can, in these ways, be discounted, all agree that some risks still need serious attention. The use of GMOs as vectors for gene therapy or live GMO vaccines for animals or humans are techniques which are developing rapidly. Theoretically, these methods could give rise to germ-line involvement with sperm or ova or recombinations with wild type organisms and precautions are necessary to preclude these dangers. Unless and until these have been shown not to be dangerous, it will be essential to confine the gene vectors to the target cell

types so that they do not invade other tissues. If live virus vectors are to be employed, the possible genetic complementation recreating a virulent form, is also not impossible with certain viruses. While scientists' capabilities may well be able to prevent such eventualities close regulatory scrutiny will still be necessary. In the case of modification of the genome of animals, it is important that the welfare of the recipient of new genetic material or its offspring is not compromised through abnormalities in normal physiological functions and behaviour (paragraphs 5.20-23).

6.13 Subject to these exceptions, however, evidence showed that most applications involving deliberate release of plant or animal GMOs were intrinsically no more hazardous than a release involving modification by classical breeding methods. Alternative views are not, in our opinion, credible. **We therefore conclude that, with the few exceptions involving bacterial or virus vectors, live vaccines, or modification of the genome of animals mentioned above (which should continue to be monitored by ACRE), deliberate release of GMOs is not inherently dangerous.**

The background to the regulations

6.14 Given our views on the perceptions of risk we now consider the present regulations and start by considering their gestation as EC Directives and the manner in which they have been applied by the United Kingdom regulatory authorities. It is clear from the evidence we received that **in framing the Directives on which the United Kingdom regulations are based, the European Commission took an excessively precautionary line which, in terms of scientific knowledge, was already obsolescent when they were being prepared in the late 1980s.** It is worrying, too, that we received allegations from so many quarters that the **advice tendered in the preparatory (avant projet) stage by industry and by national experts was studiously ignored by the Commission.** We received no satisfactory explanation from Commission witnesses that would account for these allegations. Moreover, control of the Directives apparently passed from DGIII (Industry) to DGXI (Environment) before adoption (paragraphs 4.11-13).

6.15 The result is that the EC Directives are in certain respects fundamentally misconceived:

— they both ignore OECD advice that no specific regulation for applying rDNA techniques was required (paragraph 4.5);

— the contained use Directive makes inappropriate use of containment measures which had been simply recommended by OECD as examples to be applied in the case of organisms which did not fall within the safe GILSP category (paragraph 4.10);

— the deliberate release Directive makes inappropriate use of risk assessment criteria for deliberate release of a GMO recommended by OECD. The OECD clearly did not expect them to be universally applied but only where they were appropriate to the particular case (paragraph 4.6);

— the contained use Directive seeks to apply to the laboratory a regulatory system designed by the OECD for large scale work (paragraph 4.5).

6.16 We conclude that on this occasion the Commission, in their desire to regulate, not only ran counter to the scientific advice then available but, in an effort to protect the environment from conjectural dangers, mis-applied such regulatory principles as had been proposed. We also observe the apparent confusion in responsibilities within the EC Commission and the important role played by the Biotechnology Coordinating Committee in holding the ring. We make no recommendations here save to say that **it is vital for the future development of biotechnology regulation that Commission policy be coherent and that the work of BCC is essential to that process.**

The contained use regulations

6.17 We now turn to the detailed provisions of the contained use regulations applied in the United Kingdom. We agree with witnesses that the definitions of the activities used in the regulations are inappropriate and bring risk assessment into disrepute. The classification of organisms into pathogenic (Group II) and other (Group I) organisms is a measure of hazard rather than risk and yet it has direct bearing on the notification procedures to be undergone. Secondly, the distinction between large and small scale activities (over or under 10 litres) is also arbitrary and irrelevant to risk (paragraphs 5.25-32). We would prefer a return to first principles and the abandonment of these criteria. Hazards and the risks taken with those hazards need to be better defined; riding a dangerous machine, a bicycle, is less risky on tarmac than on a tight-rope. **We conclude that the whole system is fundamentally unscientific. We therefore recommend that the Government presses for amendment of the EC contained use Directive so as to substitute a risk assessment system in place of the present classifications.**

6.18 We also note witnesses' uncertainties on interpretation of certain aspects - like the much maligned 10 litre rule, and confusion about what constitutes, in industrial use, Type A and Type B work (paragraphs 5.27-29). We recommend that the HSE clarify their intended application of these definitions. It is a particular concern of industry that large scale activities using safe organisms (Group I) require 60 days notification. Scale of operation and type of facility will bring their own hazards but these can be dealt with under the OECD's GILSP requirements. **We therefore recommend that, pending restoration of a risk-based system, under the current contained use regulations the use of safe (Group I) organisms should be subject only to notification, whatever the scale of operations.**

6.19 The notification procedures, relying as they do on these rather arbitrary hazard based classifications, have financial consequences for industry. The sixty and ninety day notification periods are significant. Delay means serious cost to industry. To both industry and research delay in experimentation can also lead to problems of priority in patent applications given that the United States gives priority to the first to invent rather than the first to file (paragraphs 5.33-36).

6.20 We take seriously the complaints by industrialists and researchers about the effects of delay and bureaucracy. For the industrialist, delay of any kind is a heavy cost to bear. Under the regulations as they stand it is likely that any large-scale activity will require a 60 day notification period and a large-scale use using unsafe organisms will require specific consent within 90 days. Clearly our recommendations on scale and notification will ease this problem of delay considerably, allowing regulations to concentrate on cases of greater import. **We urge HSE that wherever possible they aim to give specific consents for contained use of unsafe (Group II) organisms well within the 90 day maximum.**

6.21 Industry's concern about disclosure of commercially sensitive information is partly based on loss of competitive advantage to competitors and partly on the possible effect that provision of such information may have on claims of "novelty" for patent purposes (paragraphs 5.40-42). Nevertheless we feel that current arrangements are probably sufficient to protect both commercial confidentiality and intellectual property rights in the early years of development provided that provision allowing the withholding of information "for so long as it is necessary" is interpreted sensitively in a way which does not preclude patentability. **We recommend that the HSE consult with patent authorities and issue early guidance on what period they consider reasonable for withholding commercially sensitive information from disclosure under this provision.**

The deliberate release regulations

6.22 From the opinion we expressed on the perceptions of risk associated with deliberate release of GMOs, we are inevitably driven to conclude that the whole Byzantine regulatory structure needs urgent re-examination. It is essential that the risk assessment exercise operated by ACRE in the United Kingdom can become focused on those releases which genuinely require close monitoring. Risk assessment can then be tailored to fit the potential hazards arising from the more

innovative proposals instead of being wasted on the current 'generic' scrutiny across the board (paragraphs 5.43-5). We are very attracted by the recent decision of the United States authorities to exempt deliberate release of certain species of agricultural crops from prior consent (paragraphs 5.65-6). Although we make no comment on the specific provisions which the United States have made, we applaud the pragmatism of the United States authorities. We recognise that such a change in approach would probably require amendment of the EC Directive and that the United Kingdom Government could not act alone. We recognise too that such a move, though it might be thought acceptable within the United Kingdom, might be opposed by certain European political groupings. Nevertheless it is an inevitable conclusion from the evidence we received that experience of deliberate release already indicates that changes must now be made. **We therefore recommend that the United Kingdom Government, in concert with other countries active in biotechnology, presses the Commission to amend the Directive to enable certain activities to be exempt from the present provisions. Those activities should be selected by a group of EC national experts on which the United Kingdom would be represented by ACGM and ACRE. The activities so selected would be subjected to a vastly accelerated and simplified procedure of notification structured on United States lines.**

6.23 The deliberate release regulations as they stand seem to be a bureaucratic nightmare and we therefore offer some interim solutions. We were concerned to learn that the 89 questions posed in the application for consent to release were not specific to the type of GMO. Thus the same questions were posed whether the application related to a bacterium, virus, plant or animal (paragraph 5.45). This seems to us to be ridiculous. A system which relies on the provision of information without clear thought for the real use to which that information is to be put is, in our opinion, bound to be less effective than one which focuses on issues specific to the organism in question. It also imposes quite unnecessary administrative burdens on research and industry. We learned that Australia, which currently operates a voluntary system of control of deliberate release using guidelines, distinguishes between types of organisms. The Commonwealth authorities issue questionnaires which are specific to the organism. **We strongly exhort the United Kingdom as a matter of priority to press the EC Commission to follow suit and make the questionnaire specific to the type of organism, possibly under the original Directive's provisions for "streamlining".**

6.24 But witnesses' complaints as to the needless bureaucracy of the 89 questions were as nothing compared with their complaints about the effect of the 90 day consent provision governing deliberate release. This delay affected the ability of researchers, whether in industry or in universities, to meet their targets for planting within a single growing season (paragraphs 5.46-8). We heard from DOE that their handling of applications under the deliberate release regulations had, up till now, been expeditious in their view, averaging 59 days (DOE Supplementary Evidence P 228). Nevertheless, two months is a very long time - especially when compared with similar arrangements in competitor countries, particularly the USA (paragraph 5.55-6). Moreover as United Kingdom applicants are paying dearly for the procedure they have reason to expect a speedy service. **We recommend that applications under the existing regulations should be processed in not more than 30 days.**

6.25 The fees charged appeared to us to be far more onerous than the fees for contained use. They were much higher in relative terms - at £1800 for each release and £450 for repeats - and fall chiefly on the agriculture sector where profitability, it was argued, was lower than in, say, pharmaceuticals. Complaints were also vociferous from academic researchers at the universities and research councils where the fees charged would form a very high proportion of the recurrent consumable costs of a project - currently £8,000 a year per person. And large numbers of these applications would, even with streamlining, have to run simultaneously (paragraph 5.48). **We recommend that the universities and research councils should be exempt from paying fees for deliberate release applications.**

6.26 In relation to novel foods and labelling of foodstuffs which either are GMOs or have been produced using GMOs, we note that MAFF's Food Advisory Committee is currently engaged in

a new consultation exercise. The issues were well rehearsed in evidence, for example, should all products be labelled because they are produced out of or produced using a GMO in the process; or only foods which are themselves GMOs; or only viable GMOs (paragraphs 5.51-4). We note also that food safety is covered by extensive regulation of its own and is not at issue here. We consider that labelling of any kind, if it is not to mislead the public or give them cause for concern, can only be introduced to the extent that public understanding will allow. We do not accept that GMO derived foods or food constituents are inherently dangerous. **We do not think that a case can be made for the universal generic labelling of such foodstuffs. We therefore recommend that the Food Advisory Committee reject calls for such labelling.**

Process regulation and product regulation

6.27 The question of whether regulation should be based on process or product is central to our investigation. While environmental groups tended to favour adhering to process based regulation, and while the HSE and DOE regulations acknowledged that both systems were feasible, other Government Departments with a strong history in product legislation like DTI and the Department of Health considered product regulation to be more logical as did all industrial witnesses and most academics. They rejected the view that the difference in the two systems was merely "academic" (paragraphs 5.56-8).

6.28 We indicated above (paragraphs 6.10; 6.14) that we considered that, subject to certain exemptions, the act of genetic modification was not inherently risky. For example, rDNA human growth hormone is safer than the naturally derived material while being chemically identical. Nor was the act of deliberate release or marketing of a GMO inherently risky. It follows, therefore, that we also take the view that product regulation is to be preferred whenever this is practicable on the grounds that it is better targetted and more economical for both regulators and the regulated and it does not single out genetic modification unnecessarily for a different style of regulatory treatment. As MRC pointed out, judging a product, and hence the use of the GMO, was actually safer than judging a series of processes (paragraph 5.59).

6.29 **We therefore recommend that wherever a GMO derived product is not viable and can be fully characterised (described) by physical, chemical and biological tests it should be subject only to a sectoral regulatory regime. Furthermore there can be no case for labelling a GMO derived product differently from the same type of product not so derived.** We note that the EC Directives provide that product regulation may supplant process based regulation and we note a number of Commission initiatives in this area. **We recommend that the evolution from process based to product based regulation should be accelerated rapidly. In such cases it is essential that the "one key one door" principle be observed and a single tier of regulation be maintained and that the product regulation is deemed sufficient. For the future, new product based Directives should include GMO derived versions as a routine.**

6.30 By contrast, there are areas of research and experimental work either in contained use or deliberate release where, witnesses felt, process based regulation remained preferable (paragraph 5.58). **We conclude, therefore, that process based regulation on present lines should be retained for research and development in those limited areas where regulation is required - that is to say all work involving pathogenic (Group II) organisms, and for deliberate release of GMOs outside the low to negligible risk category.**

6.31 **It is a logical consequence of our analysis of product and process regulation that work on further process based EC Draft Directives on GMOs should cease forthwith. Furthermore we wholeheartedly reject the concept of a "Fourth Hurdle" of socio-economic need as an additional criterion in product regulation of biotechnology.**

Regulation and competitiveness

6.32 So far, we have considered the regulation of biotechnology on the basis of scientific principles. On those grounds alone we see compelling reason for change.

6.33 The question we now address is whether the current regulatory regime also affects the competitiveness of the United Kingdom's biotechnology products. Are the users of biotechnology being adversely effected?

6.34 It is clear to us from the evidence we received and from our own analysis of that evidence set out at Appendix 4 that users of biotechnology in the United Kingdom are placed at a disadvantage *vis à vis* certain competitor countries. In our review of the evidence we singled out Japan and the USA for ease of comparison. Both Japan and the USA have long operated systems of regulation which in their different ways are clearly more appropriate because they are product based extensions of existing regulatory provision supplemented by advisory codes for genuinely risky applications of genetic modification. More particularly, the USA system appeared to be well understood by its users, quick to respond, and cheap and undemanding in bureaucratic terms for applicants. Indeed, for some agricultural applications involving six common crops, there had recently been further relaxation in the procedures as a result of their extensive field experience to date. We do not therefore agree with United Kingdom regulators that the United States system is complex. Although numerous agencies are involved, applicants clearly know where to go and there appear to be real advantages to them under the system that obtains (paragraphs 5.62-66).

6.35 But even more important perhaps than the practical advantages which witnesses identified is the fact that the United States - and other - systems were *perceived* to be less bureaucratic and speedier. Policy statements by the United States administration that biotechnology products be considered on their merits as products and not singled out for special treatment because they were GMOs had undoubtedly reinforced this perception.

6.36 Even within the EC, enough differences have already emerged in the manner in which Member States have implemented the regulations to cause us considerable concern that even the "home ground" shows signs of considerable unevenness. Some countries like Belgium, France and the Netherlands appear to be less restrictive than the United Kingdom, for example. Moreover, United Kingdom fees for consent were thought particularly high. And of course some countries have not even implemented the Directives yet. We therefore reject the argument that the EC Directives are in the process of creating a level playing field. It is obvious to us that they are not. We conclude that even within the EC, United Kingdom users of biotechnology are and will increasingly be placed at a disadvantage (paragraphs 5.67-70).

6.37 The question now arises as to whether these unfavourable comparisons place the United Kingdom at a competitive disadvantage in relation to research into and investment in exploitation of biotechnology. Clearly the bureaucracy and costs to researchers in the universities and research councils could place the United Kingdom at a disadvantage as a location for research activity but there was little direct evidence that this had happened yet (paragraphs 5.72-3). There was more evidence that development and production by industry in the United Kingdom was beginning to be affected by the regulations, however. Multinationals told us that forthcoming investment decisions on new manufacturing plant were likely to go against the United Kingdom for a variety of reasons of which regulation was one. Small agricultural biotechnology companies were afraid of being squeezed out. And we also heard that inward investment from the United States had on occasion been lost to the Netherlands for reasons which included the regulatory system. Much was made in evidence of the decline of biotechnology in Germany and the exodus of research and manufacturing to other countries. This well illustrates the mobility of multinational companies and of individual researchers, in the face of a regulatory regime which was perceived to be hostile (paragraphs 5.74-7).

6.38 Thus the regulatory regime is perceived to be cumbersome and is already a factor which governs business decisions. But it was equally clear from evidence that witnesses considered other

factors to be more or at least as important in determining United Kingdom competitiveness (paragraph 5.79). These were inadequate methods of financing new companies, unequal patent protection, erosion of the science base and other educational and macro-economic factors which were not unique to biotechnology. Indeed, of all factors, the financial support given to biotechnology in the United States was probably the single most important determinant of the location of research and investment in biotechnology (paragraphs 5.80-90). These other factors lie outside the terms of our present enquiry and we make no recommendations in connection with them.

6.39 Nevertheless we take the view that any factor which governs the competitiveness of United Kingdom - and indeed European - industry must be taken seriously. Any regulations which might stand in the way of commercial and humanitarian exploitation of the knowledge generated by the science base must be looked at critically, especially where many operators are small firms. Since the present biotechnology regulations cannot as they stand even be justified on scientific or public interest grounds, a review becomes all the more important with a view to modifying the regulations in the manner we have already proposed.

6.40 We learned in evidence that the DTI, on the Prime Minister's initiative, had recently established seven Deregulation Task Forces to advise Ministers on priorities for the repeal or simplification of existing regulations and enforcement methods so as to minimise costs imposed on business (paragraph 5.57). These regulations include those arising from EC measures, and we understand that the biotechnology regulations may be included for consideration. Given the technical nature of the subject matter, the Task Force may wish to seek assistance from DTI's biotechnology industry advisory group, BIGRAG. We have also made our papers available to the Task Force dealing with biotechnology matters.

6.41 **We conclude that regulation places United Kingdom biotechnology research and investment at a competitive disadvantage *vis à vis* our principal overseas competitor countries; and that the implementation of the EC Directives on which the regulations are based is so uneven as to create inequalities even within the Community. Although factors other than regulation - principally investment and intellectual property rights - govern competitiveness, we further conclude that any regulation which reduces competitiveness must be viewed critically, especially when it cannot be justified on scientific or public interest grounds. We therefore recommend that the DTI Deregulation Task Force review the contained use and deliberate release regulations on the basis of this report and if necessary in consultation with BIGRAG with a view to revising both the United Kingdom regulations and where necessary the parent EC Directives.**

Public understanding

6.42 There is no evidence within the United Kingdom of the extreme antagonism against biotechnology and its products that has emerged in some other countries (paragraphs 5.91-92). We see no reason to believe that such antagonisms will necessarily develop here. Hostility in Germany arises to a considerable degree from cultural and historical reasons which have no bearing on this country; and the lobbying activities seen in the USA have no equivalent here.

6.43 But were the public to take against biotechnology for any reason, subsequent attitudes would not be easy to change. We were dismayed to learn, for example, the results of the ESRC survey of the perceived trustworthiness of sources of advice, information and opinion; and of the finding that public information without education reinforced existing beliefs (paragraph 5.91). We were also profoundly depressed by the evidence we received about the quality media coverage of biotechnology (paragraphs 5.91-2). Because public perception, if adverse, can adversely affect competitiveness and because regulation helps to condition public acceptance, we consider that some consideration of public understanding is relevant to our enquiry.

6.44 We agree with those witnesses who said that a well respected, conspicuous and transparent regulatory regime was an important means of engendering public confidence in

biotechnology and its products. But we also consider that regulation should, in the words of DTI, be "soundly based on science" (paragraphs 5.92-3). We do not consider that public reassurance is necessarily a defence of the regulatory *status quo*. Indeed adherence to an unnecessarily restrictive regime is as capable in our opinion of unnerving as of reassuring public opinion. **We therefore conclude that promotion of public understanding is important but should not preclude the evolution of regulation.**

6.45 Ultimately, we consider, **biotechnology products will gain public acceptance because they are desirable and reliable.** This has already begun to happen in such areas as medicines and washing powder, to name some of the more popular products.

6.46 Of the other methods of shaping public opinion, education in schools is one of the most important methods of introducing familiarity with the concepts of biotechnology into a wider society. We note that the science of genetic modification already features in the national curriculum and we were very impressed by the low cost DNA demonstration kit for schools prepared by the Royal Botanic Garden, Edinburgh (paragraph 5.94). We hope that the Department for Education will ensure that biotechnology is taught in an imaginative way

6.47 But education in schools is a long term solution. In the meantime a more focused programme of public education is required. Current efforts by individual scientists and companies and by MAFF (whose booklets deserve a much wider distribution) are clearly inadequate for the task. The Committee on the Public Understanding of Science was set up jointly by the Royal Society, the Royal Institution and the British Association for the Advancement of Science to promote just such activities. It has received financial help from government, from industry and from academia but in very limited amounts. All three share responsibility for promoting public awareness of the value of biotechnology. We think it would be wise for all to increase significantly funding for the purpose, perhaps channelling it through COPUS. This would be consistent with government policy on seeking to improve the general level of public awareness of science and technology set out in the recent White Paper (*Realising our Potential: A Strategy for Science, Engineering and Technology* p 7).

6.48 We also recognise that the broadcasting authorities, the press, the Open University and voluntary organisations have a role to play. In particular, we hope that the media, as a whole, will stress the potential benefits of biotechnology rather than repeating conjectures about risks which are vanishingly small. And we consider that more co-ordination of effort is required.

6.49 Some witnesses, including DTI's Biotechnology Joint Advisory Board, thought that Government should promote publicly funded initiatives to promote public perception, but that activity hitherto was patchy (paragraphs 5.95-7). In view of the importance of public perception as an additional factor which could, if adverse, govern competitiveness, we think that DTI, although not a regulator, does have a role to play as the natural champion of this aspect of biotechnology, in conjunction where appropriate with MAFF. Both departments should accept a residual responsibility for ensuring that public perceptions of biotechnology are based on reason and knowledge.

6.50 **We therefore conclude that education in schools is one of the most important methods of introducing familiarity with the concepts of biotechnology in the longer term. In the short term, scientists and industry with help from government have the chief responsibility for promoting wider public understanding. DTI, in collaboration with MAFF, is the natural champion of this aspect of biotechnology and should co-ordinate the opinion forming activities of the many bodies involved and so ensure that public perceptions are based on reason and knowledge. DTI should respond positively to recommendations for action by BJAB.**

CHAPTER 7 SUMMARY OF CONCLUSIONS AND RECOMMENDATIONS

General

7.1 The benefits of biotechnology are already well proven; biotechnology and products of biotechnology are with us to stay; and these products are likely to yield enormous future benefits to mankind (6.4).

7.2 Biotechnology is a growth area and United Kingdom scientists and industry are good at it (6.5).

7.3 In all areas where biotechnology has applications people should be able to exploit its economic benefits subject only to such regulation as may be necessary to meet identifiable disbenefits, especially to preserve safety (6.5).

7.4 Early fears about GMOs in contained use turned out to be unfounded. As a general principle, except where pathogens are involved, existing laboratory (GMP) and industrial (GILSP) practice provide sufficient safeguards under the purview of institutional biosafety committees. Except where pathogens are involved separate regulation of GMOs in contained use is unnecessary (6.9).

7.5 With a few exceptions involving bacterial or virus vectors, live vaccines, or modification of the genome of animals (which should continue to be monitored by ACRE), deliberate release of GMOs is not inherently dangerous (6.13).

7.6 In framing the Directives on which the United Kingdom regulations are based the European Commission took an excessively precautionary line which, in terms of scientific knowledge, was already out of date when they were being prepared in the late 1980s. Advice to that effect appears to have been ignored (6.14).

7.7 It is vital for the future development of biotechnology regulation that Commission policy be coherent and the work of the Biotechnology Coordinating Committee is essential to that process (6.16).

Contained use

7.8 The classification of pathogenicity of organisms and scale of activities as the basis of risk assessment in the contained use Directive is fundamentally unscientific. The Government should press for amendment of the EC Directive to substitute a risk assessment system in place of the present classifications (6.17).

7.9 Pending restoration of a risk-based system, under the current contained use regulations the use of safe (Group I) organisms should be subject only to notification whatever the scale of operations (6.18).

7.10 Whenever possible HSE should aim to give specific consents for contained use of unsafe (Group II) organisms well within the 90 day maximum (6.20).

7.11 HSE should consult with patent authorities and issue early guidance on what period they consider reasonable for withholding commercially sensitive information from disclosure (6.21).

Deliberate release

7.12 The Deliberate Release Directive should be amended to enable certain activities, selected by a group of EC national experts, to be subject to a vastly accelerated and simplified procedure of notification on United States lines (6.22).

7.13 Meanwhile, as a matter of priority, the United Kingdom should press the EC Commission to make the questionnaire specific to the type of organism, possibly under the original Directive's provision for "streamlining" (6.23).

7.14 Applications under the existing regulations should be processed in not more than 30 days (6.24).

7.15 Universities and research councils should be exempt from paying fees on applications (6.25).

7.16 No case can be made for the universal generic labelling of GMO derived foods or food constituents. The Food Advisory Committee should reject calls for such labelling (6.26).

Process regulation and product regulation

7.17 Wherever a GMO derived product is not viable and can be fully characterised (fully described) it should be subject only to a sectoral regulatory regime under existing product legislation. There is no case for labelling a GMO derived product differently from the same type of product not so derived. Evolution from process-based to product-based regulation should be accelerated rapidly. A single tier of regulation should be maintained. For the future, new product based Directives should include GMO derived versions as a matter of routine (6.29).

7.18 Process-based regulation on present lines should be retained for research and development in those limited areas where regulation is required - that is to say all work involving pathogenic (Group II) organisms, and for deliberate release of GMOs outside the low to negligible risk category (6.30).

7.19 Work on further process based EC Draft Directives should cease forthwith; and the "Fourth Hurdle" of socio-economic need must not be introduced as an additional criterion in product regulation of biotechnology (6.31).

Regulation and competitiveness

7.20 Regulation places United Kingdom biotechnology research and investment at a competitive disadvantage vis à vis our principal overseas competitors (6.41).

7.21 Implementation of the EC Directives on which the regulations are based is so uneven as to create inequalities even within the Community (6.41).

7.22 Non-regulatory factors like investment and intellectual property rights are equally if not more important in determining the competitiveness of United Kingdom biotechnology (6.41).

7.23 Any regulations must be viewed critically, especially where they cannot be justified on scientific or public interest grounds and we recommend that the DTI's Deregulation Task Force reviews the contained use and deliberate release regulations on the basis of this report (if necessary with the assistance of BIGRAG) with a view to revising both the United Kingdom regulations and where necessary the parent EC Directives (6.41).

Public understanding

7.24 Promotion of public understanding is important but should not preclude the evolution of regulation (6.44).

7.25 Biotechnology products will ultimately gain public acceptance because they are desirable and reliable (6.45).

7.26 Education in schools is one of the most important method of introducing familiarity with the concepts of biotechnology in the longer term (6.49).

7.27 In the short term, scientists and industry with the help of government have the chief responsibility for promoting wider public understanding of biotechnology by appropriate means (6.49).

7.28 DTI, in collaboration with MAFF, is the natural champion of this aspect of biotechnology and should ensure that public perceptions are based on reason and knowledge. DTI should respond positively to recommendations for action by BJAB (6.49).

APPENDIX 1

The members of the Sub-Committee who conducted the enquiry were:

L. Flowers
L. Gregson
B. Hilton of Eggardon
L. Howie of Troon (Chairman)
L. Perry of Walton
B. Platt of Writtle
L. Renwick
L. Soulsby of Swaffham Prior
L. Wade of Chorlton
L. Walton of Detchant
L. Whaddon

APPENDIX 2

Invitation to submit written evidence (United Kingdom)

The House of Lords Select Committee on Science and Technology have appointed a Sub-Committee, under the chairmanship of Lord Howie of Troon, to enquire into "Regulation of the UK Biotechnology Industry and Global Competitiveness".

The Sub-Committee invite you to submit written evidence to them on any matters relevant to their terms of reference and in particular on the questions enclosed with this letter. It may be that not all the questions will be relevant to your concerns, in which case you should be selective.

Evidence should be submitted to me, the Clerk of Sub-Committee II (Regulation of the UK Biotechnology Industry and Global Competitiveness), Select Committee on Science and Technology, House of Lords, London, SW1A OPW. Evidence must be clearly printed and take the form of an original copy. Pre-published documents and documents prepared for other purposes will not normally be received as evidence. It would assist the Sub-Committee if evidence were prefaced with an executive summary or precis.

On the basis of written evidence received the Committee will invite some witnesses to give oral evidence.

If you have any queries arising out of this letter please let me know.

Questions on which evidence is invited

1. What is your interest in biotechnology?

2. How and why is biotechnology important to UK industry?

3. What future prospects and opportunities does the technology offer?

4. Which developments in biotechnology raise issues of safety and how should they be addressed?

5. Should biotechnology be regulated by an industry specific regime?

6. From a technical point of view, is horizontal regulation (where a product is judged through the process by which it is derived) better than vertical regulation (where a product is judged by its characteristics)?

7. Should regulation evolve from a horizontal to a vertical approach in each industrial or environmental application?

8. How do current regulations compare with those of other competitor countries

   - in Europe
   - in the Far East
   - the USA?

9. What are the consequences, or likely consequences, of the regulatory regime on competitiveness of the UK industry, in particular as regards

   (1) research
   (2) product development
   (3) investment
   (4) location
   (5) sales and marketing?

10. Is there a danger that the present regulatory regime will prevent the exploitation by British industry of research conducted in the UK science base?

11. How best can issues of public acceptance be addressed?

12. What other factors do you consider will play a crucial role in the competitiveness of the UK biotechnology industry?

APPENDIX 3

Invitation to submit written evidence (Foreign)

The House of Lords Select Committee on Science and Technology have appointed a Sub-Committee to consider "Regulation of the UK Biotechnology Industry and Global Competitiveness". The Sub-Committee was set up following representations that UK industry was likely to be placed at a competitive disadvantage by this country's present regulatory regime. The enquiry is expected to last until July.

As part of their enquiry, the Sub-Committee are anxious to discover what regulatory arrangements are in place in competitor countries and I should be grateful if you could provide answers to the following questions:

1. How important does your Government perceive biotechnology to be?

2. Which developments in biotechnology are thought to raise safety issues?

3. In your country, is biotechnology regulated by a specific regulatory regime?

4. Do regulations distinguish between contained use and general release (for experiment or marketing)?

5. Is regulation in your country "horizontal" (where a product is judged through the process by which it is derived) or "vertical" (where a product is judged by its characteristics)? Which is preferred by your Government?

APPENDIX 4

Comparison of Regulation of New Biotechnologies in Major Industrialised Countries

EXECUTIVE SUMMARY

1. This appendix gives the details of the regulatory regimes covering the use and release of genetically manipulated organisms that are in place in Australia, Belgium, China, Denmark, France, Germany, Italy, Japan, the Netherlands, Portugal, Spain, Switzerland and the USA. The information is taken from evidence submitted to the enquiry. Where possible this has been supplemented by additional information obtained from the literature and personal communications listed at the end of this appendix. This report is divided into country profiles, separating contained use and deliberate release as appropriate, and, so far as available information allows, addressing sixteen separate items as follows:

(1) Government attitude and national climate
(2) Regulatory authority (legal and non-legal)
(3) Regulatory requirements (classification of activities, notifications and consents)
(4) Regulatory structures and processes (ministries, agencies and advisory committees)
(5) Simplified procedures, if any and prospects for changing regulation
(6) Enforcement (including implementation, sanctions and inspection)
(7) Fees
(8) Regulatory questions, including risk assessment (number and main focus)
(9) Time taken to process applications (in theory and practice)
(10) Public information and confidentiality
(11) Public enquiry (hearings, appeals)
(12) Liability and insurance measures
(13) Views of industry
(14) Views of environmental groups/NGOs
(15) Evidence of adverse effects on competitiveness
(16) Other factors favouring competitiveness

2. Comparisons may be drawn between the regulations governing GMOs in Great Britain with those in countries outside the EC such as USA, Japan and Australia, and with those in the other Member States of the EC. However, direct comparisons are difficult to draw even when the information about the regulations is complete because the degree to which the regulations are strictly enforced is not easily determined.

3. The principal difference between the regulation of GMOs in the EC Member States and those in the USA and Japan is that those outside the EC are based on existing legislation governing the safety, quality and efficacy of products which can be easily modulated in the light of experience. In particular, Government in the USA has argued strongly that regulation should be based on demonstrated risk and not depend solely on the fact that an organism has been genetically modified. The system of regulation in the USA is firmly product based. There is a voluntary notification scheme for many contained use applications and others require notification but no approval. The USA have also moved rapidly to simplify their regulations where they feel sufficient experience has been gained. Thus the deliberate release of genetically modified varieties of six crop plants now simply need notification before these are planted. There is however an additional complication in US regulations as they may be implemented by both federal and state authorities. Thus certain states have put in place specific regulations concerning GMOs, for example, Minnesota has passed a law regulating GMOs horizontally.

4. In Japan the government accepts the OECD ruling that biotechnology does not require specific legislation. The assessments concerning the degree of containment necessary in Japan follow the OECD recommendations. Notification is voluntary but controlled by different ministries according to product group.

5. Australia has carried out an extensive survey of regulations around the world concerning genetically modified organisms and regulations are changing from a voluntary to a

notification/consent based system for both contained use and deliberate release. However the information required for an application for consent is appropriate to the product type.

6. The EC Directives 90/219/EC and 90/220/EC on which the UK regulations are based appear to be more stringent than those in place in the USA, Japan and Australia as they require more notifications and applications for consent, more questions must be answered in the risk assessment procedure and review times are often longer. In addition, in contrast to the USA regulations, the EC Directives have been implemented more slowly and procedures to amend the regulations are more unwieldy.

7. Implementation of the EC Directives within the member states has varied. Some countries such as Italy have simply incorporated the Directives into their own regulatory system with no changes. Other such as Germany and Denmark had very strict guidelines concerning genetically modified organisms before the Directives were put in place and so have implemented a somewhat more stringent system than that required by the Directive. Great Britain implemented a very sightly more demanding regime as they extended the contained use regulations to cover animals and plants as well as the micro-organisms specified in the EC Directives. Countries such as France, Belgium and possibly the Netherlands have put in place regulations that in some respects may be less exacting in practice than the Directives. The Netherlands is adapting existing product legislation to meet the requirements of the Directive. Belgium is said to be developing a sectorally based system which categorises GMOs into various types and only requests answers to those questions directly relevant to the type of GMO. In France the deliberate release regulations are applied by the ministry governing the appropriate sector.

COUNTRY PROFILES

Australia

Australia is known for its active support of the new biotechnologies in both the public and private sectors. Regulation of GMOs is currently changing from a voluntary to a statutory-based notification/consent approach. There is a commitment to avoiding dual regulation of products, though the release of a GMO product will require prior approval from the new Genetic Manipulation Authority (GMA). The scope of proposed regulation is unclear but could be restricted to GMOs which are "likely to pose a hazard".

Unusually, the GMA will be able to take account of ethical and philosophical issues.

CONTAINED USE

Regulatory authority

A voluntary notification and assessment system has been operated by the Genetic Manipulation Advisory Committee (GMAC), which has also produced guidelines for research and large-scale uses of GMOs. This is to be replaced by the Genetic Manipulation Authority (GMA) which will have legally defined powers to approve contained uses.

Regulatory structures and processes

The GMA will be advised by a new committee to replace GMAC. Institutional Biosafety Committees (IBCs) have been important in the initial vetting of proposals and monitoring of compliance with guidelines and will continue in this role. The government intends to introduce indemnity measures for IBC members.

DELIBERATE RELEASE

Regulatory authority and requirements

A voluntary, case-by-case assessment system operated by GMAC is being replaced by a statutory case-by-case approach operated by the GMA. Guidelines have been produced by the GMAC, in line with OECD recommendations, which were amended in early 1993. The regulations do not apply to the products of cell fusion (whereas some such plants are regulated under 90/220/EC).

Example:

> For one recent trial of a plant, which has an isolation distance of 1.6m, the GMAC required using a separation distance of 200m, which was considered by the company to be excessive. Monitoring requirements for another trial (oilseed rape) were equivalent to "good agricultural practice".

Regulatory structures and processes

A Genetic Manipulation Release Committee (GMRC) is to advise the GMA. IBCs have played a major role in the regulation and will continue their role in the initial vetting of proposals and monitoring.

Simplified procedures

Under the proposed new regulations, the GMA will be able to waive the requirement for notification "where the proposal is substantially the same as one previously considered". The GMA is requested to produce an annual report for Parliament and the regulatory system would be reviewed after seven years operation.

Fees

No fees currently charged.

Regulatory questions

The 1993 GMAC guidelines separate up the risk assessment questions according to the character of the GMO, though there are 34 core questions. For example, there are 14 questions for genetically modified (GM) plants and eight for GM biocontrol agents, or in total 48 and 42 respectively. However, many of the questions have sub-questions and if these are summed-up the total number for plants are 99 questions and for biocontrol agents 60 questions. There has been a general increase in the number of questions in the new 1993 guidelines, for example, the number of core questions increased from 23 to 34.

Time taken

One recent application was processed by GMAC in less than 90 days.

Public information

Under the voluntary system a public information sheet is prepared by the applicant. The statutory system will require notifications to be made public.

Public enquiry

Under the planned system, submissions on applications will be invited, though it is not clear from whom.

Views of industry

One company considers that the new GMAC guidelines has increased the bureaucracy, time-taken to comply with regulation and information requirements.

Belgium

Government attitude

Of the EC countries, Belgium is second only to France in terms of the number of releases of GMOs in its territory (BIA p 30) and has a particularly active plant biotechnology research and development community. The Government prefers sectoral regulation of GMOs and has apparently attempted to implement the EC deliberate release directive in this way (SAGB P 122, Monsanto P 241).

Regulatory authority

It is not clear which ministries and agencies have responsibility for implementing 90/219/EC and 90/220/EC, partly because of the ill-defined role of national and regional ministries. For past releases, the Department of Agriculture and Public Health gave formal consent. An *ad hoc* interdepartmental advisory group has considered regulatory issues. No national guidelines have been produced and NIH guidelines have been used in research.

Regulatory Procedures

There are no expert advisory committees.

Simplified procedures

The Belgian government has requested the introduction of simplified procedures for authorising the release of GMOs.

Fees

No fees as yet.

Public information

Information about the nature of the release, the researchers involved, and the size and location of the release site has been made publicly available.

Views of Industry

Monsanto states that the pragmatic regulatory approach of the Belgian authorities is "...extremely beneficial to the competitiveness of Monsanto, and therefore Belgium" though impending implementation of the Directives is "... proving to be less of an attraction for research-based activities, in the main because of the uncertainty coupled with the bureaucracy they bring" (Monsanto P 241).

Views of NGOs

One Antwerp-based group is campaigning against aspects of biotechnology.

China

Very little is known about regulation in China though apparently a large number of releases have taken place, including one full-scale "commercial" release. Indications are that there has been indirect regulation through the involvement of state research agencies in all releases and that international experts are consulted prior to releases.

Denmark

Government attitude

The Danish government has taken a pro-active stance to regulate the new biotechnologies, instituting the world's first "gene law" in 1986, which has since been modified two times. It has been a leading advocate of an exceptionalist, cautious approach to regulating GMOs and attempted (without success) to maintain its right to veto the releases of GMOs in Denmark in the deliberate release Directive.

CONTAINED USE

Regulatory authority

Regulations passed under the Working Environment Act control risks to occupational health and safety and are administered by the National Labour Inspectorate. Emissions from facilities constructing or using GMOs are controlled under the Environment and Gene Technology Act (EGTA), administered by the Ministry of Environment.

Regulatory requirements

Requirements are generally more stringent than required by 90/219/EC. For example, for Group II Type A work, approvals (rather than just notification) are required. Also self-cloned Group I type micro-organisms are not exempt as they are in 90/219/EC.

Example:

> Containment requirements for Novo Nordisk's production of human insulin from GM yeast are somewhere between OECD's GILSP and containment level 1, though nearer to level 1. Regulatory requirements have relaxed since manufacture was begun in 1987, eg the permitted levels of emissions have been raised from 10^2 viable organisms per ml to 10^4 per ml and the original requirement for HEPA filtering of excess gas has been relaxed[1].

Fees

The maximum fee is 150,000 DDK (approximately £15,000) but usually less.

Regulatory structures

There are no expert advisory committees or IBCs.

Enforcement

Inspections are carried out by both the National Labour Inspectorate and County Councils.

Review time

Review times were originally up to two years long but have now been reduced on average to 2-4 months, though review times are limited to 60 days in the revised law.

Public information

Under the Freedom of Information Act, summary information on authorizations is available, including quantitative levels of emissions permitted. Decisions by the Environment Ministry are advertised in newspapers.

Public enquiry

Under the EGTA complaints against authorizations may be made by named organisations or by any person who has "an individual and considerable interest in the outcome of the case".

Views of industry

Novo Nordisk argues that its competitiveness was damaged in about 1986 when the Danish authorities delayed start-up production of human insulin and human growth hormone. However "since then things have much improved and presently we consider the burdens upon us in Denmark as technically equivalent to those found in the rest of the EC, USA and Japan". The company has stated that its interactions with the regulatory authorities were mostly positive. Novo Nordisk also argue that confidence of the public in Danish regulations and in the companies involved has led to public acceptance of the new biotechnologies (Novo Nordisk A/S p 140)

[1] Dr E Rasmussen, Diabetes Care Division, Novo Nordisk A/S.

Views of NGOs

Environmental groups appealed (unsuccessfully) against the first four authorizations for industrial use of GMOs, but they appear to have turned their attention away from contained uses of GMOs.

Evidence of adverse effects

Novo and Nordisk (before their merger) both claimed that adverse regulations in Denmark were influencing decisions over the siting of manufacturing operations and in 1988/89 Novo set up a plant manufacturing lipolase in Japan.

DELIBERATE RELEASE

Regulatory authority

The EGTA originally prohibited the release of GMOs unless specifically exempted by the Environment Minister. This has been revised to a case-by-case consent approach in line with 90/220/EC. The implementing agency is the Environment Ministry.

Regulatory structures

There are no expert advisory committees or IBCs. The MoE is advised by its own specialist ecological agencies.

Fees

The maximum fee is 200,000 DDK (approximately £20,000) but usually less.

Public information

A notice of application to release a GMO must be placed in a local newspaper. Summary information on each release is publicly available.

Public enquiry

Prior to the approval of a release of a genetically modified sugar beet in 1989, the Parliament was consulted. A public hearing was also held at the site of the release. The Danish Board of Technology have initiated quite extensive biotechnology assessment projects. Under the revised law a public hearing is held prior to each release, at which environmental groups may make representations. A provisional decision is passed on to the Parliamentary Environment Committee and the final decision issued by the Environment Minister.

Views of industry

Industry was generally been opposed to the moratorium on releases.

Views of NGOs

The environmental group NOAH has been the most active in campaigning on genetic engineering issues but has recently turned its attention to patenting, development and wide issues of the environmental consequences of high-yield, high-input agricultural systems. Development of herbicide resistant plants has caused particular anxiety in the environmental groups.

France

Government attitude

The French government has increasingly supported agricultural biotechnology and it is second only to the USA in its popularity as a site for field trials of GMOs (BIA p 30). It is strongly in favour of regulating GMO products within product sectors, though the Environment Ministry is more in favour of a horizontal approach. Many parts of the government were in fact informally opposed to the passing at the Environment Council of 90/219/EC and 90/220/EC.

CONTAINED USE

Regulatory authority

A Law was passed in 1992 which partially implements the Directives and regulations are now being devised. The Ministry of Research is responsible for controlling research, whilst the Ministry of Environment leads on environmental aspects of contained use.

Regulatory requirements

According to the French Embassy specific consents are now required for all contained use applications, which would imply a more stringent approach than required by 90/219/EC. Prior to the 1992 law, a voluntary system for registering research was in place, whilst industrial-scale operations were regulated under the Environment Ministry's emissions law.

Regulatory procedures

The Commission on Genetic Engineering (CGG), based within the Ministry of Research, advises on contained use applications. The CGG has produced guidelines.

Fees

Fees for licences are apparently higher than in the UK.

Views of industry

Industry was opposed to 90/219/EC. One major pharmaceutical company estimates that the new regulations will increase the cost of R&D by at least 30%[1].

DELIBERATE RELEASE

Regulatory authority

Under the new law of 1992, the Ministry of Research is responsible for regulating all releases of GMOs for R&D purposes. GMOs intended for marketing as products will be regulated by the appropriate sectoral ministry (usually Ministry of Agriculture) and where there is no existing sectoral authorities the Ministry of Environment is responsible. This builds on a voluntary, case-by-case assessment scheme administered by the Agriculture Ministry.

Regulatory requirements

According to one company, the documentation required prior to releasing a GMO in France has been half that needed for the UK due to fewer questions, less repetition and less irrelevant information being requested.

Regulatory structures

The existing Commission on Biomolecular Genetics (CGB), based in the Agriculture Ministry, will advise the appropriate sectoral marketing committee (AMM) on releases of GMOs.

Simplified procedures

The French Government has requested that the Commission institute a simplified procedure for authorising the release of certain GMOs.

Fees

Under the current system there is no charge from the CGB but the advice of an expert has to be taken costing 3000FF - 5000FF (£375 - £625).

[1] C. Kathuri el al, 'Biotechnology in an Uncommon market' Bio/Technology, pp1545-1547, **10**, 1992.

Risk assessment questions

The current French form is nine questions long. The focus of risk assessment is on agronomic and nutritional aspects, eg on the precise character of the inserted DNA, rather than on the possible ecological risks. Whether and how the number and focus of risk assessment questions will change remains to be seen.

Review time

France has been the quickest of EC countries in responding to release applications.

Example: Zeneca's trials with maize approved in 40 days.

Public information

Until the 1992 law, provision of information to the public was entirely at the company's discretion.

Views of NGOs

No environmental groups/NGOs have taken up the issue of the new biotechnologies.

Germany

Government attitude

Germany has experienced more hostility from environmental groups and NGOs towards the new biotechnologies than any other country. Partly in response to this, a comprehensive Gene Law was passed in 1990 but seems not to have been fully successful in creating a framework in which the new techniques can be (albeit cautiously) applied. Industrial uses of GMOs have been delayed and very few releases of GMOs have taken place (BIA p 30), both of which are in contrast to Germany's scientific and industrial strengths.

CONTAINED USE

Regulatory authority

The Gene Law is implemented by state authorities, of which there are over 20. There appears to be considerable variation in the states' regulation and a group of experts has been set up to harmonise assessment procedures. The Workers Insurance Association for Chemical Industry (BG-Chemie), together with the Labour Ministry, has responsibility for occupational health and safety in the biotechnology industry and has issued guidelines. IBCs are an important part of the regulatory approach.

Regulatory requirements

The Gene Law establishes four safety levels and four containment levels, equivalent to the GILSP and containment levels 1 to 3 of the OECD. Its notification/consent requirements are more stringent than those of 90/219/EC. For example, prior notification of 3 months is required for Group I Type A work (cf. requirement from HSE for annual notification), whilst a permit is required for Group I Type B work with review time of three months (cf. 60 day prior notification required by HSE). The criteria for classifying a microorganism as low risk (Group I) are more stringent in 90/219/EC than in the German law. For example, the Directive requires that the agent has a "proven and extended history of safe use", whilst the German Gene Law requires "experimentally proven or extended history of safe use". This may have to be revised to comply with 90/219/EC.

Examples:

(i) Prior to the Gene Law Hoechst built a plant near to Frankfurt producing human insulin using *E.coli* to the highest containment level (equivalent to OECD's level 3). Very similar production processes were contained in facilities built to the GILSP level of containment in the USA or between GILSP and level 1 in Denmark.

(ii) Hoechst's laboratories at the same site have been built to containment level 2 (equivalent to OECD's level 1) but the Hessen authorities have decreed that under the Gene Law the company cannot use them for pathogenic microorganisms without going through an approval process, which the company fears will be lengthy and costly.

(iii) The Hessen authorities unlike other state authorities, have interpreted the 10 litre volume of work as the key criterion for classifying work as commercial rather than research. All fermentation work at volumes over 10 litres therefore requires approval as production plant.

Despite the above, Hoechst considers the containment requirements (as opposed to the bureaucratic hurdles) for industrial large scale operations with *E. coli* K12 and yeast (with non-transferable plasmids) to be equivalent across industrialised countries[1].

Regulatory procedures

Some states have established advisory committees. The states are also obliged to heed the advice of the Central Commission for Biological Safety (ZKBS) and the Federal Health Office (BGA).

Simplified procedures

When used in R&D, microorganisms classified as safety levels 2 to 4 may be treated as safely level 1 agents provided that experience has shown that they may be treated as safety level 1 organisms. This provision may have to be removed to comply with 90/219/EC. There is apparently a consensus amongst the major political parties in the Parliament that the Law has to be changed in order to simplify it and reduce the regulatory burden.

Enforcement

Inspections are conducted by the state authorities and by the BG-Chemie.

Fees

Authorisation fees are apparently higher than in the UK.

Review times

Review times are generally one month longer than required in 90/219/EC, but may well be longer in practice. Although there are legal provisions to react to the laggardness of authorities, companies decline from creating an unfavourable relationship with the authorities or risking alienation from the public by invoking them.

Example:

According to Hoechst, for applications which should be processed in no longer than 2 to 3 months, the Hessen authority are taking 8-12 months.

Public information

Information beyond that specified by 90/219/EC has to be made available for commercial facilities using high risk agents.

Public enquiry

For commercial work conducted in safety levels 2-4 (equivalent to Group II Type B operations) there is the opportunity for a public hearing to be held. There is also opportunity in some cases for objections to be filed in an administrative Court.

[1] Dr D. Brauer, Hoechst AG, Personal Communication

Liability and insurance

Strict liability applies to operators of facilities using GMOs to the level of DM 160 million (£62 million). Liability cover must be arranged by operators of facilities at safety levels 2 to 4.

Views of industry

There is much criticism of the German Law from industry, though in the late 1980s it supported the passing of the law. The general complaint is that regulation creates unnecessary and costly bureaucracy and requirements, which slows down research and development and production.

Example:

> Bayer point out that 95% of biotechnology research in Germany takes place at safety levels 1 & 2 and argue that: "These two levels of no or negligible risks are under heavy administrative control and produce bureaucratic burdens that significantly inhibit scientific progress" (Bayer p 14).

Opinion of NGOs

There have been active coalitions of individuals, the Greens, the Gene-Ethics Network and local environmental groups opposed to construction of biotechnology plants. They have frequently stalled or slowed down such projects. Their opposition has been based on possible ecological risks but also on their perception that decision-making has not been sufficiently participative.

Evidence of adverse effects

Several Germany firms have located R&D and production facilities in Japan and the USA partly, they claim, for regulatory reasons.

Examples:

(i) Boehringer Mannheim has decided to produce a new therapeutic protein in Ireland, probably due to a more favourable regulatory environment and attractive benefits and subsidies from the Irish Government.

(ii) Bayer decided to produce factor VIII at Berkeley, USA rather than at Wuppertal in Germany. This was because "legal and general conditions and the chances to achieve an approval of a production facility in a foreseeable time frame was significantly better in the United States than in Germany" (Bayer p 15).

(iii) Hoechst is now developing facilities in the United States, Japan, Australia and France rather than in Germany, partly because of regulatory issues. It has stated that future funding will be directed towards these overseas sites .

Deliberate Release

Regulatory Authority

The Federal Health Office (BGA) grants licences for deliberate release of GMOs, either in research or as final products. IBCs carry out an initial assessment of the application.

Regulatory requirements and procedures

The BGA is advised by the expert advisory committee, the ZKBS. Before making its decision, the BGA has to come to an agreement of understanding with the Federal Environment Office (UBA) and, for agricultural, forestry or veterinary GMOs, with the Federal Biological Office (BBA).

Review time

Review of the MPI Plant Breeding's application to release GM petunias took over one year.

Public enquiry

A public hearing must be held to discuss each application to release a GMO.

Liability and insurance

Strict liability up to DM 160 million (£62 million) and compulsory insurance, as for contained use above. The Commission of the EC considers this measure to go beyond the requirements of 90/220/EC.

Views of NGOs

Most environmental groups in Germany are opposed to the deliberate release of any GMO, at least until very thorough tests have been conducted in laboratories or microcosms. The opposition often relates, however, to genetic engineering *per se*.

Evidence of adverse effects

The small number of releases of GMOs in Germany clearly reflects an unfavourable context for such research in that country. The recent approval of five new outdoor trials of GMOs, and of a genetically engineered live animal vaccine, may suggest some change in perceptions.

Italy

The Directives have been incorporated into Italian law by Decrees, though this does not imply that the law will be implemented or enforced in practice. A Scientific Committee for Biosafety has, however, been set up recently, attached to the presidency of the Council of Ministers (Cabinet).

Japan

Government attitude

The Japanese Government accepts the OECD's (1986) opinion that there is no scientific basis for specific regulation of biotechnology (Japanese Embassy P 238). It is relying on voluntary regulation and use of guidelines, developed by the appropriate sectoral divisions. It favours regulating GMOs to be marketed as products by sectoral regulations. There are, however, some differences within government with the Environment Agency producing a White Paper in 1991 arguing for a move towards statutory regulation of GMOs. It was shelved following intense lobbying from Ministries.

CONTAINED USE

Regulatory authority

Since regulation is voluntary there is no legal authority as such. However the following agencies are responsible for producing guidelines and advising on different activities:

Ministry of Education: control of research in national and private universities.

Science and Technology Agency (STA): control of laboratory scale (< 20 litres) research in national and private institutes.

Ministry of Health and Welfare (MHW); Ministry of Agriculture, Fisheries and Forestry (MAFF), Ministry of International Trade and Industry (MITI): control of industrial applications.

Regulatory principles and guidelines have been based entirely on the OECD's 1986 report. A research programme can, apparently, fall into the jurisdiction of more than one authority. There is no body attempting to co-ordinate the various regulatory authorities.

Regulatory requirements

The research guidelines are based on NIH guidelines but have been revised more slowly than in the USA, so tend to be somewhat more stringent. Routine experiments do not require prior approval, whilst some 'non-standard experiments' do.

Views of industry

Industry has called for the consolidation of the different sets of guidelines, but no change is likely in the near future.

Views of NGOs

There has been some opposition by local groups to the construction of contained use facilities.

DELIBERATE RELEASE

Regulatory authority

MAFF supervises the safety evaluation prior to the release of GMOs. It issued guidelines for GM plants in 1989 and guidelines for GM animals are in preparation. STA has also been involved in producing guidelines for GM plants and micro-organisms. For GM microorganisms, the Environment Agency has prepared guidelines. Guidelines adopt OECD's principles of case-by-case, step-by-step assessment of field trials. Despite the voluntary approach, however, there have been very few releases of GMOs in Japan (see BIA p 30), though MAFF has extensively tested a recombinant DNA tomato.

Regulatory procedures

The Environment Agency has established an Experts Group on Biotechnology and Environmental Protection to consider general issues such as monitoring and environmental problems. This group has produced a number of reports.

Netherlands

Government attitude

The Dutch Parliament has rejected an all-encompassing regulatory regime for the new biotechnologies. The Government is adapting existing legislation to the task of regulating GMOs and favours the 'one door/one key' principle.

Regulatory authority

Some parts of 90/219/EC are to be implemented in a law to be passed in the summer 1993. The Nuisance Act and Chemical Substances Act are currently used to regulate the contained use and deliberate release of GMOs. Guidelines on large-scale industrial use and deliberate release have been prepared, based on the OECD 1986 report.

Regulatory requirements

The Dutch have not used the classification of Group I and Group II microorganisms but have used categories for containment such as 'Good Microbiological Practice' and GILSP.

Simplified procedures

The term 'limited period' used in the deliberate release Directive for the duration of a single notification system for multiple releases has been interpreted to mean a period of up to five years. The Dutch Parliament intend to review how regulation is developing in 1994 in the light of experience.

Views of NGOs

Several NGOs are actively campaigning on the genetic engineering issue and there have even been some direct attacks on fields of genetically modified plants.

Evidence of effects on competitiveness

Of United States companies choosing to locate in the EC, many have chosen the Netherlands, eg Synergen, EuroCetus and Centocor. This is widely perceived as being for regulatory and tax inducement reasons.

Portugal and Spain

Regulatory authority

According to the Commission of the EC, Portugal has now implemented the Directives. There is currently no specific regulation of contained use or deliberate release of GMOs or guidelines in Spain However the Spanish Government research departments and agencies and universities have undertaken some self-regulation of work with GMOs. There is a Government Expert Committee on the risks of biotechnology. The OECD guidelines have been reviewed by a range of Spanish ministries.

Regulatory procedures

No IBCs required as yet though some companies have their own policy of using IBCs.

Fees

No fees charged as yet.

Review times

In practice for one company, about 90 days.

Switzerland

Government attitude

In 1992 a new article of Federal Constitution requires government to develop legislation to control genetic engineering. The government decided against a comprehensive law, favouring adaptation of existing laws and rules. The extent to which the EC's Directives will be implemented is unclear.

Regulatory authority

The Swiss Interdisciplinary Commission for Biological Safety in Research and Technology has been responsible for issuing guidance on work with GMOs, based on NIH and OECD guidelines.

Views of industry

Hoffmann la Roche argues that regulations based on 90/219/EC will introduce longer waiting periods and unnecessary additional bureaucracy for research projects with low risk (Group I Type A) (Hoffmann-La Roche Ltd p 105)

Views of NGOs

Several NGOs are campaigning specifically on genetic engineering (Basel Appeal Against Gene Technology, Swiss Working Group on Gene Technology). In 1992 Swiss Greenpeace attempted to occupy fields where GM potatoes were being tested. These groups want more public debate and more open decision-making, tighter federal law and a moratorium on releasing GMOs until the risks are clearer. The opposition, however, is concentrated in German-speaking Switzerland.

Evidence of adverse effects

Ciba-Geigy recently built a new biotechnology plant in Huningue (France) rather than in Basel because, it claims, of regulatory difficulties in Switzerland, spurred by opposition from several environmental groups (Ciba Pharmaceuticals p 63).

United States of America

Government Attitude

The USA is the world leader in scientific and technical development of the new biotechnologies witnessed, for example by the number of new biotechnology companies, inward investment and deliberate releases of GMOs (BIA p 30). The American Government has strongly advocated that regulation should be based on demonstrated risks and not turn on the fact that an organism has been modified by use of particular processes. It favours voluntary or statutory regulation of GMOs in research and development, production and at marketing, under sectoral divisions: the wide-spread applications of GMOs precluded a "unitary, statutory approach."

Contained Use

Regulatory Authority

A voluntary registration and notification system is operated by the National Institutes of Health (NIH). For federally funded research, the procedure is obligatory. NIH guidelines are used. NIH has an expert recombinant DNA Advisory Committee (RAC) to review higher risk and other categories of federally funded research. Assessment of lower risk experiments is conducted by the IBCs, which are a long standing and important part of the regulatory system. The Department of Health and Human Services and Food and Drug Administration (FDA) have some responsibility for industrial applications and the Centre for Disease Control (CDC), FDA and NIH have issued guidelines on industrial practices, equipment and facilities which take into account the 1986 OECD report. The Occupational Safety and Health Administration announced in the 1986 Coordinated Framework that no new regulations appeared to be necessary for laboratory workers but it issues general safety standards.

States may enact additional regulation within certain limits, for example, California regulates the movement of GMOs for use in industrial operations within the state through issuance of special permits and inspection of the receiving laboratory. Likewise some city authorities (Cambridge, Berkeley and Worcester) have introduced regulations which require universities and industry to observe NIH guidelines. Permits are also required in these cities for large-scale operations; they are usually obtained within 30 days.

Regulatory Requirements

Certain experiments require the review and approval of the RAC and NIH, most importantly the construction of GMOs containing the genes for biosynthesis of toxic molecues, though RAC's major reviewing function is now devoted to somatic gene therapy experiments. Other experiments require the approval of the IBC, but can usually be initiated a few days after filing the registration[1]. A third category is experiments which must be notified to the IBC but can be initiated straightaway, whilst other experiments, for example those involving self cloning are exempt from control. There is no requirement for notification of these experiments to NIH or any other authority besides the IBC. The Government has stated that the appropriate large scale (greater than 10 litres) containment requirement for many low risk GMOs is no greater than those appropriate for the unmodified parental organism. Four containment categories are in operation with the GILSP category used extensively. According to the NIH guidelines there should be a Biological Safety Officer (BSO) at large scale facilities and a health surveillance programme for personnel engaged in higher risk large scale work. There are no specific regulatory requirements (design standards) for construction of facilities for GMO operations. A variety of permits are required for constructing a laboratory or factory but these are no different from those required for bacteriological, immunological or chemical operations (except in the aforementioned cities in which an additional permit is required). FDA require assessment of containment conditions (with respect to environmental, workers' health and

[1] D. Brauer and H.D. Schlumberger. 'The US system for the regulation of recombinant DNA operations in research, development and production', unpublished manuscript 1993.

product protection) for all production facilities over 10,000 square feet in size that are involved in producing foods and drugs whether they are GMOs or not.

According to the NIH guidelines, prior to receiving GMOs from another centre an investigator must have approval from the IBC. GMOs must be labelled and packaged following NIH guidelines before transportation.

Example:

> Under the NIH scheme, no notification is required for a GMO expressing a non-toxic gene in a disabled host with a poorly mobilisable plasmid under 10 litres. Under 90/219/EC this would be classed as a Group 1 Type A operation and require annual notification. For such a GMO used over 10 litres in the USA, a registration document needs to be lodged with the IBC, but no further containment than that required by GILSP is needed. Under 90/219/EC this would be classed as a Group 1 Type B operation and would require 60 days prior notification. Higher levels of containment would only be required in the USA if the GMO is a pathogen or expresses a toxic gene product.

Regulatory Procedures

Approximately 50% of firms conducting rDNA research have voluntarily registered their IBCs with the NIH and apparently follow the NIH guidelines more closely than public sector organisations.

Public Enquiry

None except that required by local law. For example until recently a public hearing was required in Cambridge, Massachusetts, prior to issuing a permit for the large scale use of GMOs.

DELIBERATE RELEASE

Regulatory Authority

A variety of departments and agencies are involved in regulating deliberate releases.

(i) US Department of Agriculture

Plants

USDA regulation in this area is administered by the Animal and Plant Health Inspection Service (APHIS). APHIS regulates, through issue of permits of various kinds under the Act, all plants constructed using a plan pathogen for example *Agrobacterium*. This does not necessarily cover plants constructed using biolistic methods. GM plants produced by these techniques would not require permits though federal funded research work would be reviewed under NIH and USDA guidelines. APHIS also issues permits for release, import and movement of GM Plants from one state to another under the Federal Plant Pest Act (FPPA) and Plant Quarantine Act (PQA) for plants containing pathogenic sequences. Such a permit usually covers multiple shipments. It also operates a 30 day notification system for the inter-state transport of other GM plants. Prior to marketing a GM plant must be granted a non-regulated status under the above laws through a petition procedure, though it is currently not clear what data would have to be submitted in support of the petition. In the one case so far, Calgene's flavr-savr tomato, APHIS published a notice of an application for non-regulated status in the Federal register, allowing 60 days for public comment, and consulted with other federal agencies and responded to the application in 180 days. Plant GMOs constructed through self cloning are not covered by this regulation but a procedure of voluntary notification and 'letter of agreement' from APHIS is issued. APHIS inform the state authorities of intended field trials.

For plants containing pesticidal genes, for example *Bacillus thuringiensis*, an analysis is required under the National Environment Protection Act (NEPA) and may result in a full Environmental Impact Statement. EPA and FDA are involved in regulating such plants.

Animals

USDA controls the release of GM animal through issuing permits. Animals considered to be plant pests could also be controlled under the FPPA. GM animals derived from infectious, contagious, pathogenic or oncogenic organisms could be subject to regulation under the Animal Quarantine Statute and the Virus-Serum-Toxin Act. Federally funded releases of GM animals would be regulated by NIH guidelines.

Fish

There is currently no clear control over GM fish, though the USDA operates a voluntary system of review, advised by its Agricultural Biotechnology Recombinant DNA Advisory Committee (ABRAC) which has been followed by the few known applications in this field.

Vaccines

USDA regulates animal vaccines under the Virus-Serum-Toxins Act.

(ii) US Environmental Protection Agency (EPA)

Plants

Under the "coordinated framework", EPA is consulted for its view under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) regarding any plant with pesticidal activity. EPA intend to introduce regulations under FIFRA on such plants later this year.

Micro-organisms

EPA regulates, or intends to regulate GM microorganisms under the FIFRA and Toxic Substances Control Act (TSCA). Under FIFRA all microorganisms sold as pesticides must be registered by EPA and conditions may be applied. The Act also requires the issue of an Experimental Use Permit (EUP) for research and development work on site of over 10 acres. EPA has now made acquisition of EUPs for all research trials with GM organisms obligatory, having operated a voluntary scheme for a number of years. EUPs are issued within 120 days. EPA uses two regulatory categories for small scale trials (less than 10 acres); level I notification is 30 days and level II notification is 90 days (for GM pesticides derived from source organisms that are pathogenic or non indigenous pathogenic microbial pesticides) as well as the large scale testing category, which requires an EUP. In practice all small scale tests of GM pesticides have so far been classified as level II.

In the US the toxicology and ecological/environmental data required to register a biopesticide is relatively simple compared to that required for a new chemical pesticide, whilst in the EC data requirements are similar. This US-EC difference is likely to be reflected and accentuated in the regulation of GM pesticides.

EPA intends to regulate other GM microorganisms under TSCA, a gap-filling law. Firms are required to supply EPA with information on the characteristics of any new chemical 90 days before commercial manufacture begins. Whilst it devises the regulations EPA has requested voluntary compliance with its policy of considering GM microorganisms not regulated by FIFRA to be controlled by TSCA. To comply, pre-manufacture notifications (PMNs) are required for intergeneric microorganisms (unless the transferred DNA is well characterised and non-coding). This also applies to experimental field tests. The PMN must contain an environmental risk assessment. Within 5 days of receiving a PMN the EPA must issue an announcement in the Federal register. If at the end of 90 days EPA has taken no action, the manufacturer may proceed with the use of the microorganism.

If GM microorganisms are plant pesticides they are subject to the PPA and PQA and consultation between EPA and USDA comes into operation. Prior to marketing, a petition for non-regulated status under the above laws would have to be submitted to the USDA.

EPA's legal position in using the TSCA is unclear. Also it is a notification rather than a licensing statute and the burden of proof lies with the Agency not the applicant. TSCA applies to

all commercial chemicals not just hazardous ones so it extends regulations outside the risk-based approach.

(iii) National Institutes of Health

Under NIH guidelines all deliberate releases of GMOs for research and development purposes, except for certain plants, require review and approval by the RAC, NIH and IBC. Furthermore any experiment which might involve the transfer of a drug resistant trait to microorganisms which are not known to acquire it naturally and which could compromise the use of the drug in human or veterinary medicine, has to be approved. It is not known how this last requirement is interpreted in practice. Whilst NIH guidelines apply to federally funded research compliance with them is voluntary for the private sector.

(iv) States

Some States have introduced their own legislation. In Minnesota a law was passed in 1992 controlling GMOs horizontally. The law requires application for consent, review by an advisory committee, public notice and fees to be payable, but exemptions are granted if a Federal permit is held. In North Carolina the Genetic Engineering Review Board are preparing detailed regulations to be used by the state Department of Agriculture when evaluating field trials. Although the North Carolina law adds a new level of review it does not impose any additional data requirements upon researchers. The states of Hawaii, Illinois and Wisconsin require notification to the state authority before release of GMOs into the environment.

Regulatory requirements

The actual risk assessments for GM plants are conducted by APHIS based on information on the plant and experimental protocol provided by the applicant as well as the agency's experience.

Regulatory procedures

USDA's ABRAC has an advisory role but no statutory authority. It produced guidelines in 1991. Submissions to ABRAC are voluntary.

Simplification procedures

A single application may be submitted for releases of the same plant in more than one state, the releases having to start within one year of the granting of the permit. In one case 50 field trials were conducted under one application.

USDA now has a notification system for release of certain GM plants which requires 30 days notice. This applies to maize, cotton, potatoes, soyabean, tobacco and tomato which have been modified by insertion of certain genes. The trials site can still be quite large, for example in one case 30 acres. There is still to be a commitment to supply annual test reports and reports on any adverse effects as well as to provide access to sites and records to APHIS and state officials.

Enforcement

Unlike the other countries examined here, two unauthorised releases of GMOs into the environment have taken place in the USA, but with no ill effect.

Fees

USDA and EPA do not charge any fees.

Regulatory questions

The APHIS permit form for GM plants has approximately 14 questions. The application forms are typically 15-20 pages long[1]. Under the new notification scheme a two page notification form is to be submitted to APHIS.

[1] D. Brauer and H.D. Schlumberger. 'The US system for the regulation of recombinant DNA operations in research, development and production', unpublished manuscript 1993.

Review times

APHIS aims to respond to applications in 120 days but it often does so more quickly. The new notification scheme requires 30 days. APHIS responds to an application for non-regulated status for a plant (prior to marketing) within 180 days. EPA responds to requests for EUP/s in 30-120 days depending on the level of associated risk whilst it responds to PMNs within 90 days.

Public information

It is the practice of US agencies to publish notice of every application for release or marketing of a GMO. The agencies also publish their risk assessments. Permits for release of GMOs are published in the Federal register giving information on the applicant, the recipient organism, the coding gene and the state in which the release will take place.

Public enquiry

None except that required under local laws. Under the North Carolina legislation a public hearing may be carried out on a deliberate release application if scientific questions are filed by the public. This has occurred in two or three cases.

Views of NGOs

Environmentalists have argued for a horizontal approach. Use of TSCA has been criticised because it will not apply to academic research and the EPA, rather than the applicant has to demonstrate the burden of proof. There have been some specific protests against releases of GMOs in 1986 and 1987 in California and Missouri respectively, but opposition appears to have turned to foods derived from GMOs.

Evidence on effects on competitiveness

SAGB estimated that in 1989 EC firms invested $234 billion in biotechnology in the USA. US firms only invested $15 million in the EC. Many major European firms have invested heavily in the US biotechnology sector eg Hoffmann La Roche, Schering AG, Sanofi, Ciba-Geigy, Glaxo, Hoechst, Bayer and BASF.

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[1] *Biotechnology in a Global Economy*, US Congress, Office of Technology Assessment, 1991

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APPENDIX 5

Acronyms

ABPI	Association of the British Pharmaceutical Industry
ACGM	Advisory Committee on Genetic Modification
ACOST	Advisory Council on Science and Technology
ACRE	Advisory Committee on Releases to the Environment
ADA	Adenosine deaminase
AFRC	Agricultural and Food Research Council
APHIS	Animal and Plant Health Inspection Service (US)
BBL	British Bio-technology Limited
BCC	Biotechnology Coordinating Committee (EC)
BIA	BioIndustry Association
BIGRAG	Biotechnology Industry Government Regulatory Advisory Group
BJAB	Biotechnology Joint Advisory Board
CBI	Confederation of British Industry
CEST	Centre for Exploration of Science and Technology
CEFIC	European Chemical Industry Council
CIA	Chemical Industries Association
COPUS	Committee on the Public Understanding of Science (Royal Society)
DNA	Deoxyribonucleic Acid
DOE	Department of the Environment
DTI	Department of Trade and Industry
EPA	Environmental Protection Agency (US)
ESRC	Economic and Social Research Council
FAWC	Farm Animal Welfare Council
FDA	Food and Drug Administration (US)
GILSP	Good Industry Large Scale Practice (OECD)
GLSP	Good Large Scale Practice (ACGM)
GMAG	Genetic Manipulations Advisory Group
GMO	Genetically Modified Organism
GMP	Good Microbiological Practice (GMAG/ACGM)
HSE	Health and Safety Executive
HUGO	Human Genome Organisation
IBC	Institutional Biosafety Committee
IPMS	Institution of Professionals, Managers and Specialists
MAFF	Ministry of Agriculture, Fisheries and Food
MRC	Medical Research Council
NERC	Natural Environment Research Council
NGO	Non-Governmental Organisation
NIH	National Institutes of Health (US)
NRA	National Rivers Authority
OECD	Organisation for Economic Cooperation and Development
PCR	Polymerase Chain Reaction
RAE	Royal Academy of Engineering
RCEP	Royal Commission on Environmental Pollution
rDNA	Recombinant DNA
RNA	Ribonucleic Acid
SAGB	Senior Advisory Group on Biotechnology
SASA	Scottish Agricultural Science Agency
SERC	Science and Engineering Research Council
SME	Small and Medium Sized Enterprises
USDA	United States Development Agency

APPENDIX 6

Glossary

Amino acid	The chemical building blocks of proteins. There are 20 naturally occurring amino acids.
Antibodies	A special protein molecule made by the immune system to defend the organism from infection or invasion by any foreign proteins. Monoclonal antibodies are very pure forms of single types of antibody.
Antigen	A generic term for a molecule with which an antibody reacts.
Bacteria	Unicellular microorganisms containing a single chromosome.
Cell	The structural and functional unit of all living organisms. Bacteria and algae consist of just one cell. Larger organisms are multicellular allowing specialisation of cellular function.
Chromosomes	A large molecule of DNA together with associated proteins. The DNA strand consists of a series of genes strung together linearly with non-genic regions interposed. The number of chromosomes present in a cell is characteristic of a species. Humans have 23 pairs of chromosomes per cell.
Chymosin	An enzyme used to clot milk in cheese making.
Cytoplasm	The part of the cell surrounding the nucleus which contains the site for manufacturing proteins - the 'factory' portion of the cell.
DNA	Deoxyribonucleic acid. A ladder-like helical double-stranded molecule made up of nucleotides which form the genetic code instructing the cell to manufacture proteins.
Enzymes	These are proteins which facilitate the specific processes necessary for a cell's functioning. The enzyme is itself unchanged at the end of the process. In genetic modification restriction enzymes are used to cut DNA chains at specific sites and ligation enzymes are used to 'stick' the ends together again.
Escherichia coli	(E. coli). A bacterium found in the gut of humans and animals which is normally involved in the digestion of particular sugars. While some strains may be pathogenic, those used in genetic manipulation are harmless. Laboratory strains of these bacteria are frequently used to produce recombinant proteins.
Factor VIII	A component of blood essential for clotting. This component is deficient in haemophiliacs.
Genes	Segments of the DNA strands which consist of anything from tens of bases to tens of thousands of bases. A single gene carries the instructions necessary for manufacturing a particular protein.
Gene therapy	The introduction of new normal genes into the cells of humans or animals in order to cure an inherited disease. In humans only somatic (body) cell gene therapy is permitted; the change would not be passed on to descendants.

Genome	All of the DNA contained in a single set of chromosomes of an organism.
Germ cells	Cells that divide to produce sperm or eggs.
HEPA filter	High efficiency particulate filter used where high levels of containment are required.
Hormones	Chemical messenger molecules which are manufactured and secreted into the bloodstream in small quantities to regulate specific biological processes elsewhere in the organism.
Immune system	The mechanism of an organism which combats infection.
Interferon	A term covering the types of molecules produced by a cell as a response to virus infection which temporarily interferes with the growth of the virus in that or nearby cells.
Marker sequences	A sequence of nucleotide bases which can be attached to a gene or the genetic material of a particular organism to trace its whereabouts.
Nucleotides	These are the building blocks from which nucleic acids (DNA and RNA) are made. They consist of a sugar with an attached coding unit (a base) and a phosphate group. In DNA the bases are adenine (A), cytosine (C), guanine (G) and thymine (T). In RNA uracil (U) replaces thymine.
Nucleus	The part of a cell where the DNA resides, separated from the cytoplasm by a nuclear membrane.
Oncogene	A gene which is involved in causing cancer.
Pathogen	A virus, bacterium or other infective agent that causes disease.
Plasmid	A small piece of DNA, often of bacterial origin, capable of self replication within a cell independently of the DNA in the nucleus. Plasmids are frequently used as vectors in genetic modification.
Proteins	These are complex, often very large, molecules composed of amino acids which perform most of the cell's work. They include enzymes, hormones, antibodies, receptors and structural molecules like collagen.
rDNA	Recombinant DNA. DNA that has been modified by joining together different pieces of DNA using new techniques of genetic modification.
Ribosomes	Small, particulate entities within the cytoplasm which attach to messenger RNA and translate that message into a particular amino acid sequence. Ribosomes are the 'protein factories' of the cell.
RNA	Ribonucleic acid. A single stranded molecule otherwise similar to DNA. Different sorts of RNA have different functions. Messenger RNA is a working copy of the genes.
Solanine	A toxic chemical present in a group of plants including the potato.
Somatic cells	All body cells except the germ cells. Changes in these cells are not inheritable.
Transgenic organism	These are animals or other organisms which have received additions of parts of the genetic code of other species, eg to cause them to produce human hormones. The new genetic information will be passed on to the offspring.

Vaccine	A substance that confers protection against a pathogen. The vaccine is sufficiently similar to the pathogen to produce a response from the organism's immune system but does not cause an acute form of the disease.
Vector	The 'tool' used to transport recombinant DNA into a host cell.
Virus	The simplest, smallest form of life. Viruses are incapable of replicating themselves and so attack host cells causing them to produce copies of the virus.
Yeast	A group of unicellular fungi widely used in brewing and baking.

APPENDIX 7

List of witnesses

The following witnesses gave evidence. Those marked * gave oral evidence.

* Advisory Board for the Research Councils (ABRC)
* Advisory Committee on Genetic Modification (ACGM)
* Advisory Committee on Releases to the Environment (ACRE)
* Agricultural and Food Research Council (AFRC)
* Agricultural Genetics Company Ltd
* Animal Biotechnology Cambs Ltd
* Association of the British Pharmaceutical Industry (ABPI)
Bayer AG, Pharma Research and Development
Professor D R Berry
Biocatalysts Ltd
Biochemical Society
* BioIndustry Association
* Sir Walter Bodmer FRS
Professor D Boulter
Professor S Brenner FRS
Brewers' Society
* British Bio-technology Group plc
* British Society of Plant Breeders Ltd
British Sugar Beet Seed Producers' Association
British Veterinary Association
Professor C F A Bryce and Professor M Wright
Bunting Biological Control Ltd
Professor D C Burke
Cantab Pharmaceuticals
* Celltech Biologics plc
Centre for Exploitation of Science and Technology (CEST) (Dr John Savin)
* Chemical Industries Association
Ciba Pharmaceuticals
Cobb Breeding Company Ltd (J Hunnable, Managing Director)
* Confederation of British Industry (CBI)
Dr Y Cripps
Professor J E Dale
Denton Hall Burgin & Warrens
* Department of the Environment
Department of Health
* Department of Trade and Industry
Peter Dunnill, Advanced Centre for Biochemical Engineering, University College London
Dupont de Nemours (France) S.A.
John Durant
* EC Commission
Gerard Fairtlough
Farm Animal Welfare Council (FAWC)
Farm and Food Society
* Food and Drink Federation
French Ministry of Agriculture and Fisheries
Genetics Forum
* Glaxo Group Research Ltd
Professor G Goldspink
* Green Alliance
* Greenpeace
Professor D Grierson

Professor J B Harris
* Health and Safety Executive (HSE)
* Hoechst UK Ltd
* Hoechst AG
F Hoffmann-La Roche AG
Institution of Professionals, Managers and Specialists
Italian Embassy
Japan BioIndustry Association
Japanese Embassy
Dr J Kinderlerer
Professor M D Lilly
Mrs J MacDonald
* Medical Research Council (MRC)
Medical Technology Assessment and Policy Centre (MEDTAP) Batelle Europe
Dr B Miller
* Ministry of Agriculture, Fisheries and Food (MAFF)
Monsanto Europe (Dr K M Baker, Director, Public Policy)
National Consumer Council
National Farmers' Union of England and Wales
National Office of Animal Health Ltd (NOAH)
National Rivers Authority
Natural Environment Research Council (NERC)
Netherlands Embassy
Novo Nordisk A/S
Nuffield Council on Bioethics
Professor D Onions
Organisation for Economic Co-operation and Development (OECD)
E R Ørskov OBE
Professor J W Parsons
Professor Sir Keith Peters
Pfizer Ltd
Pharmaceutical Proteins Ltd (Ron James, Managing Director)
Potato Marketing Board
Processors & Growers Research Organisation
Public Health Laboratory Service
Ross Breeders Ltd
Royal Academy of Engineering
Royal Agricultural Society of England
Royal Botanic Gardens, Kew
Royal College of Veterinary Surgeons
* Science and Engineering Research Council (SERC)
Scottish Agricultural Science Agency
Scottish Biotechnology Taskforce
* Senior Advisory Group Biotechnology (SAGB)
Margaret Sharp and Simon Shackley
Shell Research Ltd
Professor A R Slabas
* SmithKline Beecham Pharmaceuticals
Society for General Microbiology
Swiss Federal Office for Education and Science, Berne
Professor Joyce Tait, on behalf of the Economic and Social Research Council (ESRC)
J F Thorley
United Kingdom Agricultural Supply Trade Association Ltd (UKASTA)
United States Embassy
Professor Sir David Weatherall FRS
Wellcome Foundation Ltd
Professor M Williamson
* Zeneca

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